



# Comparison Study between Primary Closure Versus Secondary Closure Surgery for Pilonidal Sinus in Saudi Arabia: 25 Years' Systematic Review and Meta-analysis

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## **Authors' contributions**

*This work was carried out in collaboration between both authors. Both authors conducted database search, reviewed papers and collected and analysed data and wrote the manuscript. Both authors read and approved the final manuscript.*

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## **ABSTRACT**

**Background:** Pilonidal sinus disease is a chronic inflammation and infection of the sacrococcygeal region. It is a common disease, affecting roughly 26 per 100 000 populations, usually appears at age between 15&25 years old and predominantly affects young males. It can cause pain, sepsis,

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and reduced quality of life and has an impact on the individual's ability to attend work or education. Risk factors for the condition include male gender, young age, obesity, hairiness, deep natal cleft, and poor hygiene.

**Aim of Study:** To conduct a systematic review and meta-analysis for studies done in Saudi Arabia comparing lay open versus primary closure for pilonidal sinus done in the past 25 years.

**Materials and Methods:** We have performed an electronic search for PubMed, Cochrane library and Google Scholar, resulted in 241 studies. Then second filter was done for full text excluding 224 studies were unrelated not met inclusion criteria and 17 studies were obtained. 6 studies compared lay open and primary closure techniques, 5 studies only lay open ,4 studies primary closure. Furthermore two papers were excluded from analysis as one not mentions the surgery type and one paper measure the knowledge of the community about pilonidal disease.

**Results:** Complication rate (infection mean) was 4.505 in lay open group and 9.447 with primary closure group. Recurrence rate was higher in lay open versus primary closure techniques.

**Conclusion:** Lay open procedure was associated with shorter operative time and reduced risk of recurrence or complication rate in comparison to primary closure technique, but it takes more time for hospital stay and wound healing.

*Keywords: Pilonidal sinus; pilonidal disease; excision and primary closure; lay open.*

## 1. INTRODUCTION

Pilonidal disease (PD) is a widespread condition affecting the area between the tailbone and the coccyx [1]. It involves a range of issues, such as infections and abscesses, as well as the formation of a persistent sinus cavity [2]. The frequency of this condition differs among different countries and ethnic groups [3]. The exact cause is still debated, with theories suggesting both genetic and environmental factors. The primary factor believed to contribute to the disease is the way hair grows in the area. Despite numerous surgical approaches being suggested, there is no definitive agreement on the best method for treatment in the medical literature. The ideal surgical procedure should be straightforward, require a short hospital stay, have a low chance of recurrence, cause minimal pain, and reduce the need for extensive postoperative care, allowing for a quicker return to work. Treating pilonidal disease through surgery is difficult due to the common occurrence of wound infections, slow healing, and the risk of the condition recurring. In some cases, the surgery can lead to complications that are more severe than the original condition, such as wound separation. Both open and minimally invasive techniques, like marsupialization, lead to a wound that heals over several weeks but have been found to have a low rate of recurrence due to the open approach for hair removal. While primary closure, which has a higher chance of recurrence, is generally preferred due to lower rates of wound separation and infection, it also results in less pain, fewer follow-up appointments, a shorter

duration off work, and a quicker recovery period [4-22].

### 1.1 Aim of the Work

To conduct a systematic review and meta-analysis for studies done in Saudi Arabia comparing between excision of pilonidal sinus and lay open versus closure technique, regarding wound healing, wound complications, and recurrence rate.

## 2. MATERIALS AND METHODS

We followed the Cochrane Handbook of Systematic Reviews [23], the PRISMA 2020 Update, and the Standards for Preferred Reporting Items of Systematic Reviews and Meta-Analyses as well as Assessing the Methodological Quality of Systematic Reviews (AMSTAR) guidelines for conducting our review [24-26].

**Search strategy:** We searched three databases, PubMed, Scopus, and Web of Science from January 1999 to July 20, 2024, using MeSH terms to form the following search strategy: ("Lay Open " OR "Primary closure") AND (Pilonidal sinus "OR "Pilonidal disease") AND ("Saudi Arabia"). As a backup check, the references of the included studies were manually searched to identify other potentially eligible studies. Exclusion criteria were: research done outside Saudi Arabia, done before 1999, PD in the non-sacral region of the study subject; no full text, or data missing or even wrong.

**Quality assessment:** The risk of bias of the studies included in the systematic review was independently assessed by the two reviewers using the Cochrane Collaboration Risk of Bias Tool. Each reviewer independently reviewed titles, abstracts, and full texts. Conflicts were resolved by consensus during discussion of the abstract and full review. The Cochrane Collaboration tool was used to assess seven aspects of study quality (random sequence generation, allocation concealment, blinding (participants and personnel), blinding of outcome assessment, incomplete outcome data, selective reporting, and other forms of bias). Low, unclear, or high risk of bias was assigned to each item [27].

So, our PICO is:

Population: Patients who underwent pilonidal surgery in Saudi Arabia.

Intervention: lay Open method for pilonidal sinus

Control: primary Closure method for pilonidal sinus

Outcomes: recurrence rate, wound healing, time return to work and complications

**Data extraction:** A standardized extraction form was prepared using MS Excel. Authors independently extracted the following data from each of the included study: Study characteristics and endpoint outcomes.

**Data analysis:** We used MedCalc® Statistical Software version 22.026 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2024), and continuous outcomes were presented as mean differences (MD) and dichotomous outcomes as risk ratios (RR) with 95% confidence intervals. In case of detected heterogeneity (Chi-square P value < 0.05), a random-effects model was employed, and a leave-one-out test was used to solve the heterogeneity; otherwise, a fixed-effects model was used. The results were considered significant if the P-value was less than 0.05. We used I square value and its p-value to quantify degree of heterogeneity. We used random effect model when I square value is more than 50%. Publication Bias: We assessed publication bias using Egger test and funnel plot methods [28]. Where the data were too diverse for combining effect sizes in a meaningful or valid manner, we used a narrative approach to summarize the data. For continuous outcomes, standardized effect size was determined to get the pooled effect size, and if the number of events were

reported, then proportion meta-analysis was used.

### 3. RESULTS

We undertook full bibliographic searches in January 2024, updating them in June 2024 and again in July 18th, 2024. The two review authors independently read a total of 241 titles and abstracts. A total of 17 studies were included in the final review. We excluded 86 duplicated articles and 138 other articles because of irrelevant topics, the remaining 17 studies were included. Six studies compared lay open and primary closure techniques, 5 studies only lay open, 4 studies primary closure, one study does not mention the surgery type [15] and one paper measure the knowledge of the community about pilonidal disease, [8] both were excluded from the meta-analysis. Study characteristics: (Table 1) Sample sizes in the trials ranged from 25 to 800 participants (total 3984). Studies included 602 females and 3382 males with a ratio of 17/73.

Six studies comparing between excision of pilonidal sinus via lay open technique versus closed techniques were included 4 were retrospective studies and 2 were prospective. Four studies of these were used for meta-analysis of wound healing time (Figs. 1a-d).

Mean follow-up period was 2.433 years in lay open groups while it was 2.095 years in the primary closure groups as shown in Table 3. Mean complication (infection) rate in the primary closure group was 9.447 versus 4.505 in lay open group as shown in Table 4. Three studies included comparing operative time/ min in lay open group versus two studies in primary closure group shows significant longer time in primary closure group versus lay open group  $p$ -value < 0.0001. Nine studies included comparing hospitalization/ days in lay open group versus 9 studies in primary closure group shows significant longer time in lay open group versus primary closure group  $p$ -value < 0.0001. (Table 3). Six studies comparing time taken for wound healing/days in lay open group versus 4 studies in primary closure group shows insignificant longer time in lay open group versus primary closure group  $p$ -value  $P = 0.5650$ . 4 studies included comparing complications in lay open group versus 6 studies in primary closure group shows significant higher rate of complications in primary closure group versus lay open group  $p$  value of < 0.0001. Nine studies

included comparing recurrence in lay open group versus 9 studies in primary closure group shows significant higher recurrence rate in lay open group versus primary closure group  $p$ -value <

0.0001. (Table 4, Fig. 2 a,b.). We could identify 4 studies compare lay open with primary closure meta-analysis was done in wound healing (Figs. 1a-d).

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Review:      Model: SMD - Fixed & Random Effect

              SMD              95%-CI  %W (common) %W (random)
Chiedozietal2002  15.2000 [13.5883; 16.8117]  4.3      24.6
Al-Salamahetal2007 11.1951 [10.0428; 12.3474]  8.5      25.0
Shirah2016         4.6154 [ 4.2123;  5.0184] 69.4     25.3
Aldaqaletal2013   5.0000 [ 4.2033;  5.7967] 17.8     25.1

Number of studies combined: k = 4
Number of observations: o = 1391

              SMD              95%-CI  z|t p-value
Common effect model 5.7019 [5.3661; 6.0376] 33.28 < 0.0001
Random effects model 8.9633 [0.8386; 17.0881] 3.51  0.0392

Quantifying heterogeneity:
tau^2 = 25.6774 [8.0023; >256.7738]; tau = 5.0673 [2.8288; >16.0242]
I^2 = 98.8% [98.2%; 99.2%]; H = 9.16 [7.39; 11.35]

Test of heterogeneity:
      Q d.f. | p-value
251.61  3 < 0.0001
    
```

Fig. 1a. Summary of meta-analysis

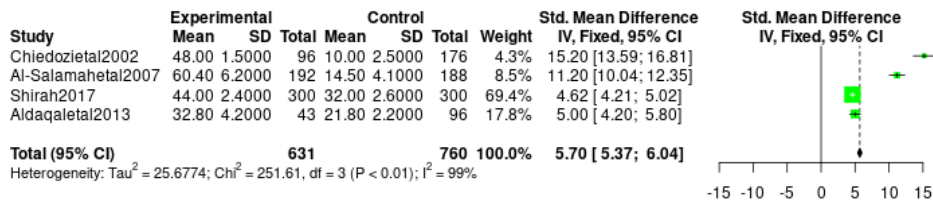


Fig. 1b. Forest plot of random model

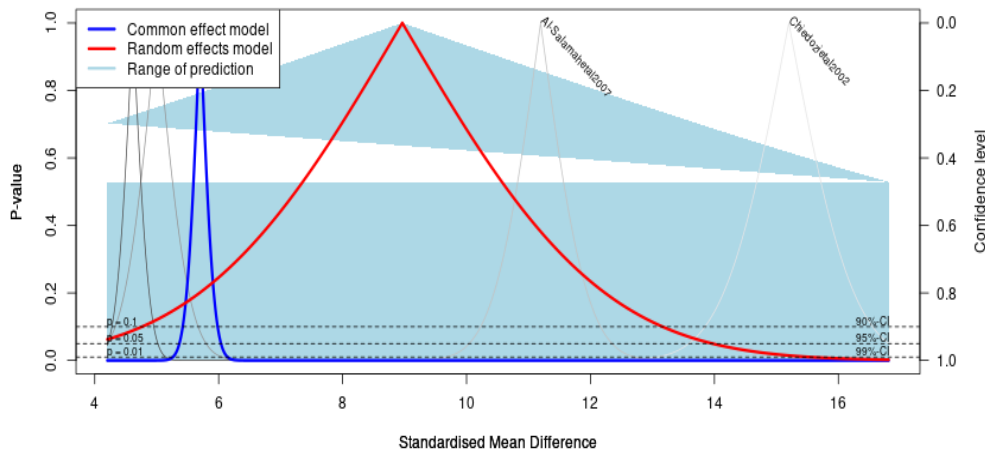
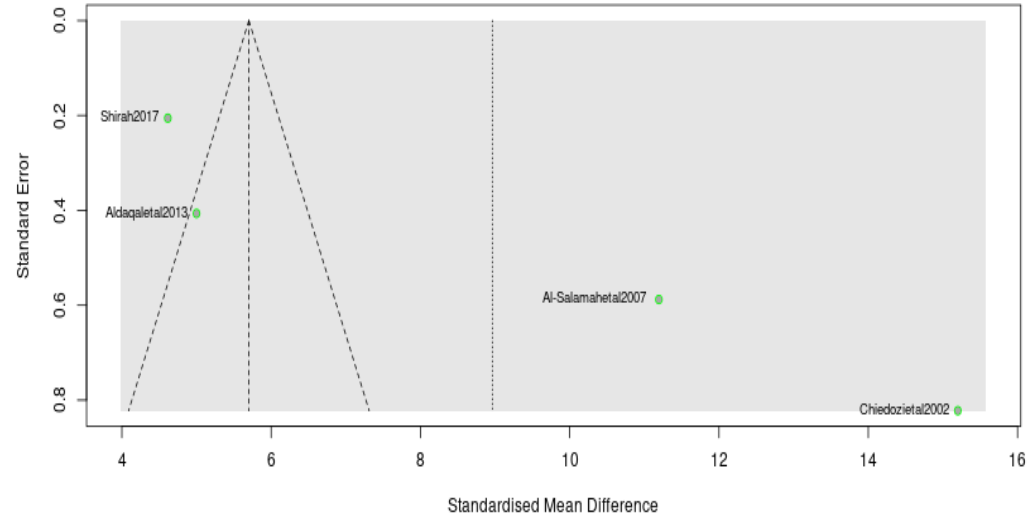


Fig. 1c. Drapery plot



**Fig. 1d. Funnel plot**

**Table 1. Summary of the studies retrieved**

Study	year	Operative type	Patient number	age	Sex male	Sex female	anaesthesia	Operative time	Hospital stay	Follow up	Healing time	Recurrence %	Time to return to work	Complications Infections %	Study type
Al-Homoud 7	2001	Lay open	98	25	86	12	GA	na	5.4	0.5	72	4	na	Na	retrospective
Chiedozi et al 3	2002	Lay open	96	24.7	255	17	na	na	10	3	48	7.3	na	Na	Retrospective
Seleem & Al-Hashemy 10	2005	Primary closure	176	26.4	23	2	LA	19.3	0.3	3	10	9.1	na	9.1	prospective
		Open and fibrin glue	25								14	0		4	
Al-Salamah et al 4	2007	Lay open	192	22.8±6.4	180	12	GA	43±5	4±1.1	2.9	60.4±6.2	3.12	42.2±5.3	3.12	prospective
		Primary closure	188	22.4±6.1	17	13	na	58±4.5	3.6±1.4	3.1	14.5±4.1	3.7	15.6±3.4	4.2	
al-khayat et al 11	2007	Primary closure	94	21.9	82	12	na	71.5	1.67	0.5	na	0	na	12	retrospective
Khazada & Abdul Samad 12	2007	Primary closure	60	35	53	7	GA	na	6	1 year	na	5	21	10	prospective
Ghannam&Hafez16	2011	Lay open	86	23.3	75	11	GA	16	2	2 years	35.5	2.3	16.1	3	prospective
Aldaqa et al 6	2013	Lay open	43	24.5	118	24	na	na	na	0.16	32.8±4.2	6.3	na	na	Prospective
		Primary closure	96	26.7±6.9	62	4	GA	na	na	na	na	21.8±2.2	7	na	14.6
Closed	66	50.4±8.5													
Shirah 19	2016	Lay open	300	27.5	233	67	na	na	1	5	44±2.4	0	na	na	Prospective
Shirah 15	2017	Primary closure	300	27	193	107	na	na	na	na	32±2.6	4.7	na	0	
Shirah 17	2017	Lay open	472	27.64	326	146	na	na	1	3	na	0	na	0	na
Hussain et al 18	2017	Lay open	800	40	59	0	GA &spinal	na	6	1	27 days	0.87	na	na	prospective
		Primary closure	59								na	3.39	na	6.78	
Almajid et al 9	2017	All	347	23.4 ± 8	323	24	GA 201 S 146	na	4.4 ± 4.6	1.6	na	7.2	na	na	retrospective
Albabbain et al 5	2021	Lay open	183	21	329	40	na	na	na	1	na	22.8	na	7.9	retrospective
		Primary closure	164												
		closure	207												

**Table 2. Patient numbers, age and sex**

	Patient number		age		Sex female		sex male	
	lay open	primary closure	lay open	primary closure	lay open	primary closure	lay open	primary closure
Valid	9	9	8	9	9	9	9	9
Missing	0	0	0	0	0	0	0	0
Mean	273.667	198.667	24.262	27.760	30.222	36.667	246.333	129.444
Std. Deviation	225.235	136.062	2.078	5.990	28.973	52.331	206.180	105.367
Minimum	86.000	60.000	21.000	21.900	2.000	0.000	23.000	17.000
Maximum	800.000	472.000	27.500	40.000	87.000	146.000	713.000	326.000
25 <sup>th</sup> percentile	98.000	94.000	23.175	24.500	12.000	7.000	86.000	59.000
50 <sup>th</sup> percentile	192.000	176.000	24.050	26.700	17.000	13.000	233.000	82.000
75 <sup>th</sup> percentile	347.000	300.000	25.350	27.640	40.000	24.000	323.000	193.000
Sum	2396.000	1588.000	194.100	249.840	272.000	330.000	2217.000	1165.000

Note. Excluded 6 rows from the analysis that correspond to the missing values of the split-by variable Operative type

**Table 3. Operative time, hospital stay, follow up and time to return to work**

	Operative time		Hospital stay		Follow up years		Time to return to work	
	lay open	primary closure	lay open	primary closure	lay open	primary closure	lay open	primary closure
Valid	3	2	9	9	9	8	2	2
Missing	6	7	0	0	0	1	7	7
Mean	26.100	64.750	3.078	2.141	2.433	2.095	29.150	18.300
Std. Deviation	14.729	9.546	3.201	2.193	1.686	1.681	18.455	3.818
Minimum	16.000	58.000	0.000	0.000	0.500	0.160	16.100	15.600
Maximum	43.000	71.500	10.000	6.000	5.000	5.000	42.200	21.000
25 <sup>th</sup> percentile	17.650	61.375	1.000	1.000	1.000	0.875	22.625	16.950
50 <sup>th</sup> percentile	19.300	64.750	2.000	1.000	2.000	2.000	29.150	18.300
75 <sup>th</sup> percentile	31.150	68.125	4.000	3.600	3.000	3.025	35.675	19.650
Sum	78.300	129.500	27.700	19.270	21.900	16.760	58.300	36.600

Note. Excluded 6 rows from the analysis that correspond to the missing values of the split-by variable Operative type

**Table 4. Recurrence, healing times and complications (infection)**

	Recurrence %		Complications Infections %		Healing time days	
	lay open	primary closure	lay open	primary closure	lay open	primary closure
Valid	9	9	4	6	6	4
Missing	0	0	5	3	3	5
Mean	5.288	4.354	4.505	9.447	42.817	25.175
Std. Deviation	7.116	3.023	2.307	3.692	21.549	18.082
Minimum	0.000	0.000	3.000	4.200	14.000	10.000
Maximum	22.800	9.100	7.900	14.600	72.000	50.400
25 <sup>th</sup> percentile	0.870	3.390	3.090	7.360	29.125	13.375
50 <sup>th</sup> percentile	3.120	4.700	3.560	9.550	41.750	20.150
75 <sup>th</sup> percentile	7.200	6.300	4.975	11.500	57.300	31.950
Sum	47.590	39.190	18.020	56.680	256.900	100.700

Note. Excluded 6 rows from the analysis that correspond to the missing values of the split-by variable Operative type

**Meta-analysis: proportion**

Variable for studies	studys
Variable for total number of cases	n
Variable for number of positive cases	recurrence

Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Al-Homoud et al 2001	98	4.082	1.123 to 10.122	2.32	5.04
Chiedozi et al o 2002	96	7.604	3.184 to 14.844	2.27	5.01
Chiedozi et al p2002	176	5.170	2.403 to 9.557	4.15	5.65
Seleem&Al-Hashemy 2005	176	0.000	0.000 to 2.074	4.15	5.65
Al-Salamah et al o 2007	192	1.625	0.351 to 4.590	4.52	5.73
Al-Salamah et al p2007	188	1.968	0.503 to 5.131	4.43	5.71
al-khayat et al 2007	94	0.000	0.000 to 3.848	2.23	4.98
Khanzada&AbdulSamad 2007	60	8.333	2.761 to 18.386	1.43	4.36
Ghannam&Hafez 2011	86	2.674	0.400 to 8.673	2.04	4.87
Aldaqaletal 2013	132	4.773	1.825 to 9.930	3.12	5.38
Kasim et al 2015	66	10.606	4.372 to 20.639	1.57	4.50
Shirah o 2017	300	0.000	0.000 to 1.222	7.05	6.04
Shirah p 2017	300	1.567	0.488 to 3.707	7.05	6.04
Shirah o 2017	472	0.000	0.000 to 0.778	11.08	6.27
Shirah o 2017	800	0.109	0.00171 to 0.666	18.76	6.44
Hussain et al 2017	300	1.130	0.265 to 3.085	7.05	6.04
Almajid et al 2017	347	2.075	0.851 to 4.189	8.15	6.12
Albabtain et al 2017	368	6.196	3.959 to 9.167	8.64	6.15
Total (fixed effects)	4251	1.454	1.116 to 1.859	100.00	100.00
Total (random effects)	4251	2.371	1.211 to 3.905	100.00	100.00

**Test for heterogeneity**

Q	135.9555
DF	17
Significance level	P < 0.0001
I <sup>2</sup> (inconsistency)	87.50%
95% CI for I <sup>2</sup>	81.73 to 91.44

**Publication bias**

Egger's test	
Intercept	4.8792
95% CI	1.4759 to 8.2824
Significance level	P = 0.0078
Begg's test	
Kendall's Tau	0.4040
Significance level	P = 0.0192

**Fig. 2a. Meta analysis of recurrence in all studies**

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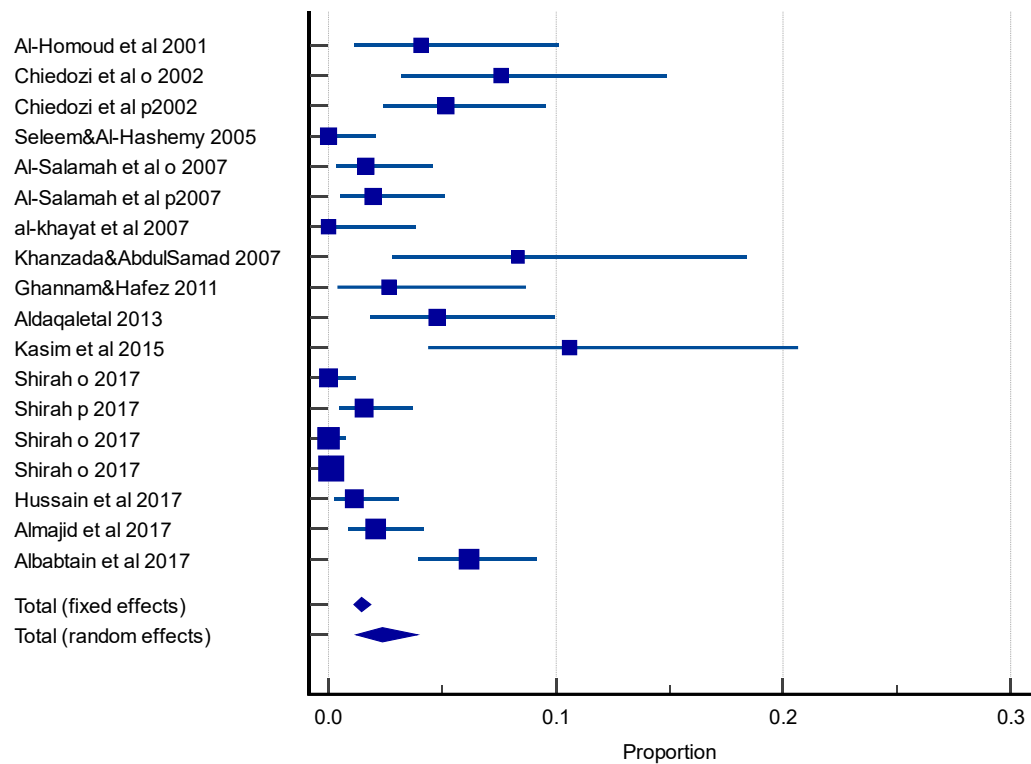


Fig. 2b. Meta analysis of recurrence in all studies

**Meta-analysis: proportion**

Variable for studies	studys
Variable for total number of cases	n
Variable for number of positive cases	infections

Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Chiedozi et al p2002	176	5.170	2.403 to 9.557	10.31	10.50
Seleem&Al-Hashemy 2005	176	2.273	0.623 to 5.717	10.31	10.50
Al-Salamah et al o 2007	192	1.625	0.351 to 4.590	11.25	10.63
Al-Salamah et al p2007	188	2.234	0.638 to 5.507	11.01	10.60
al-khayat et al 2007	94	12.766	6.774 to 21.238	5.54	9.35
Khanzada&AbdulSamad 2007	60	16.667	8.293 to 28.522	3.55	8.25
Ghannam&Hafez 2011	86	3.488	0.725 to 9.858	5.07	9.15
Kasim et al 2015	66	22.121	12.830 to 34.030	3.90	8.50
Hussain et al 2017	300	2.260	0.897 to 4.651	17.54	11.16
Albabtain et al 2017	368	2.147	0.925 to 4.203	21.50	11.35
Total (fixed effects)	1706	3.899	3.034 to 4.926	100.00	100.00
Total (random effects)	1706	5.552	3.026 to 8.783	100.00	100.00

**Test for heterogeneity**

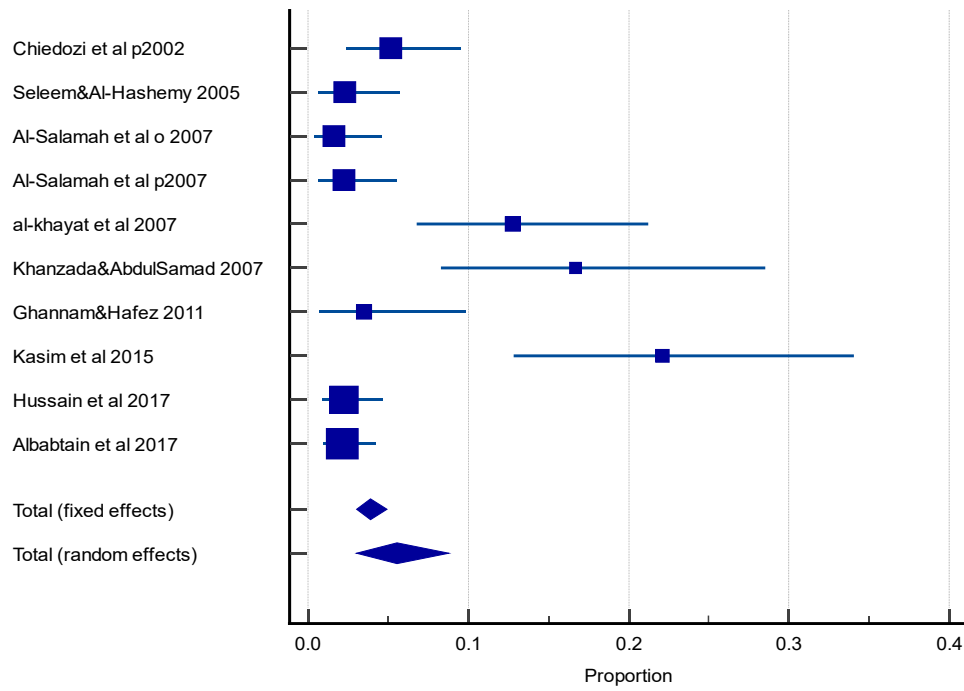
Q	59.2337
DF	9
Significance level	P < 0.0001
I <sup>2</sup> (inconsistency)	84.81%
95% CI for I <sup>2</sup>	73.76 to 91.20

**Publication bias**

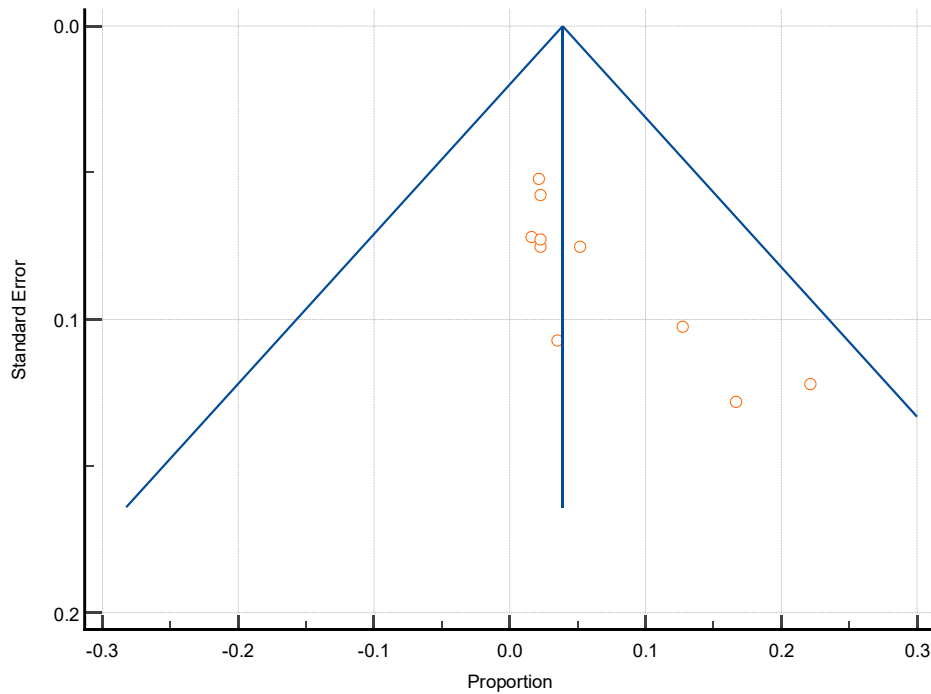
Egger's test	
Intercept	7.3405
95% CI	3.3954 to 11.2856
Significance level	P = 0.0026
Begg's test	
Kendall's Tau	0.8090
Significance level	P = 0.0011

**Fig. 3a. Meta analysis of infection in the studied groups report infection**

C:\pns healing 2studies.mc1 Friday, July 26, 2024 11:01 MedCalc® Statistical Software version 22.026 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2024)



**Fig. 3b. Meta analysis of infection in the studied groups report infection**



**Fig. 3c. Meta analysis of infection in the studied groups report infection**

#### 4. DISCUSSION

In this meta-analysis, 6 studies included comparing between excision of pilonidal sinus via

lay open technique versus closed techniques were included. Four were retrospective studies and 2 were prospective. The total number of the studied cases were 3984 cases with male to

female ratio 3382/602 and mean age was 24.262 years in the lay open group and 27.760 years in primary closure group. Mean follow-up period was 2.26 years with longest follow-up of 5 years [19]. 2396 cases were operated by lay open technique versus 1588 cases by primary closure technique.

This systematic review and meta-analysis aimed to compare the outcomes of the lay open technique versus primary closure in the surgical treatment of pilonidal sinus disease in Saudi Arabia over the past 25 years. Our findings indicate that while the lay open technique is associated with a shorter operative time and reduced risk of complications, it also requires a longer hospital stay and healing period compared to primary closure.

#### **4.1 Operative Time and Hospital Stay**

The analysis showed a significantly shorter operative time for the lay open technique compared to primary closure. This could be attributed to the simpler nature of the lay open procedure, which involves excising the sinus tract and leaving the wound open to heal by secondary intention. In contrast, primary closure requires additional steps for wound closure, contributing to a longer operative duration. However, the lay open method necessitated a longer hospital stay, likely due to the extended wound healing process and the need for more intensive postoperative care to manage the open wound [9,29].

#### **4.2 Complications and Recurrence**

Our results revealed a lower complication rate for the lay open technique compared to primary closure. The primary complication observed was infection, with the lay open group showing a mean infection rate of 4.505%, significantly lower than the 9.447% observed in the primary closure group. This may be due to the open wound's ability to drain freely, reducing the risk of abscess formation and subsequent infection [9,29].

Interestingly, the recurrence rates between the two techniques although differ significantly, with 5.288% for lay open and 4.354% for primary closure. While the primary closure technique showed a slightly lower recurrence rate, the difference was statistically significant, suggesting that both methods are comparable in terms of long-term outcomes. McCallum et al [29].

reported recurrence rate less likely to occur in lay open technique unlike primary closure this discrepancy may be attributed to large sample size in lay open technique, heterogeneity of studies included and the high studies design bias

#### **4.3 Wound Healing and Return to Work**

Wound healing time was significantly longer for the lay open technique, averaging 42.817 days compared to 25.175 days for primary closure. This extended healing period is expected with an open wound healing by secondary intention, which requires more time for granulation tissue to fill the defect and for epithelialization to occur. Consequently, patients undergoing the lay open procedure experienced a delayed return to work, impacting their overall quality of life and productivity. In agreement with our findings, the meta-analysis by [26], included (18 trials n=1573). 12 trials compared open healing with primary closure. The study reported that wounds heal more quickly after primary closure than after open healing but at the expense of increased risk of recurrence.

### **5. CONCLUSION**

In conclusion, the lay open technique for pilonidal sinus surgery in Saudi Arabia is associated with a shorter operative time and lower complication rate compared to primary closure. However, it requires a longer hospital stay and wound healing period, impacting the patient's return to normal activities. Both techniques demonstrated comparable recurrence rates. These findings suggest that the choice between lay open and primary closure should be individualized, considering the patient's circumstances, the surgeon's experience, and the available healthcare resources. Further well-designed, randomized controlled trials are needed to confirm these results and guide clinical practice in the management of pilonidal sinus disease.

### **6. STRENGTHS AND LIMITATIONS**

A key strength of this study is the comprehensive nature of the systematic review and meta-analysis, which included a substantial number of studies and patients, thereby enhancing the robustness of the findings. Additionally, the focus on studies conducted in Saudi Arabia provides valuable insights into the local context and surgical practices.

However, several limitations must be acknowledged. The included studies varied in

their design, with a mix of retrospective and prospective studies, which could introduce heterogeneity in the results. Moreover, the variability in follow-up durations across studies might have influenced the reported outcomes. Another limitation is the potential for publication bias, as studies with negative results are less likely to be published, potentially skewing the overall findings. Owing to the nature of the surgical treatment for pilonidal sinus, blinding of surgeons, patients, and assessors is not possible and some risk of bias exists; therefore, results must be interpreted with caution. Many small variations in surgical technique occur, including depth and extent of dissection, undermining of tissues, and type of suture materials used. We have attempted to group interventions to maintain clinical relevance whenever possible. This, as in all meta-analyses, represents a compromise, which has to be reached to provide meaningful comparison.

#### DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

#### CONSENT AND ETHICAL APPROVAL

It is not applicable.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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