Interventional treatments for prolapsing haemorrhoids: network meta-analysis

J. Z. Jin 🝺 *, S. Bhat 🝺 , K.-T. Lee, W. Xia and A. G. Hill 🝺

Department of Surgery, South Auckland Clinical Campus, University of Auckland, Middlemore Hospital, Auckland, New Zealand

*Correspondence to: South Auckland Clinical Campus, PO Box 93311 Otahuhu, Auckland 1640, New Zealand (e-mail: James.jin@auckland.ac.nz)

Abstract

Background: Multiple treatments for early-moderate grade symptomatic haemorrhoids currently exist, each associated with their respective efficacy, complications, and risks. The aim of this study was to compare the relative clinical outcomes and effectiveness of interventional treatments for grade II–III haemorrhoids.

Methods: A systematic review was conducted according to PRISMA criteria for all the RCTs published between 1980 and 2020; manuscripts were identified using the MEDLINE, Embase, and CENTRAL databases. Inclusion criteria were RCTs comparing procedural interventions for grade II–III haemorrhoids. Primary outcomes of interest were: symptom recurrence at a minimum follow-up of 6 weeks, postprocedural pain measured on a visual analogue scale (VAS) on day 1, and postprocedural complications (bleeding, urinary retention, and bowel incontinence). After bias assessment and heterogeneity analysis, a Bayesian network meta-analysis was performed.

Results: Seventy-nine RCTs were identified, including 9232 patients. Fourteen different treatments were analysed in the network meta-analysis. Overall, there were 59 RCTs (73 per cent) judged as being at high risk of bias, and the greatest risk was in the domain measurement of outcome. Variable amounts of heterogeneity were detected in direct treatment comparisons, in particular for symptom recurrence and postprocedural pain. Recurrence of haemorrhoidal symptoms was reported by 54 studies, involving 7026 patients and 14 treatments. Closed haemorrhoidectomy had the lowest recurrence risk, followed by open haemorrhoidectomy, suture ligation with mucopexy, stapled haemorrhoidopexy, and Doppler-guided haemorrhoid artery ligation (DG-HAL) with mucopexy. Pain was reported in 34 studies involving 3812 patients and 11 treatments. Direct current electrotherapy, DG-HAL with mucopexy, and infrared coagulation yielded the lowest pain scores. Postprocedural bleeding was recorded in 46 studies involving 5696 patients and 14 treatments. Open haemorrhoidectomy had the greatest risk of postprocedural bleeding, followed by stapled haemorrhoidectomy and stapled haemorrhoidopexy had significantly higher odds of urinary retention than rubber band ligation and DG-HAL with mucopexy. Nine studies reported bowel incontinence comparing five treatments involving 1269 participants. Open haemorrhoidectomy and stapled haemorrhoidopexy had the highest probability of bowel incontinence.

Conclusion: Open and closed haemorrhoidectomy, and stapled haemorrhoidopexy were associated with worse pain, and more postprocedural bleeding, urinary retention, and bowel incontinence, but had the lowest rates of symptom recurrence. The risks and benefits of each treatment should be discussed with patients before a decision is made.

Introduction

Haemorrhoids are common and affect up to 38.9 per cent of the adult population¹. Patients typically experience symptoms such as perianal pain, bleeding after defaecation, discharge, and difficulties with perianal hygiene and prolapse, with a substantial impact on quality of life².

The anatomical degree of prolapse for haemorrhoids is based on Goligher's grading³. Grade I refers to non-prolapsing haemorrhoids that bleed only. Grade 2 haemorrhoids intermittently prolapse with spontaneous reduction, whereas grade 3 haemorrhoids require manual reduction. Grade IV haemorrhoids are considered most severe; they are permanently prolapsed externally and cannot be reduced manually. Although this grading is used routinely, the anatomical grade of severity does not necessarily correlate with patient-reported symptom severity⁴.

The treatment of prolapsing haemorrhoids of grade II–III varies, ranging from office-based procedures to surgical excision, and the choice of intervention can depend on patient or surgeon preference. However, the treatment of choice for grade IV haemorrhoids usually involves a form of surgical excision, such as Milligan–Morgan (open) haemorrhoidectomy, or Ferguson (closed) haemorrhoidectomy. Other techniques such as Doppler-guided haemorrhoid artery ligation (DG-HAL) with mucopexy have also been shown to be effective for grade 4 haemorrhoids⁵. The decision regarding the treatment of haemorrhoids depends on patient or surgeon preference and the availability of resources⁶. This study

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aimed to assess the available treatments for patients with prolapsing-grade haemorrhoids, excluding studies with permanently prolapsed grade IV haemorrhoids, as the latter are commonly treated with surgical excision, rather than less invasive procedures^{5,6}.

Given the number of procedures available, the use of a network meta-analysis (NMA) to pool the evidence presented in multiple RCTs simultaneously through direct and indirect comparisons could provide a comprehensive insight. RCTs usually compare the treatment efficacy of two treatments directly, resulting in difficulty in gauging each treatment's relative effectiveness and complication profiles when comparing numerous treatments. Therefore, this systematic review and NMA aimed to compare the clinical outcomes and effectiveness of interventional treatments for grade II–III haemorrhoids.

Methods

This systematic review and NMA was conducted in accordance with the PRISMA guidelines, with extension for network metaanalysis (NMA)^{7,8}.

Search strategy

The MEDLINE, Embase, and Cochrane Central Register of Clinical Trials (CENTRAL) were searched systematically using a comprehensive search strategy involving free text and Medical Subject Headings. The complete search string is included in the study protocol (*Appendix* S1). Articles were restricted to those published in the English language between 1 January 1980 and 15 September 2020. RCTs comparing interventional treatments for patients with grade II or III haemorrhoids were considered for inclusion. Studies that had participants with grade I haemorrhoids were also included as long as over 50 per cent of study participants had grade II or III haemorrhoids. Studies were excluded if more than 3 per cent of the total study population had grade IV haemorrhoids.

Only studies reporting on interventional treatments in an elective setting were included; studies documenting treatments for haemorrhoids in the emergency setting were excluded, as were those reporting on medical treatments for haemorrhoids.

Study selection and data collection

The RCTs for inclusion were identified by two review authors by independent screening of titles and abstracts. Full texts of potentially included studies were then sought and further selection for inclusion was undertaken independently by two review authors, based on the full text. Consensus among the review authors was required before inclusion of each study, and any discrepancies were adjudicated by a senior author.

The following data were extracted from each study independently by two review authors: study characteristics (first author, year of publication, and country), selection criteria (inclusion and exclusion criteria), participant characteristics (sample size, haemorrhoid grade), interventional treatments compared, and outcome measures. Any discrepancies in extracted data were resolved by discussion, and a final decision was taken by the senior author.

Outcomes of interest

The primary outcomes were symptom recurrence, postprocedural pain, and postprocedural complications. Symptom recurrence was defined according to the patient's self-reported symptoms at a minimum follow-up of 6 weeks after the procedure. Postprocedural pain was measured on day 1 using a visual analogue scale (VAS). Postprocedural complications, defined as any deviation from the normal postprocedural course, were also included in the outcomes. The complications analysed included postprocedural bleeding, urinary retention, and bowel incontinence. Secondary outcomes were repeat treatment, length of hospital stay and time to return to work or resumption of normal activity. Repeat treatment was defined as any additional treatment required within the postprocedure follow-up interval and included a repeat of the same treatment or a different treatment.

Bias assessment

The Cochrane Collaboration's risk-of-bias tool 2.0⁹ was used to assess the risk of bias in included RCTs based on the following domains: randomization process, deviation from intended interventions, missing outcome data, measurement of outcome, and selection of reported result. For each of these risk domains, studies were categorized as having either a low, uncertain or high risk of bias. The overall risk of bias was calculated according to the algorithm's overall judgement.

Statistical analysis

An intention-to-treat Bayesian NMA with a non-informative prior was undertaken in R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria)¹⁰.

For each outcome, a network plot of all treatments assessed was constructed to visually represent all direct comparisons between included interventional treatments. Nodes on the network plot were used to depict the number of participants receiving a particular treatment and the thickness of each connecting line correlated with the number of studies assessing a particular direct comparison. Interventional treatments assessed in only one study and not connected to at least two treatments through the network plot were excluded from the analysis of that outcome to minimize bias resulting from single-trial effects. Rubber band ligation (RBL) was used as the reference treatment in the network plot for all outcomes. Continuity corrections were applied to dichotomous (categorical) outcomes with no events, by adding an arbitrary constant of 1 to both the numerator and denominator of each treatment arm¹¹. Where continuous data were presented as median and range or interquartile range, mean and standard deviation estimates were calculated^{12,13}. If the standard deviation was not reported, it was calculated from the standard error, P value, confidence interval or interquartile range according to guidance in the Cochrane Handbook for Systematic Reviews of Interventions¹⁴. Standard deviations that could not be calculated were imputed using the largest value in other trials for that outcome. Categorical and continuous outcomes were reported as an odds ratio (OR) and mean difference (MD) respectively, with 95 per cent credible interval (CrI). Final results for each outcome were illustrated in a league table, showing OR or MD (with 95 per cent CrI) for each treatment comparison, surface under the cumulative ranking (SUCRA) curve, indicating each treatment ranking with its respective ranking probability, and forest plot, illustrating the OR (or MD) of each treatment relative to a reference treatment¹⁵. SUCRA values range from 0 to 100 per cent; higher values indicate a greater likelihood of a particular treatment being in a top rank, whereas lower values mean a particular treatment is more likely to be in a bottom rank¹⁶. A nodesplitting analysis was conducted to assess for inconsistency between direct and indirect treatment comparisons in each network¹⁷. Heterogeneity owing to differences between studies within each direct treatment comparison was evaluated by the I²

statistic; a value of more than 50 per cent was indicative of significant heterogeneity between the studies¹⁸.

For each outcome, analyses were performed using both fixedand random-effects NMA models. The goodness of fit of each model was assessed by means of leverage plots displaying the corresponding effective number of parameters, total residual deviance, and deviance information criterion (DIC)¹⁹. DIC values were compared and the model with the lower value (fewer outliers on visual examination of the leverage plot) was chosen. In most instances, a random-effects model was used, which assumes variation between studies owing to heterogeneity and generates a wider CrI.

An NMA relies on the assumption of transitivity, which refers to potential modifiers of the treatment effect being distributed equally across all included RCTs²⁰. In the present NMA, the transitivity assumption was analysed by collecting and comparing data on potential modifiers of the outcomes such as participant age, sex, grade of haemorrhoids, geographical location of studies, and duration of follow-up, in each direct treatment comparison.

Sensitivity analyses were also undertaken, including only studies comparing treatments for patients with grade II and grade III haemorrhoids, recognizing that the initial treatment for grade I haemorrhoids is seldom surgical, and so studies including patients with grade 1 haemorrhoids were excluded.

Results

In total, 2367 articles were screened for relevance based on title and/or abstract. After full-text assessment, 79 $RCTs^{21-99}$ were included, with 9232 patients. Thirty-three full-text articles were

excluded based on the inclusion of a significant number of participants with grades I and IV haemorrhoids (Fig. 1). Table 1 provides a summary of the studies included in the NMA.

Risk-of-bias analysis

The risk of bias of included RCTs is summarized in Fig. 2 and described for each study in *Appendix S2*. Bias was mostly attributable to lack of blinding among the outcome observers, in 52 RCTs (64 per cent). Overall, 59 trials (73 per cent) were judged as being at high risk of bias, and the domain showing the greatest risk was measurement of outcome.

Risk of heterogeneity and inconsistency

There were variable amounts of heterogeneity between studies within particular direct treatment comparisons for each outcome. For symptom recurrence, significant heterogeneity was detected among direct comparisons between RBL versus injection sclerotherapy (IJS) and Milligan–Morgan versus laser haemorrhoidectomy. Postprocedural pain was associated with significant heterogeneity among multiple direct treatment comparisons. There were few comparisons with significant heterogeneity for repeat treatment, duration of hospital stay, time off work, postprocedural bleeding, urinary retention, and bowel incontinence (Appendix S3). The node-splitting analysis revealed few instances of inconsistency in the overall network. For symptom recurrence, it revealed an overall consistent profile except for two instances of inconsistency in the network, which were mainly attributable to direct comparisons between laser haemorrhoidectomy versus open haemorrhoidectomy and laser haemorrhoidectomy versus RBL. For



Fig. 1 PRISMA flow diagram showing selection of articles for review

Table 1 Summary of included studies

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Filgate et al. (2019)** HET versus RRL 30 30 Fillageri et al. (2012)** RFL versus CHR 90 90 Fillageri et al. (2013)** RFL versus SHM 62 38 Gaglo et al. (2013)** RFL versus BL 30 30 Garcel et al. (1985)** RFL versus BL 32 21 60 Green et al. (2013)** RFL versus BL 30 7 67 8 82 Gupta (2003)** RFL versus BL 30 100 100 100 Cupta (2003)** RFL versus BRC 100 100 100 Cupta (2003)** RFL versus RFL/SL-M 80 80 Gupta et al. (2004)** SL M versus RFC/SL-M 80 80 Gupta et al. (2003)** SH versus RFL 50 50 Hatton et al. (2004)** SH versus CRY 53 246 48 Hetzer et al. (2004)** SH versus CRY 53 246 80 Jampanah and and (2005)** HV versus CRY 53 246 848 848 Jampanah and and (2005)** HV versus CRY 53 246 848 848 Jampanah and and (2005)** HV versus CRY 53 246 819 Jampanah and and (2005)**<	Elshazly et al. (2015) ³⁷	MM versus SL-M		138	62	200	
Filingeri et al. (2013) ⁶⁶ REL versus CHR 90 90 Cagloo et al. (2013) ⁶⁶ REL versus MM 62 38 100 Carlel et al. (1985) ¹⁶ REL versus IJS 67 111 40 218 Cianundo et al. (2011) ¹⁶ DC-HAL versus RBL 39 21 60 Carea et al. (1981) ¹⁶⁴ REL versus IJS 7 67 8 82 Capta (2003) ¹⁶⁴ REL versus IRC 100 100 100 Gupta (2004) ¹⁶⁴ REL versus IRC 100 100 100 Gupta et al. (2004) ¹⁶⁴ RE- versus BC-HAL 48 48 Hetzer et al. (2007) ¹⁶⁴ SL- M versus RC/SL-M 50 50 Juaga et al. (2011) ¹⁶⁷ DC- V versus BC 50 50 Infantino et al. (2012) ¹⁷³ SH versus DC-HAL 16 16 Japanah and Hosseini (2005) ¹⁶⁴ Hersus DC-HAL 16 16 Japanah and Indeseini (2005) ¹⁶⁴ REL versus IJS versus CRY 63 246 99 Jamicom and Jamal (1991) ¹⁷⁹ BEL versus IJS versus CRY 63 249 81 Juada hana (12013) ¹⁷⁴	Filgate et al. (2019) ³⁸	HET versus RBL		30		30	
Filingeri et al. (2013) ⁴⁺ RFC versus CHR 30 30 Garbe et al. (2013) ⁴⁺ REL versus IJS 67 111 40 218 Giamundo et al. (2011) ⁴⁺ REL versus IJS 7 67 8 82 Greea et al. (1981) ⁴⁺ REL versus ISC 7 67 8 82 Gupta (2003) ⁴⁺ REL versus IRC 100 100 100 Gupta (2003) ⁴⁺ REL versus IRC/SLM 100 80 80 Gupta (2003) ⁴⁺ REL versus IRC/SLM 128 128 44 48 Heitzer et al. (2004) ⁴⁺ REL versus IRC 12 28 40 Hinton et al. (2003) ⁴⁺ SE versus IRC 50 50 50 Huang et al. (2004) ²⁺ SE versus IRC 56 56 56 56 Infantito et al. (2004) ²⁺ SE versus IRC 63 246 94 848 Jenson and Hoaseini (2005) ⁴⁺ FH versus IS versus CKY 63 246 848 848 Jenson and Jamal (1991) ²⁺ RE versus IS versus REC 51 50 50 50 50 50	Filingeri et al. (2012) ³⁹	RBL versus CHR		90		90	
Gagioo et al. (2013)** RBL versus MM 62 38 100 Garnell et al. (1985)** RBL versus JDS 67 111 40 218 Granul et al. (2013)** DG-HAL versus RBL 39 21 60 Gree at cl. (1985)** RBL versus MM n.r. 60 100 100 Gupta (2003)** REC versus MM 100 100 100 Gupta (2004)** RE-Wersus RBL 80 80 Gupta et al. (2007)** SE-Wersus PC-SLAM 12 28 40 Hinton et al. (2007)** SE-Wersus PC 50 50 50 Infantino et al. (2007)** SE-Wersus PC 63 246 99 408 Jampoom and Jamal (1991)** REL versus JD-SHAL 16 29 481 Jutabha et al. (2007)** SE-Wersus PC 63 246 99 408 Jampoom and Jamal (1991)** REL versus JD-SHAL 16 29 451 Varialyouna et al. (2007)** REL versus JD-SHAL 60 60 <	Filingeri et al. (2013) ⁴⁰	RFC versus CHR		30		30	
Cartell et al. (1985) RBL persus IJS 67 111 40 218 Ciamundo et al. (2011) ⁻¹⁻ DCI-HAL versus RBL 39 21 60 Green et al. (1981) ⁻¹⁻ RBL versus IJS 7 67 8 82 Cupta (2003) ⁻¹⁻ RBL versus IRC 100 100 100 Cupta (2004) ⁻¹⁻ REL versus REL 80 80 80 Cupta (2004) ⁻¹⁻ SL-M versus DCI-HAL 48 48 Hetzer et al. (2002) ⁻⁰⁻ SH versus DCI-HAL 12 28 40 Hinton et al. (1990) ⁻¹⁻ DCV versus BPC 50 50 Huang et al. (2007) ⁻² SH versus DC-HAL 169 169 Izadpanah and Hosseini (2005) ⁻⁴ FH versus DCV 63 246 99 Izadpanah and Hosseini (2005) ⁻⁴ FH versus DC-HAL 169 169 Izadpanah and Hosseini (2005) ⁻⁴ FH versus DC-HAL 60 60 Kainaluoma et al. (2003) ⁻⁵ RPC versus HET 32 49 81 Juatab et al. (2003) ⁻⁵ RPC versus	Gagloo et al. (2013) ⁴¹	RBL versus MM		62	38	100	
Grammund et al. (2011)** DC-HAL versus RBL 39 21 60 Greea et al. (2003)** RFC versus MM nr. nr. Gupta (2003)** RFC versus RBL 100 100 Gupta (2004)** RFC versus RBL 80 80 Gupta et al. (2001)** SL-M versus RFC/SL-M 128 128 Gupta et al. (2001)** SL-M versus RFC/SL-M 48 48 Herzer et al. (2002)** SL-W versus FFH 12 28 40 Hinton et al. (1990)*1 DCV versus PFC 50 50 50 Inadpanah and Hosseini (2005)** FH versus DC-HAL 169 169 169 Jamjoom and Jarmal (1991)** REL versus IDS versus CRY 848 848 94 81 Jutabha et al. (2003)** RH versus DC-WC 63 246 99 408 Jamjoom and Jarmal (1997)** REL versus IDS versus REL 32 49 81 Jutabha et al. (2003)** RH versus BCC 16 29 45 Karaellos et al. (2003)** RH versus BC	Gartell et al. $(1985)^{42}$	RBL versus IJS	67	111	40	218	
Careca et al. $(1981)^{-1}$ REL Dersus INS / 6/ 8 8/2 Gupta (2003) ⁶⁶ REL versus IRC 100 100 100 Gupta (2004) ⁶⁷ REL versus REL 80 80 Gupta (2004) ⁶⁷ SL-M versus DC-HAL 48 48 Hetzer et al. (2007) ⁶⁰ SH versus DC-HAL 12 28 40 Hinton et al. (2007) ⁶⁰ SH versus DC-HAL 169 169 169 Ipanjoom and Jamal (1990) ⁶¹ DCV versus FPC 50 50 Izadpanah and Hosseini (2005) ⁶⁴ FH versus DC-HAL 169 169 Izadpanah and Hosseini (2005) ⁶⁴ FH versus DC-HAL 16 29 45 Izadpanah and Hosseini (2005) ⁶⁴ FH versus DC-FAL 63 246 99 48 Junabha et al. (2003) ⁶⁵ REL versus IDS versus CRY 64 60 6	Giamundo et al. (2011) ⁴³	DG-HAL versus RBL	_	39	21	60	
Gupta (2002) H-U UPSUS MM 1.0 100 Gupta (2004) ¹⁰ RFU cresus RL 80 80 Gupta et al. (2001) ¹⁰ SL-M versus RL/SL-M 48 48 Hetzer et al. (2002) ¹⁰ SL-M versus DC-HAL 48 48 Hinton et al. (2002) ¹⁰ SL-M versus DC-HAL 48 48 Hetzer et al. (2002) ¹⁰ SL-M versus DC-HAL 169 169 Lanag et al. (2005) ¹² SL versus DC-HAL 169 169 Izadpanah and Hosseini (2005) ¹⁴ FL versus DC-HAL 169 169 Jamjoorn and Jamal (1997) ¹⁵ RB. versus DC-V 63 246 99 48 Jutabha et al. (2003) ¹⁵ RB. versus DC-V 63 246 99 48 Jutabha et al. (2003) ¹⁵ RB. versus BC 16 29 45 Karalutoma et al. (2003) ¹⁵ RB. versus MM 00 40 Khan and Malki (2006) ¹⁰ FL versus SH 100 100 Khan and Malki (2006) ¹⁰ FL versus SH 13 122 122 Lu et al. (2003) ¹⁴ MM versus MAD versus RLUS 66 66 112 </td <td>$Greca et al. (1981)^{11}$</td> <td>RBL versus IJS</td> <td>/</td> <td>6/</td> <td>8</td> <td>82</td>	$Greca et al. (1981)^{11}$	RBL versus IJS	/	6/	8	82	
Gupta (2004) RED UPSUS RAC. 100 100 100 Gupta (2004) RED UPSUS RAC. 128 128 208 Gupta et al. (2004) SL-M versus REC/SL-M 48 48 Hetzer et al. (2002) SH versus FH 12 28 40 Intron et al. (1990) SH versus FDC-HAL 50 50 Huang et al. (2007) SH versus DC-HAL 506 596 Izadpanah and Hosseini (2005) SH versus DC-HAL 169 169 Izadpanah and Hosseini (2005) RE Uversus Usersus CRY 848 848 Jennicom and Jianal (1991) REU versus Usersus CRY 844 848 Jentable et al. (2003) REU versus WM 60 60 Kanellos et al. (2003) REU versus WM 60 60 Kanal et al. (2004) MM versus HarS 15 15 30 Khan and Malki (2006) HW versus SH 100 100 100 Khan and Malki (2006) SH versus MA 122 122 122 122 122 122	Gupta (2003) ¹⁰	RFC versus MM		100		n.r.	
Gupta et al. (2009)** NFU UPSUS RD 80 80 80 80 Gupta et al. (2001)** SL-M UPSUS RPC/SL-M 128 128 Gupta et al. (2002)** SL-M UPSUS RPC/SL-MAL 48 48 Hinton et al. (2002)** SL-M UPSUS RPC 50 50 Inhang et al. (2007)** SH VPSUS DC-HAL 169 169 Izadpanah and Hosseini (2005)** SH VPSUS DC-HAL 169 169 Izadpanah and Hosseini (2005)** SH VPSUS DC-HAL 169 169 Izadpanah and Hosseini (2005)** REU VPSUS DC-HAL 160 60 Kairaluoma et al. (2003)** REU VPSUS BPC 16 29 451 Kairaluoma et al. (2003)** REU VPSUS BPC 16 29 451 Khair et al. (2003)** SH vPSUS BPC 16 29 451 Khair et al. (2003)** SH vPSUS BPC 16 29 451 Khair et al. (2004)** MM vPSUS BPC 51 15 30 Khair et al. (2001)** HE vPSUS BPC 51 15 30	Gupta $(2003)^{47}$	RBL VERSUS IRC		100		100	
Chyper Let II. (2009) Der Mersus RPC SHAL 128 126 Gupta et al. (2001) SH versus DG-HAL 48 48 Hetzer et al. (2002) SH versus DG-HAL 50 50 Huang et al. (2007) SH versus DG-HAL 169 169 Infantino et al. (2012) SH versus DG-HAL 169 169 Izadpanah and Hosseini (2005) SH versus DG-HAL 169 48 Jamjoom and Jamal (1991) BE versus SU Sversus CRY 848 848 Varialuoma et al. (2003) REL versus SU Sversus RE-IJS 249 81 Varialuoma et al. (2003) REL versus SU Sversus RE-IJS 243 243 Khan et al. (2003) REL versus SH 40 40 Khan et al. (2004) MW versus SH 15 15 30 Khan et al. (2004) MM versus SH 102 102 102 Lau et al. (2004) SH versus GH 13 122 222 Lau et al. (2004) MM versus SH 100 100 Lew et al. (2004) MM versus SH 100	Gupta (2004) Gupta et al. $(2000)^{48}$	RFC VEISUS RBL		80	100	80 100	
Opper tail (2017)* Derive Period *** **	Gupta et al. (2009)	SL-M VERSUS REC/SL-M			120	120	
Interfact full (200) ¹⁴ Driversus BPC 50 50 Huang et al. (2007) ¹⁶³ SH versus BPC 50 50 Infantine et al. (2012) ¹³ SH versus DC-HAL 169 169 Izadpanah and Hosseini (2005) ⁵⁴ FH versus DC-V 63 246 99 408 Jamjoorn and Jamal (1991) ⁵⁵ REL versus HET 32 49 81 Jutabha et al. (2009) ⁵⁷ REL versus HET 32 49 81 Jutabha et al. (2003) ⁵⁶ SH versus BEC 16 29 45 Kairaluoma et al. (2003) ⁵⁶ SH versus BEC 15 15 020 Khan et al. (2000) ⁶⁷ REL versus BEC 51 51 102 Khan et al. (2001) ⁶¹ MM versus SH 13 122 225 Lau et al. (2000) ⁶⁴ DG-HAL versus SH 13 122 225 Lau et al. (2014) ⁶⁵ DG-HAL versus SH 13 122 225 Leavit al. (2016) ⁶⁶ DG-HAL versus SH 91 300 393 Leun et al. (2016) ⁶⁶ DG-HAL versus SH 91 302 393 Leun et al. (2016) ⁶	Hetzer et al. $(2002)^{50}$	SH upreus FH		12	28	40	
	Hinton et al. $(1990)^{51}$	DCV uersus BPC		12	50	50	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Huang et al. $(2007)^{52}$	SH uersus FH			596	596	
Izadpanah and Hoseini (2005)*4 FH versus DCV 63 246 99 408 Jamjoon and Jamal (1991)*5 RBL versus CRY 848 848 848 Jamjoon and Jamal (1991)*5 RBL versus HET 32 49 811 Jutabha et al. (2003)*5 RBL versus BPC 16 29 455 Karaluona et al. (2003)*5 RBL versus IN 60 60 Kanellos et al. (2003)*5 RBL versus IN 243 243 Khan et al. (2000)*6 FH versus SH 40 40 Khan et al. (2001)*1 MM versus HarS 15 15 30 Khan et al. (2006)*2 JS versus BPC 51 51 100 100 Leur et al. (2004)*4 MM versus SH 13 12 25 Leur et al. (2016)*5 DG-HAL versus SH 100 100 100 Lewis et al. (193)*6 MM versus ABL versus CRY 46 66 112 Leur et al. (2016)*6 DG-HAL versus SR 91 302 393 Leur et al. (2017)*7 TST versus DG-HAL 40 40 40 40 Varge et	Infantino et al. $(2012)^{53}$	SH versus DG-HAL			169	169	
$\begin{array}{llllllllllllllllllllllllllllllllllll$	Izadpanah and Hosseini (2005) ⁵⁴	FH versus DCV	63	246	99	408	
	Jamjoom and Jamal (1991) ⁵⁵	RBL versus IJS versus CRY		848		848	
Jutabhe at l_{2009}^{57} RBL versus BPC 16 29 45 Kairaluoma et al. (2003) ⁵⁸ SH versus MM 60 60 Kanellos et al. (2003) ⁵⁹ RBL versus IJS versus RBL-IJS 243 243 Khan et al. (2001) ⁶¹ MM versus HarS 15 15 30 Khan et al. (2001) ⁶¹ MM versus BRC 51 51 30 Kim et al. (2014) ⁶¹ MM versus SH 122 122 Lau et al. (2004) ⁶⁴ MM versus SH 13 12 25 Leard et al. (2016) ⁶⁵ DG-HAL versus SH 100 100 Lehur et al. (2016) ⁶⁶ DG-HAL versus RH 40 40 80 Lewis et al. (1983) ⁶⁸ MM versus NAD versus RL versus CRY 46 66 112 Liu et al. (2016) ⁶⁶ NBL versus RL Versus CRY 46 66 112 110 100 Mure et al. (2005) ⁷⁰ RBL versus RBL versus CRY 46 48 94 94 Mikuni et al. (2007) ⁷⁴ MM versus SOH 23 27 50 Naderan et al. (2007) ⁷⁴ MM versus SBL 44 43 87 <td>Jensen et al. (1997)⁵⁶</td> <td>BPC versus HET</td> <td></td> <td>32</td> <td>49</td> <td>81</td>	Jensen et al. (1997) ⁵⁶	BPC versus HET		32	49	81	
Kairaluoma et al. (2003) ⁵⁸ SH versus MM 60 60 60 Kanellos et al. (2003) ⁵⁹ RBL versus IS versus RBL-IJS 243 243 Khali et al. (2000) ⁶⁰ FH versus SH 40 40 Khan and Malik (2006) ⁶² IJS versus PC 51 51 30 Kim et al. (2014) ⁶⁴ MM versus SH 13 122 122 Lau et al. (2016) ⁶⁵ DG-HAL versus SH 100 100 Leard et al. (2016) ⁶⁶ DG-HAL versus SH 91 302 393 Leurg et al. (2017) ⁶⁷ TST versus DG-HAL 40 40 80 Versus ABD versus MBL-US 160 140 300 303 Lewis et al. (2017) ⁶⁷ TST versus DG-HAL 44 43 87 Marques et al. (2006) ⁷⁰ RBL versus RBL-US 160 140 300 Marques et al. (2002) ⁷¹ MM versus SOH 34 34 Murie et al. (2017) ⁷² FH versus RBL 44 43 87 Naderan et al. (2017) ⁷⁴ RBL versus IS 42 44 86 Nikoni et al. (2017) ⁷⁴ RBL versus RBL	Jutabha et al. (2009) ⁵⁷	RBL versus BPC		16	29	45	
Kanellos et al. (2003) ⁵⁰ RBL versus RBL-UJS 243 243 243 Khalil et al. (2000) ⁶⁰ FH versus SH 40 40 Khan et al. (2001) ⁵¹ MM versus HarS 15 15 30 Khan et al. (2001) ⁶¹ JJS versus BPC 51 51 102 122 122 Lau et al. (2004) ⁶⁴ MM versus SH 13 12 25 160 100 <td>Kairaluoma et al. (2003)⁵⁸</td> <td>SH versus MM</td> <td></td> <td></td> <td>60</td> <td>60</td>	Kairaluoma et al. (2003) ⁵⁸	SH versus MM			60	60	
Khall et al. (2000) ⁶⁰ FH versus SH 40 40 Khan et al. (2001) ⁶¹ MM versus HarS 15 15 30 Khan and Malik (2006) ⁶² IJS versus BPC 51 51 102 124 et al. (2016) ⁶⁵ DG-HAL versus SH 100 122 121 10	Kanellos et al. (2003) ⁵⁹	RBL versus IJS versus RBL-IJS		243		243	
Khan and Malk (2006)62 JS versus BArS 15 15 30 Kin and Malk (2006)62 JS versus BPC 51 51 102 Lau et al. (2014)63 SH versus MM 12 222 Leardi et al. (2016)65 DG-HAL versus SH 13 12 25 Leardi et al. (2016)66 DG-HAL versus SH 91 302 393 Leung et al. (2016)66 DG-HAL versus SH 91 302 393 Leung et al. (2017)67 TST versus DG-HAL 40 40 80 Lewis et al. (2019)67 REL versus RBL-US 160 140 300 Mary et al. (2005)70 REL versus REL-JJS 160 140 300 Mary et al. (2005)71 REL versus REL 46 48 94 Mikuni et al. (2002)74 MM versus SOH 34 34 Naderan et al. (2017)73 LASER versus IR 41 43 87 Naderan et al. (2017)74 RBL versus ISS 42 44 86 Nyström et al. (2017)75 DCV versus FH n.r. n.r. n.r. Niksoiyan et al. (2016)75 DCV versus IS	Khalil et al. (2000) ⁶⁰	FH versus SH			40	40	
Khan and Malik (2006) ⁶² JJS versus BPC 51 51 102 Kim et al. (2014) ⁶³ SH versus MM 122 122 Lau et al. (2016) ⁶⁵ DG-HAL versus SH 13 12 25 Lear di (2016) ⁶⁶ DG-HAL versus SH 91 302 393 Leung et al. (2016) ⁶⁶ DG-HAL versus SH 91 302 393 Leung et al. (2017) ⁶⁷ TST versus DC-HAL 40 40 40 Leung et al. (2020) ⁶⁹ RBL versus RBL-UJS 160 140 300 Marques et al. (2002) ⁷⁰ RBL versus RBL 46 48 94 Mikuni et al. (2002) ⁷¹ MM versus SOH 34 34 Murie et al. (2017) ⁷³ LASER versus IMS 23 27 50 Nasir et al. (2017) ⁷⁴ RBL versus IJS 42 44 86 Nikoojan et al. (2016) ⁷⁵ DCV versus FH n.r. n.r. n.r. Nikshoar et al. (2016) ⁷⁶ IRC versus FH 40 40 40 Poen et al. (2001) ⁹ RBL versus REL 26 64 90 90 Poen et al. (2000)	Khan et al. (2001) ⁶¹	MM versus HarS		15	15	30	
Kim et al. $(2014)^{6^2}$ SH versus MM122122122Lau et al. $(2004)^{6^4}$ MM versus SH131225Leardi et al. $(2016)^{6^5}$ DG-HAL versus SH91302393Leung et al. $(2017)^{6^7}$ TST versus DG-HAL404080Lewis et al. $(1983)^{6^8}$ MM versus MAD versus RBL versus CRY4666112Liu et al. $(2017)^{6^7}$ RBL versus RBL-IJS160140300Marques et al. $(2006)^{70}$ RBL versus RBL464894Mikuni et al. $(2002)^{1}$ MM versus SOH3434Murie et al. $(2002)^{1}$ HN versus SOH3434Naderan et al. $(2017)^{73}$ LASER versus MM2327Nasir et al. $(2017)^{74}$ RBL versus IJS424486Nikshoar et al. $(2017)^{74}$ RBL versus IJS424486Nikshoar et al. $(2017)^{74}$ RBL versus FHn.r.n.r.Nikshoar et al. $(2017)^{74}$ RBL versus FH4040Vpström et al. $(2017)^{76}$ IS versus FH178178Parveen et al. $(2017)^{76}$ RBL versus RL266490Poen et al. $(2007)^{79}$ RBL versus RL266490Poen et al. $(2007)^{79}$ RBL versus RH2794121Quah and Seow-Choen $(2004)^{81}$ MM versus RBL1230648Rowsell et al. $(2007)^{84}$ FH versus SH1230648Rowsell et al. $(200$	Khan and Malik (2006) ⁶²	IJS versus BPC	51	51		102	
Lau et al. $(2004)^{1^{-1}}$ MM versus SH131225Leardi et al. $(2016)^{66}$ DG-HAL versus SH100100Lehur et al. $(2016)^{66}$ DG-HAL versus SH91302393Leung et al. $(2017)^{67}$ TST versus DG-HAL404080Lewis et al. $(1983)^{68}$ MM versus MAD versus RBL versus CRY4666112Liu et al. $(2012)^{16^{50}}$ RBL versus RBL-JIS160140300Marques et al. $(2006)^{170}$ RBL versus RBL-JIS160140300Murie et al. $(2020)^{12}$ MM versus SOH3434Nurie et al. $(2020)^{12}$ HV versus RBL444387Naderan et al. $(2017)^{12}$ LASER versus MM232750Nair et al. $(2017)^{12}$ LASER versus SH424486Nikooiyan et al. $(2017)^{12}$ CV versus FHn.r.n.r.Nikooiyan et al. $(2016)^{15}$ DCV versus FH178178Parveen et al. $(2019)^{16}$ IJS versus RBL266490Poen et al. $(2001)^{17}$ SH versus SL-M2794121Quah and Seow-Choen $(2004)^{81}$ MM versus SC-M2794121Quah and Seow-Choen $(2004)^{81}$ MM versus RBL1230648Rowsell et al. $(2007)^{95}$ BL versus RBL1230648Rowsell et al. $(2007)^{85}$ MM versus RBL266490Schuurman et al. $(2019)^{85}$ ICV versus RBL23	Kim et al. (2014)	SH versus MM		10	122	122	
Leard et al. (2016)DG-HAL versus SH100100Lehur et al. (2017)DG-HAL versus SH91302393Leung et al. (2017)TST versus DG-HAL404080Lewis et al. (2019)RBL versus SAD versus RBL versus CRY4666112Liu et al. (2019)RBL versus RBL-IJS160140300Marques et al. (2006)RBL versus RBL464894Mikuni et al. (2002)MM versus SOH3434Murie et al. (2017)MM versus SOH2327Nasir et al. (2017)LASER versus MM2327Nasir et al. (2017)RBL versus IJS4244Nikobora et al. (2016)ICC versus FHn.r.Nikshoar et al. (2016)ICC versus FH4040Nyström et al. (2019)ISC versus FH99359Parveen et al. (2020)RBL versus IRC89359Poen et al. (2020)LASER versus FH versus SL-M2794121Quah and Seow-Choen (2004)IRC versus BPC305888Ricci et al. (2008)IRC versus BPC305888Ricci et al. (2008)IRC versus RBL1230648Rowsell et al. (2001)St-M versus SBL6080140Schuurman et al. (2019)St-M versus BPC305888Schuurman et al. (2019)St-M versus BL6080140Schuurman et al. (2019)St-M versus CHAL3637 </td <td>Lau et al. (2004)⁶¹</td> <td>MM versus SH</td> <td></td> <td>13</td> <td>12</td> <td>25</td>	Lau et al. (2004) ⁶¹	MM versus SH		13	12	25	
Lenur et al. (2016)DC-HAL Versus SH91302393Leung et al. (2017)TST versus DG-HAL404080Lewis et al. (2019)REL versus MAD versus RBL versus CRY4666112Liu et al. (2019)REL versus RBL-IJS160140300Marques et al. (2006)REL versus RBL-IJS160140300Mikuni et al. (2002)MM versus SOH3434Murie et al. (2017)MM versus SOH34387Naderan et al. (2017)LASER versus MM232750Nasir et al. (2017)LASER versus MM232750Nikoiyan et al. (2017)LASER versus JS424486Nikoiyan et al. (2018)DCV versus FHn.r.n.r.Nikshoar et al. (2019)IS versus RBL266490Poren et al. (2019)IS versus RL266490Quah and Seow-Choen (2004)LASER versus FH versus SL-M2794121Quah and Seow-Choen (2004)LASER versus FH versus SL-M2794121Quah and Seow-Choen (2004)LASER versus RBL12305888Ricci et al. (2003)RC versus RBL1230648Rowsell et al. (2004)Hversus RBL266490Schuurman et al. (2017)SL versus RBL12305888Ricci et al. (2004)MM versus BPC305888Schuurman et al. (2004)H94 <td< td=""><td>Leardi et al. (2016)</td><td>DG-HAL versus SH</td><td></td><td>01</td><td>100</td><td>100</td></td<>	Leardi et al. (2016)	DG-HAL versus SH		01	100	100	
Lewis et al.(2017)151 VErsus DO-FAL404080Lewis et al.(2028)RBL versus RBL-IJS160140300Marques et al.(2006)RBL versus RBL-IJS160140300Murie et al.(2027)RBL versus RBL464894Mikuni et al.(2027)MM versus SOH3434Naderan et al.(2017)MM versus RBL444387Naderan et al.(2017)LASER versus RBL424486Nikoioyan et al.(2017)DCV versus FHn.r.n.r.Nikshoar et al.(2018)FK versus SMM232750Nasir et al.(2017)DCV versus FHn.r.n.f.Nikshoar et al.(2018)FK versus SMM178178Parveen et al.(2019)SH versus RBL266490Poen et al.(2000)LASER versus FH versus SL-M2794121Quah and Seow-Choen(2004)MW versus BPCn.r.n.r.Randall et al.(2004)GO888888Ric et al.(2000)SL-W versus SH2222Saeed et al.(2000)GO863773Senagore et al.(2001)SL-W versus SH8686Senagore et al.(2004)SL-W versus FH146146Schuurman et al.(2001)SL-W versus FH146146Schuurman et al.(2004)SL-W versus SH	Lenur et al. $(2016)^{-7}$	DG-HAL VERSUS SH		91	302	393	
Lewis et al. (2019)Initial versus BAL versus SEL versus CK14000112Marques et al. (2006)RBL versus RIC464894Mikuni et al. (2002)MM versus SOH3434Murie et al. (1980)Yersus RBL444387Naderan et al. (2017)LASER versus MM232750Nasir et al. (2017)LASER versus MM232750Nasir et al. (2017)RBL versus IJS424486Nikooiyan et al. (2016)IRC versus FH4040Nyström et al. (2019)IRC versus FH4040Nyström et al. (2019)IJS versus RBL266490Poen et al. (2010)IJS versus RBL266490Poen et al. (2000)LASER versus FH versus SL-M2794121Quah and Seow-Choen (2004)IRC versus BPCn.r.n.r.Randall et al. (2009)ERC versus RBL12305888Ricci et al. (2001)FH versus SH222222Saeed et al. (2001)MM versus BPC363773Senagore et al. (2001)SL-M versus DG-HAL363773Senagore et al. (2017)SL-M versus BL6080140Schuurman et al. (2019)MM versus SG-M8686Senagore et al. (2004)Sh versus FH145146Schuurman et al. (2019)MM versus ABL363773Senagore et al. (2004)Sh versus FH1	Letting et al. (2017)	151 VEISUS DG-FIAL		40	40	00 110	
Interat.Into tersus RDL-105Into100100100100100Marques et al. (2006)RBL versus RDC464894Mikuni et al. (1980)MM versus SOH3434Murie et al. (1980)FH versus RBL444387Naderan et al. (2017)LASER versus MM232750Nasir et al. (2017)RBL versus IJS424486Nikooiyan et al. (2016)DCV versus FHn.r.n.r.Nikshoar et al. (2018)IRC versus FH4040Nyström et al. (2019)SH versus RDL266490Poen et al. (2000)IJS versus RBL266490Poskus et al. (2020)LASER versus FH versus SL-M2794121Quah and Seow-Choen (2004)MM versus BPCn.r.n.r.n.r.Randall et al. (1994)DCV versus BPC305888Ricci et al. (2000)FH versus RBL1230648Rowsell et al. (2001)FH versus SH222222Schuurman et al. (2012)MM versus BPC222222Schuurman et al. (2013)MM versus RBL6080140Schuurman et al. (2013)SL-M versus RBL363773Senagore et al. (2004)Sh versus FH464646Senagore et al. (2004)SH versus FH464648Senagore et al. (2004)SH versus SH542680 <td>Lewis et al. $(2010)^{69}$</td> <td>PRI HORENE PRI IIS</td> <td></td> <td>40</td> <td>140</td> <td>300</td>	Lewis et al. $(2010)^{69}$	PRI HORENE PRI IIS		40	140	300	
Marques et al. (2002) ¹¹ MD versus SOH3434Murie et al. (1980) ⁷² FH versus RBL444387Naderan et al. (2017) ⁷³ LASER versus MM232750Nasir et al. (2017) ⁷⁴ RBL versus IJS424486Nikooiyan et al. (2016) ⁷⁵ DCV versus FHn.r.n.r.Nikshoar et al. (2016) ⁷⁶ IRC versus FH4040Nyström et al. (2019) ⁷⁸ JJS versus RBL266490Poen et al. (2010) ⁷⁷ SH versus RBL266490Poen et al. (2000) ⁷⁹ RBL versus IRC89359133Poskus et al. (2020) ⁸⁰ LASER versus FH versus SL-M2794121Quah and Seow-Choen (2004) ⁸¹ MM versus BPCn.r.n.r.Randall et al. (1994) ⁸² DCV versus RBL1230648Rowsell et al. (2000) ⁸⁴ FH versus RBL1230648Rowsell et al. (2017) ⁸⁵ MM versus RBL222222Saeed et al. (2017) ⁸⁵ MM versus RBL6080140Schuurman et al. (2012) ⁸⁶ SL-M versus RBL363773Senagore et al. (2004) ⁸⁸ SH versus RBL363773Senagore et al. (2004) ⁸⁸ SH versus SH146146Schuarpar et al. (2004) ⁸⁸ SH versus SH146146	Margues <i>et al.</i> $(2006)^{70}$	RBL margue IRC	46	48	140	94	
Initial citerInitial citerInitial citerInitial citerInitial citerMurie et al. $(2017)^{73}$ LASER versus MM232750Nasir et al. $(2017)^{74}$ RBL versus IJS424486Nikooiyan et al. $(2016)^{75}$ DCV versus FHn.r.Nikshoar et al. $(2016)^{76}$ IRC versus FH4040Nyström et al. $(2010)^{78}$ IJS versus RBL266490Parveen et al. $(2000)^{79}$ RBL versus IRC89359133Poskus et al. $(2020)^{80}$ LASER versus FH versus SL-M2794121Quah and Seow-Choen $(2004)^{81}$ MM versus BPCn.r.n.r.Randall et al. $(1994)^{82}$ DCV versus RBL1230648Ricci et al. $(2000)^{84}$ FH versus SH222222Saeed et al. $(2017)^{85}$ MM versus RBL6080140Schuurman et al. $(2017)^{85}$ SL-M versus DG-HAL363773Senagore et al. $(2004)^{86}$ SH versus FH146146Shuaran et al. $(2017)^{85}$ MM versus RBL168686Senagore et al. $(2004)^{88}$ SH versus FH146140Shuaran et al. $(2004)^{88}$ SH versus FH146146Shuaran et al. $(2004)^{88}$ SH versus FH146146Shuaran et al. $(2004)^{88}$ SH versus FH146146Shuaran et al. $(2004)^{89}$ SH versus FH146146	Marques et al. $(2002)^{71}$	MM versus SOH	10	10	34	34	
Naderan et al. $(2017)^{73}$ LASER versus MM232750Nasir et al. $(2017)^{74}$ RBL versus IJS424486Nikooiyan et al. $(2016)^{75}$ DCV versus FHn.r.Nikshoar et al. $(2018)^{76}$ IRC versus FH4040Nyström et al. $(2019)^{78}$ IJS versus RM178178Parveen et al. $(2019)^{78}$ IJS versus RBL266490Poen et al. $(2020)^{80}$ IASER versus FH versus SL-M2794121Quah and Seow-Choen $(2004)^{81}$ MM versus BPC305888Ricci et al. $(2000)^{84}$ IRC versus RBL1230648Rowsell et al. $(2017)^{85}$ DCV versus RBL1230648Rowsell et al. $(2001)^{86}$ SL-M versus SD-HAL363773Senagore et al. $(2001)^{86}$ SL-M versus DG-HAL363773Senagore et al. $(2004)^{88}$ SH versus FH146146Schuurman et al. $(2004)^{88}$ SH versus FH146146Shabahang et al. $(2004)^{88}$ SH versus LASER542680	Murie et al. $(1980)^{72}$	FH versus RBL		44	43	87	
Nasir et al. $(2017)^{74}$ RBL versus IJS424486Nikooiyan et al. $(2016)^{75}$ DCV versus FHn.r.Nikshoar et al. $(2018)^{76}$ IRC versus FH4040Nyström et al. $(2010)^{77}$ SH versus MM178178Parveen et al. $(2019)^{78}$ IJS versus RBL266490Poen et al. $(2000)^{79}$ RBL versus IRC89359133Poskus et al. $(2020)^{80}$ LASER versus FH versus SL-M2794121Quah and Seow-Choen $(2004)^{81}$ MM versus BPCn.r.n.r.n.r.Randall et al. $(1994)^{82}$ DCV versus RBL12305888Ricci et al. $(2000)^{84}$ FH versus SH222222Saeed et al. $(2017)^{85}$ MM versus RBL6080140Schuurman et al. $(2012)^{86}$ SL-M versus RM868686Senagore et al. $(2004)^{83}$ SH versus FH146146146Senagore et al. $(2004)^{86}$ SH versus FH146146146	Naderan et al. $(2017)^{73}$	LASER versus MM		23	27	50	
Nikooiyan et al. $(2016)^{75}$ DCV versus FHn.r.Nikshoar et al. $(2018)^{76}$ IRC versus FH4040Nyström et al. $(2010)^{77}$ SH versus MM178178Parveen et al. $(2000)^{79}$ RBL versus RBL266490Poen et al. $(2000)^{79}$ RBL versus IRC89359133Poskus et al. $(2020)^{80}$ LASER versus FH versus SL-M2794121Quah and Seow-Choen $(2004)^{81}$ MM versus BPC305888Ricci et al. $(2008)^{83}$ IRC versus RBL1230648Rowsell et al. $(2000)^{84}$ FH versus SH222222Saeed et al. $(2017)^{85}$ MM versus RBL6080140Schuurman et al. $(2012)^{86}$ SL-M versus MM868686Senagore et al. $(2004)^{83}$ SH versus FH146146Senagore et al. $(2004)^{88}$ SH versus FH146146Shabahang et al $(2004)^{89}$ MM versus LASER542680	Nasir et al. (2017) ⁷⁴	RBL versus IJS		42	44	86	
Nikshoar et al. $(2018)^{36}$ IRC versus FH4040Nyström et al. $(2010)^{77}$ SH versus MM178178Parveen et al. $(2019)^{78}$ IJS versus RBL266490Poen et al. $(2000)^{79}$ RBL versus IRC89359133Poskus et al. $(2020)^{80}$ LASER versus SL-M2794121Quah and Seow-Choen $(2004)^{81}$ MM versus BPCn.r.n.r.Randall et al. $(1994)^{82}$ DCV versus BPC305888Ricci et al. $(2000)^{84}$ FH versus SH2222Saeed et al. $(2017)^{85}$ MM versus RBL1230648Rowsell et al. $(2017)^{85}$ MM versus RBL6080140Schuurman et al. $(2012)^{86}$ SL-M versus GH-HAL363773Senagore et al. $(2004)^{83}$ SH versus FH146146Senagore et al. $(2019)^{89}$ MM versus LASER542680	Nikooiyan et al. (2016) ⁷⁵	DCV versus FH				n.r.	
Nyström et al. $(2010)^{77}$ SH versus MM178178Parveen et al. $(2019)^{78}$ IJS versus RBL266490Poen et al. $(2000)^{79}$ RBL versus RBC89359133Poskus et al. $(2020)^{80}$ LASER versus FH versus SL-M2794121Quah and Seow-Choen $(2004)^{81}$ MM versus BPCn.r.n.r.Randall et al. $(1994)^{82}$ DCV versus RPC305888Ricci et al. $(2000)^{84}$ IRC versus RBL1230648Rowsell et al. $(2000)^{84}$ FH versus SH2222Saeed et al. $(2017)^{85}$ MM versus RBL6080140Schuurman et al. $(2012)^{86}$ SL-M versus MM8686Senagore et al. $(2004)^{83}$ SH versus FH146146Shabahang et al. $(2019)^{89}$ MM versus LASER542680	Nikshoar et al. $(2018)^{76}$	IRC versus FH			40	40	
Parveen et al. $(2019)^{78}$ IJS versus RBL 26 64 90 Poen et al. $(2020)^{79}$ RBL versus RBC 89 35 9 133 Poskus et al. $(2020)^{80}$ LASER versus FL versus SL-M 27 94 121 Quah and Seow-Choen $(2004)^{81}$ MM versus BPC n.r. n.r. Randall et al. $(1994)^{82}$ DCV versus BPC 30 58 88 Ricci et al. $(2000)^{84}$ IRC versus RBL 12 30 6 48 Rowsell et al. $(2000)^{84}$ FH versus SH 22 22 22 Saeed et al. $(2017)^{85}$ MM versus RBL 60 80 140 Schuurman et al. $(2012)^{86}$ SL-M versus MM 86 86 Senagore et al. $(2004)^{83}$ SH versus FH 146 146 Senagore et al. $(2004)^{89}$ MM versus LASER 54 26 80	Nyström et al. (2010) ⁷⁷	SH versus MM			178	178	
Poen et al. $(2000)^{79}$ RBL versus IRC89359133Poskus et al. $(2020)^{80}$ LASER versus FH versus SL-M2794121Quah and Seow-Choen $(2004)^{81}$ MM versus BPCn.r.Randall et al. $(1994)^{82}$ DCV versus BPC305888Ricci et al. $(2008)^{83}$ IRC versus RBL1230648Rowsell et al. $(2008)^{84}$ FH versus SH2222Saeed et al. $(2017)^{85}$ MM versus RBL6080140Schuurman et al. $(2012)^{86}$ SL-M versus DC-HAL363773Senagore et al. $(2004)^{88}$ SH versus FH146146Schabapag et al. $(2019)^{89}$ MM versus LASER542680	Parveen et al. (2019) ⁷⁸	IJS versus RBL	26	64		90	
Poskus et al. $(2020)^{80}$ LASER versus FH versus SL-M 27 94 121 Quah and Seow-Choen $(2004)^{81}$ MM versus BPC n.r. Randall et al. $(1994)^{82}$ DCV versus BPC 30 58 88 Ricci et al. $(2008)^{83}$ IRC versus RBL 12 30 6 48 Rowsell et al. $(2008)^{84}$ FH versus SH 22 22 Saeed et al. $(2017)^{85}$ MM versus RBL 60 80 140 Schuurman et al. $(2012)^{86}$ SL-M versus DG-HAL 36 37 73 Senagore et al. $(2004)^{88}$ SH versus FH 146 146 Schabapag et al. $(2004)^{89}$ MM versus LASER 54 26 80	Poen et al. (2000) ⁷⁹	RBL versus IRC	89	35	9	133	
Quah and Seow-Choen (2004)MM versus BPCn.r.Randall et al. (1994)DCV versus BPC305888Ricci et al. (2008)RC versus RBL1230648Rowsell et al. (2008)FH versus SH2222Saeed et al. (2017)MM versus RBL6080140Schuurman et al. (2012)SL-M versus DC-HAL363773Senagore et al. (2004)SL-M versus FH868686Senagore et al. (2004)SH versus FH146146Shabahang et al. (2019)MM versus LASER542680	Poskus et al. (2020) ⁸⁰	LASER versus FH versus SL-M		27	94	121	
Randall et al. $(1994)^{56}$ DCV versus BPC 30 58 88 Ricci et al. $(2008)^{83}$ IRC versus RBL 12 30 6 48 Rowsell et al. $(2000)^{84}$ FH versus SH 22 22 Saeed et al. $(2017)^{85}$ MM versus RBL 60 80 140 Schuurman et al. $(2012)^{86}$ SL-M versus DG-HAL 36 37 73 Senagore et al. $(1993)^{87}$ LASER versus MM 86 86 Senagore et al. $(2004)^{88}$ SH versus FH 146 146 Shabahang et al. $(2019)^{89}$ MM versus LASER 54 26 80	Quah and Seow-Choen (2004) ⁸¹	MM versus BPC				n.r.	
Ricci et al. (2008) ⁵² IRC versus RBL 12 30 6 48 Rowsell et al. (2000) ⁸⁴ FH versus SH 22 22 Saeed et al. (2017) ⁸⁵ MM versus RBL 60 80 140 Schuurman et al. (2012) ⁸⁶ SL-M versus DG-HAL 36 37 73 Senagore et al. (1993) ⁸⁷ LASER versus MM 86 86 Senagore et al. (2004) ⁸⁸ SH versus FH 146 146 Shabahang et al. (2019) ⁸⁹ MM versus LASER 54 26 80	Kandall et al. (1994)° ²	DCV versus BPC		30	58	88	
Kowsell et al. (2000)** FH versus SH 22 22 Saeed et al. (2017) ⁸⁵ MM versus RBL 60 80 140 Schuurman et al. (2012) ⁸⁶ SL-M versus DG-HAL 36 37 73 Senagore et al. (1993) ⁸⁷ LASER versus MM 86 86 Senagore et al. (2004) ⁸⁸ SH versus FH 146 146 Shababang et al. (2019) ⁸⁹ MM versus LASER 54 26 80	K1CC1 et al. $(2008)^{65}$	IKC versus KBL	12	30	6	48	
Saeed et al. $(2017)^{}$ MM versus RBL 60 80 140 Schuurman et al. $(2012)^{86}$ SL-M versus RBL 36 37 73 Senagore et al. $(1993)^{87}$ LASER versus MM 86 86 Senagore et al. $(2004)^{88}$ SH versus FH 146 146 Shababang et al. $(2004)^{89}$ MM versus LASER 54 26 80	Kowsell et al. $(2000)^{34}$	FH versus SH		<i>c</i> o	22	22	
Scnuurman et al. (2012) ⁵⁵ SL-M VERSUS DG-HAL 36 37 73 Senagore et al. (1993) ⁸⁷ LASER versus MM 86 86 Senagore et al. (2004) ⁸⁸ SH versus FH 146 146 Shababang et al. (2019) ⁸⁹ MM versus LASER 54 26 80	Saeed et al. $(201/)^{53}$	MM versus KBL		60	80	140	
Senagore et al. (2004) ⁸⁸ EASER Versus MM 86 86 Shabahang et al. (2019) ⁸⁹ SH versus FH 146 146	Schuurman et al. $(2012)^{33}$	SL-M VERSUS DG-HAL		36	3/	/3	
Senagore et al. (2004) Sin versus Fin 146 146 Shabahang et al. (2019) ⁸⁹ MM versus LASER 54 26 80	Semagore et al. $(1993)^{-1}$	LASEK VEISUS MIM			80 146	80 140	
	Shabababg et al. (2004)	MM uersus LASER		54	26	140 20	

Table 1. (continued)

Reference	Treatments compared	H	Total		
		I	II	III	
Shanmugaiah and Selvam (2020) ⁹⁰	RBL versus IJS		72		72
Shanmugam et al. (2010) ⁹¹	RBL versus SH		60		60
Templeton <i>et al.</i> $(1983)^{92}$	IRC versus RBL	137	82	55	274
Tsunoda et al. $(2017)^{93}$	DG-HAL versus HarS			41	41
Van de Stadt et al. (2005) ⁹⁴	MM versus SH		20	20	40
Varma et al. (1991) ⁹⁵	IJS versus BPC				n.r.
Walker et al. (1990) ⁹⁶	IRC versus IJS	165	87	78	330
Wilson et al. (2002) ⁹⁷	MM versus SH			89	89
Yang et al. (1993) ⁹⁸	DCV versus BPC	25	20	5	50
Zhai et al. (2016) ⁹⁹	SH versus DG-HAL			100	100

RBL, rubber band ligation; IJS, injection sclerotherapy; DG-HAL, Doppler-guided haemorrhoid artery ligation with mucopexy; SL-M, suture ligation with mucopexy; MM, Milligan–Morgan (open) haemorrhoidectomy; IRC, infrared coagulation; SH, stapled haemorrhoidopexy; FH, Ferguson (closed) haemorrhoidectomy; LigaH, LigaSureTM haemorrhoidectomy; MAD, maximal anal dilatation; HarS: Harmonic[®] scalpel haemorrhoidectomy; HET, haemorrhoid energy therapy; CHR, combined haemorrhoidal radiocoagulation; RFC, radiofrequency coagulation; n.r., not reported; DCV, direct current electrotherapy; BPC, bipolar coagulation; CRY, cryotherapy; RBL-JJS, combined rubber band ligation and injection sclerotherapy; TST, tissue-selecting technique; SOH, semi-open haemorrhoidectomy; LASER, laser haemorrhoidectomy.



Fig. 2 Cochrane risk-of-bias 2.0 summary chart

the repeat treatment outcome, the node-splitting analysis revealed inconsistencies in the network that were attributable to direct comparisons between bipolar coagulation (BPC) *versus* infrared coagulation (IRC) and BPC *versus* open haemorrhoidectomy.

Comparison of procedural treatments

The following elective interventions and procedures were identified for the treatment of predominantly grade II and/or III haemorrhoids: open haemorrhoidectomy performed with a scalpel, conventional scissors or diathermy; closed haemorrhoidectomy performed with a scalpel, conventional scissors or diathermy; stapled haemorrhoidectomy (SH), haemorrhoidopexy or the Longo procedure for prolapsed haemorrhoids; transanal haemorrhoid dearterialization with mucopexy or DG-HAL with mucopexy or performed without Doppler; haemorrhoidectomy using a radiofrequency device; haemorrhoidectomy using a LigaSureTM device (Medtronic, Minneapolis, MN, USA); Harmonic[®] (Johnson and Johnson, Raritan, NJ, USA) or ultrasonic scalpel haemorrhoidectomy; laser haemorrhoidectomy with a Nd : YAG or carbon dioxide laser; suture ligation or mucopexy on its own; RBL; IJS; IRC Bipolar Coagulation; direct current electrotherapy (DCV) at 16 or 30 mA; semi-open haemorrhoidectomy; cryotherapy; and use of a heater $probe^{21-99}$.

The league tables, SUCRA plot, and forest plot for all comparisons of interventional treatments for each of the outcomes are shown in *Table 2* and *Appendix S4*.

Analysis of transitivity

There was variation in the grade of haemorrhoids included in the treatment comparisons across the studies. Treatment comparisons in patients with grade 1 haemorrhoids also varied, and included RBL, IRC, IJS, BPC, and DCV. Other studies contained a varying proportion of patients with grade II and III haemorrhoids. The duration of follow-up ranged from 6 weeks to 5 years. Participant age and the proportion of female participants did not vary across the included studies. However, the geographical location of the studies was diverse, with most conducted in Europe. Study characteristics are summarized in Fig. 3.

Primary outcomes

Symptom recurrence

Fifty-four studies comparing 14 treatments across 7026 participants were analysed in the network, with 29 unique direct comparisons (Figs 4 and S1). A random-effects model was performed based on the lower DIC statistic. Compared with RBL, closed haemorrhoidectomy (OR 0.16, 95 per cent CrI 0.04 to 0.68), suture

Table 2 Overall summary of surface under cumulative ranking scores across outcomes

	SUCRA score										
	Recurrence	Pain on visual analogue scale	Repeat treatment	Prolonged hospital stay	Time off work	Postprocedural bleeding	Urinary retention	Bowel incontinence			
BPC	0.55	_	_	-	_	0.43	_	_			
CRY	0.38	-	-	_	-	-	-	-			
DCV	0.40	-	-	_	-	0.92	-	-			
DG-HAL	0.59	0.78	0.56	0.79	0.62	0.17	0.29	0.70			
FH	0.92*	0.05	-	0.17	0.34	0.39	0.48	_			
HarS		0.24	-	0.75	0.26	0.15	0.55	_			
IJS	0.14	-	0.15	_	-	0.75	0.71	_			
IRC	0.21	0.92*	0.13	0.59	-	0.68	0.74	_			
LASER	0.26	0.42	0.00	0.40	0.63	0.64	0.71	_			
LigaH	-	0.53	-	_	-	_	-	_			
MM	0.85	0.09	0.93*	0.35	0.19	0.22	0.18	0.23			
RBL	0.34	0.47	0.45	0.80*	0.93*	0.71	0.77*	0.83*			
RBL-IJS	0.63	-	0.31	_	-	0.93*	-	_			
RFC	0.17	0.77	-	_	-	0.30	-	_			
SH	0.69	0.52	0.76	0.80*	0.64	0.24	0.12	0.05			
SL-M	0.86	0.71	0.88	0.11	0.20	0.46	0.46	0.69			

The higher the SUCRA score, the lower the likelihood of that outcome. *Best intervention for that outcome. BPC, bipolar coagulation; CRY, cryotherapy; DCV, direct current electrotherapy; DG-HAL, Doppler-guided haemorrhoid artery ligation with mucopexy; FH, Ferguson (closed) haemorrhoidectomy; HarS, Harmonic[®] scalpel haemorrhoidectomy; IJS, injection sclerotherapy; IRC, infrared coagulation; LASER, laser haemorrhoidectomy; LigaH, LigaSure[™] haemorrhoidectomy; MM, Milligan–Morgan (open) haemorrhoidectomy; REL, rubber band ligation; RBL-IJS, combined rubber band ligation and injection sclerotherapy; RFC, radiofrequency coagulation; SH, stapled haemorrhoidecx; SL-M, suture ligation with mucopexy.

ligation with mucopexy (OR 0.24, 0.08 to 0.74), open haemorrhoidectomy (OR 0.27, 0.12 to 0.58), and SH (OR 0.41, 0.18 to 0.98) showed a significantly decreased odds of symptom recurrence (Figs 5 and S1). The highest SUCRA scores, representing treatments associated with the least symptom recurrence, were 0.93 (closed haemorrhoidectomy), 0.86 (suture ligation and mucopexy), and 0.85 (open haemorrhoidectomy). IJS ranked as the treatment associated with the most symptom recurrence, with a SUCRA score of 0.14 (Table 2).

Postprocedural pain

Thirty-four studies comparing 11 treatments across 3812 participants were analysed for pain using a VAS on day 1 after operation. A random-effects model was chosen based on the lower DIC statistic. Compared with RBL, open (MD 1.64, 95 per cent CrI 0.15 to 3.04) and closed (MD 1.97, 0.28 to 3.58) haemorrhoidectomy were associated with significantly more postprocedural pain. There were no significant differences in postprocedural pain on the VAS in comparisons between the eight remaining treatment modalities, which were IRC, DG-HAL, radiofrequency coagulation, suture ligation with mucopexy, LigaSureTM haemorrhoidectomy, SH, and laser haemorrhoidectomy (Fig. S2). The highest SUCRA scores, representing the least painful treatments, were 0.92 (IRC), 0.78 (DG-HAL), and 0.77 (radiofrequency coagulation). Closed haemorrhoidectomy ranked as the most painful treatment, with a SUCRA score of 0.05 (Table 2).

Postprocedural bleeding

Forty-six studies reported post-procedural bleeding, in which 14 treatments were compared across 5696 participants. A randomeffects model was used based on the lower DIC statistic. Compared with RBL, open haemorrhoidectomy (OR 3.66, 95 per cent CrI 1.79 to 7.00), SH (OR 4.53, 1.46 to 11.56), and DG-HAL (OR 5.82, 1.43 to 17.02) were associated with a significantly higher odds of postprocedural bleeding (Fig. S3). The highest SUCRA scores, reflecting the lowest postprocedural bleeding rates, were 0.93 (RBL and IJS combined), 0.92 (DCV), and 0.75 (IJS). Harmonic[®] scalpel haemorrhoidectomy ranked as the treatment reflecting the highest rate of postprocedural bleeding, with a SUCRA score of 0.15 (*Table 2*).

Urinary retention

Thirty studies reported urinary retention, comparing 10 treatments across 3116 participants. A random-effects model was used based on the lower DIC statistic. Compared with RBL, DG-HAL (OR 6.73, 95 per cent CrI 1.09 to 22.99), open haemorrhoidectomy (OR 7.71, 2.37 to 19.20), and SH (OR 9.56, 2.13 to 28.17) were associated with a significantly higher odds of urinary retention (Fig. S4). The highest SUCRA scores, reflecting treatments least likely to result in urinary retention, were 0.77 (RBL) and 0.74 (IRC). SH ranked as being most likely to result in urinary retention, with a SUCRA score of 0.12 (Table 2).

Bowel incontinence

Five treatments were compared among nine studies with 1269 patients. A fixed-effects model was used based on the lower DIC statistic. Compared with RBL, open haemorrhoidectomy (OR 4.42, 95 per cent CrI 1.04 to 32.42) and SH (OR 6.96, 1.30 to 58.49) were significantly more likely to result in bowel incontinence. SH also resulted in significantly more bowel incontinence than DG-HAL (OR 4.43, 1.66 to 12.80) or suture mucopexy (OR 4.34, 1.33 to 15.72) (Fig. S5). The lowest SUCRA scores, reflecting the treatments most likely to result in bowel incontinence, were 0.05 (SH) and 0.23 (open haemorrhoidectomy) (Table 2).

Secondary outcomes

Appendix S4 shows the network plot, league table, SUCRA plot, and SUCRA table for all secondary outcomes.

Repeat treatment

Eighteen studies compared seven different treatments involving 2819 participants. A random-effects model was used based on the lower DIC statistic. Compared with RBL, open haemorrhoidectomy was associated with a significantly lower odds of repeat treatment (OR 0.12, 95 per cent CrI 0.01 to 0.48), whereas bipolar



Fig. 3 Analysis of transitivity across included treatments

a Distribution of grade of haemorrhoids, **b** average duration of follow-up, **c** percentage of women, and **d** average age distribution of participants. DG-HAL, Dopplerguided haemorrhoid artery ligation with mucopexy; RBL, rubber band ligation; IJS, injection sclerotherapy; IRC, infrared coagulation; SL-M, suture ligation with mucopexy; MM, Milligan–Morgan (open) haemorrhoidectomy; SH, stapled haemorrhoidopexy; FH, Ferguson (closed) haemorrhoidectomy; BPC, bipolar coagulation; RFC, radiofrequency coagulation; DCV, direct current electrotherapy; CRY, cryotherapy; LASER, laser haemorrhoidectomy; HarS, Harmonic[®] scalpel haemorrhoidectomy. In **b–d**, Median (crosses), median values (bold lines), i.q.r. (boxes), and range excluding outliers (circles) are shown.

coagulation (OR 39.47, 1.09 to 228.61) and DCV (OR 62.61, 1.11 to 363.35) were associated with a significantly higher odds of repeat treatment (Fig. S6). The lowest SUCRA scores, reflecting treatments most likely to result in repeat treatment, were IRC (0.13) and IJS (0.15). The highest SUCRA scores reflecting treatments least likely to result in repeat treatment were 0.99 (open haemorrhoidectomy) and 0.81 (SH) (Table 2).

Duration of hospital stay

Twenty-one studies reported duration of inpatient hospital admission, with 10 treatment comparisons and 2907 participants. The mean length of stay across the network was 1.6 days. A random-effects model was used based on the lower DIC statistic. Compared with RBL, closed haemorrhoidectomy (MD 1.20, 95 per cent CrI 0.32 to 2.09) and suture ligation with mucopexy (MD 1.41, 0.04 to 2.80) were associated with a significantly longer hospital admission (Fig. S7). The highest SUCRA scores, representing treatments with the shortest hospital admission, were 0.80 (RBL and SH) and 0.79 (DG-HAL). Closed haemorrhoidectomy ranked as the treatment associated with the longest hospital admission, with a SUCRA score of 0.17 (Table 2).

Time off work

Eighteen studies reported time off work, comparing nine treatments with a total of 2103 participants. The mean time off work across the network was 14.7 days. A random-effects model was used based on the lower DIC statistic. Compared with RBL, closed haemorrhoidectomy (MD 13.24, 95 per cent CrI 0.78 to 26.21), Harmonic[®] scalpel haemorrhoidectomy (MD 15.79, 1.47 to 30.34), open haemorrhoidectomy (MD 15.36, 4.35 to 26.64), and bipolar coagulation (MD 20.05, 0.72 to 39.73) were associated with significantly longer time off work (Fig. S8). The highest SUCRA score, reflecting the treatment associated with the least time off work, was 0.93 (RBL). Open haemorrhoidectomy ranked as the treatment associated with the most time off work, with a SUCRA score of 0.19 (Table 2).

Sensitivity analysis

A sensitivity analysis of symptom recurrence was analysed for 45 studies with 5337 participants comparing 14 treatments. A random-effects model was chosen based on the lower DIC value. Overall, there was no significant difference in the results compared with the initial analysis (Fig. S9). A sensitivity analysis was conducted for postprocedural bleeding, in which 38 studies compared 14 treatments, involving 4482 participants. A fixed-effects model was chosen based on the lower DIC value. Overall, the results of the sensitivity analysis showed no significant difference compared with the main analysis (Fig. S10). No studies reporting on postprocedural pain on the VAS, urinary retention, bowel incontinence, repeat treatment, duration of hospital stay or time off work were omitted as none included grade I haemorrhoids.

Discussion

This systematic review and NMA compared treatment modalities ranging from minimally invasive, clinic-based procedures to excisional therapy requiring anaesthesia for prolapsing haemorrhoids.



Fig. 4 Network plot and surface under cumulative ranking curves for recurrence

a Network plot of studies analysed for the outcome recurrence. The nodes represent the number of participants receiving each treatment, and the line thickness represents the number of studies assessing each direct treatment or procedure comparison. **b** Surface under cumulative ranking (SUCRA) plot and treatments. Higher rankings are associated with smaller outcome values; BPC, bipolar coagulation; CRY, cryotherapy; DCV, direct current electrotherapy; DG-HAL, Doppler-guided haemorrhoid artery ligation with mucopexy; FH, Ferguson (closed) haemorrhoidectomy; JS, injection sclerotherapy; IRC, infrared coagulation; LASER, laser haemorrhoidectomy; MM, Milligan–Morgan (open) haemorrhoidectomy; RBL, rubber band ligation; RFC, radiofrequency coagulation; SCL-RBL, combined injection sclerotherapy and rubber band ligation; SH, stapled haemorrhoidopexy; SL-M, suture ligation with mucopexy.

Treatment														
	FH	SL-M	MM	SM	SCL-RBL	DG-HAL	BPC	DCV	CRY	RBL	LASER	IRC	RFC	IJS
F	4	1.48 (0.27, 7.90)	1.64 (0.40, 6.77)	2.56 (0.56, 11.60)	2.95 (0.46, 17.67)	3.25 (0.68, 14.95)	3.63 (0.79, 16.15)	5.24 (1.52, 18.13)*	5.60 (0.89, 34.57)	6.20 (1.47, 25.73)*	7.78 (1.27, 48.73)*	8.18 (1.87, 36.08)*	11.19 (1.42, 87.60)*	9.66 (2.12, 42.77)*
SL-I	0.68 (0.13, 3.67)		1.11 (0.36, 3.55)	1.73 (0.55, 5.76)	1.98 (0.40, 9.97)	2.17 (0.77, 6.43)	2.46 (0.67, 9.16)	3.55 (0.63, 20.78)	3.80 (0.75, 19.23)	4.20 (1.36, 13.11)*	5.28 (1.07, 27.20)*	5.50 (1.67, 19.11)*	7.50 (1.43, 44.33)*	6.51 (1.94, 22.18)*
MI	0.61 (0.15, 2.53)	0.90 (0.28, 2.76)		1.56 (0.77, 3.16)	1.77 (0.45, 6.89)	1.96 (0.80, 4.82)	2.22 (0.64, 7.30)	3.21 (0.66, 15.15)	3.40 (0.88, 13.22	3.76 (1.74, 8.14)*	4.73 (1.40, 16.67)*	4.94 (1.98, 12.62)*	6.74 (1.36, 35.75)*	5.83 (2.34, 14.47)*
S	0.39 (009, 1.77)	0.58 (0.17, 1.81)	0.64 (0.32, 1.29)		1.14 (0.27, 4.70)	1.26 0.54, 2.91)	1.43 (0.36, 5.02)	2.05 (0.39, 10.23)	2.19 (0.52, 9.27)	2.41 (1.02, 5.71)*	3.04 (0.78, 12.25)	3.18 (1.19, 8.61)*	4.33 (0.81, 24.21)	3.76 (1.36, 10.08)*
SCL-TB	0.34 (0.06, 2.19)	0.50 (0.10, 2.50)	0.56 (0.15, 2.23)	0.88 (0.21, 3.68)		1.10 (0.27, 4.57)	1.24 (0.27, 5.88)	1.80 (0.27, 11.88)	1.92 (0.37, 1004)	2.12 (0.69, 6.65)	2.64 (0.50, 15.21)	2.78 (0.80, 10.09)	3.84 (0.54, 27.35)	3.28 (1.06, 10.73)*
DG-HA	0.31 (0.07, 1.48)	0.46 (0.16, 1.30)	0.51 (0.21, 1.25)	0.80 (0.34, 1.85)	0.91 (0.22, 3.71)		1.13 (0.31, 3.90)	1.63 (0.31, 8.35)	1.74 (0.41, 7.34)	1.92 (0.81, 4.53)	2.43 (0.58, 10.34)	2.53 (0.98, 6.61)	3.43 (0.65, 19.66)	2.98 (1.12, 7.93)*
arator BP	0.28 (0.06, 1.26)	0.41 (0.11, 1.50)	0.45 (0.14, 1.56)	0.70 (0.20, 2.60)	0.80 (0.71, 3.75)	0.88 (0.26, 3.20)		1.44 (0.36, 5.85)	1.54 (0.31, 7.34)	1.69 (0.59, 5.08)	2.14 (0.43, 11.41)	2.24 (0.69, 7.44)	3.07 (0.50, 19.82)	2.63 (0.85, 8.38)
DC DC	/ 0.19 (0.06, 0.66)*	0.28 (0.05, 1.59)	0.31 (0.07, 1.51)	0.49 (0.10, 2.59)	0.56 (0.08, 3.67)	0.61 (0.12, 3.22)	0.70 (0.17, 2.78)		1.07 (0.16, 7.44)	1.18 (0.26, 5.50)	1.49 (0.22, 10.32)	1.56 (0.32, 7.73)	2.12 (0.26, 18.35)	1.83 (0.38, 8.78)
CR	0.18 (0.03, 1.13)	0.26 (0.05, 1.33)	0.29 (0.08, 1.13)	0.46 (0.11, 1.92)	0.52 (0.10, 2.72)	0.57 (0.14, 2.45)	0.65 (0.13, 3.22)	0.93 (0.13, 6.42)		1.10 (0.33, 3.85)	1.39 (0.25, 7.94)	1.45 (0.38, 5.71)	1.97 (0.38, 15.21)	1.70 (0.48, 6.35)
RB	0.16 (0.04, 0.68)*	0.24 (0.08, 0.58)*	0.27 (0.12, 0.58)*	0.41 (0.18, 0.98)*	0.47 (0.15, 1.44)	0.52 (0.22, 1.24)	0.59 (0.20, 1.69)	0.85 (0.18, 3.85)	0.91 (0.26, 3.04)		1.26 (0.35, 4.61)	1.31 (0.72, 2.45)	1.79 (0.38, 9.13)	1.56 (0.90, 2.67)
LASE	0.13 (0.02, 0.79)*	0.19 (0.04, 0.93)*	0.21 (0.06, 0.71)*	0.33 (0.08, 1.27)	0.38 (0.07, 2.02)	0.41 (0.10, 1.72)	0.47 (0.09, 2.33)	0.67 (0.10, 4.50)	0.72 (0.13, 4.04)	0.80 (0.22, 2.84)		1.05 (0.25, 4.19)	1.42 (0.20, 10.56)	1.24 (0.30, 4.83)
IR	0.12 (0.03, 0.53)*	0.18 (0.05, 0.60)*	0.20 (0.08, 0.50)*	0.31 (0.12, 0.84)*	0.36 (0.10, 1.25)	0.40 (0.15, 1.02)	0.45 (0.13, 1.44)	0.64 (0.13, 3.12)	0.69 (0.18, 2.62)	0.76 (0.41, 1.39	0.96 (0.24, 3.92)		1.37 (0.26, 7.66)	1.88 (0.57, 2.36)
RF	0.9 (0.01, 070)*	0.13 (0.02, 0.70)*	0.15 (0.03, 0.74)*	0.23 (0.04, 1.23)	0.26 (0.04, 1.86)	0.29 (0.05, 1.54)	0.33 (0.05, 2.01)	0.47 (0.05, 3.89)	0.51 (0.07, 3.51)	0.56 (0.11, 2.63)	0.70 (0.09, 5.00)	0.73 (0.13, 3.82)		0.87 (0.16, 4.43)
IJ	0.10 (0.02, 0.47)*	0.15 (0.05, 0.51)*	0.17 (0.07, 0.43)*	0.27 (0.10, 0.74)*	0.30 (0.09, 0.97)*	0.34 (0.13, 0.89)*	0.38 (0.12, 1.17)	0.55 (0.11, 2.64)	0.59 (0.16, 2.09)	0.64 (0.37, 1.11)	0.81 (0.21, 3.29)	0.85 (0.42, 1.74)	1.16 (0.23, 6.41)	

Fig. 5 League table of treatment comparisons for recurrence

Numbers in each cell represent the odds ratio (95 per cent credible interval) for recurrence between the procedure specified in the column versus that specified in the row. FH, Ferguson (closed) haemorrhoidectomy; SL-M, suture ligation with mucopexy; MM, Milligan-Morgan (open) haemorrhoidectomy; SH, stapled haemorrhoidectomy; SL-RBL, combined injection sclerotherapy and rubber band ligation; DG-HAL, Doppler-guided haemorrhoid artery ligation with mucopexy; BPC, bipolar coagulation; DCV, direct current electrotherapy; CRY, cryotherapy; RBL, rubber band ligation; LASER, laser haemorrhoidectomy; IRC, infrared coagulation; RFC, radiofrequency coagulation; JJS, injection sclerotherapy. *Statistically significant. Greater intensity of shading reflects the greater the effect size.

The key findings were that for grades II and III haemorrhoids, which are not prolapsed permanently, conservative clinic-based procedures have a greater odds of symptom recurrence, and lower odds of pain and postprocedural complications than excisional treatments.

This study allowed simultaneous comparisons of the clinical outcomes and effectiveness of a multitude of treatments for

grade II–III haemorrhoids. An NMA was appropriate to answer a question of this nature, where multiple outcomes were analysed and common treatments were compared through direct and indirect comparisons across the included population¹⁰⁰. The present study presents evidence for what is commonly observed in clinical practice: excisional therapies are typically preferred after more conservative clinic-based procedures have not proved

successful⁵. The ranking of treatments based on their complication profile confirms that significant postprocedural complications, such as bleeding, urinary retention, and bowel incontinence, are much more common after excisional compared with non-excisional therapy. This study has also highlighted differences in treatment outcomes such as postprocedural pain scores measured on a VAS, time off work, and duration of hospital stay; excisional treatments, which are more invasive, were found to have higher complication rates.

There were some differences in the distribution of grades across treatments compared, which may have affected transitivity assumptions. In the clinical setting, participants could be offered any of the treatments, but the choice of procedure in clinical practice depends on both patient and surgeon factors. Nonetheless, the treatments compared in this study are broadly applicable to the study population. This was confirmed by the sensitivity analysis that excluded grade I haemorrhoids, and resulted in either no studies being omitted or did not result in a significant change to the outcome of interest. Other factors affecting the outcomes included variation in the duration of followup among the analysed studies. The minimum 6-week postprocedure follow-up for symptom recurrence likely led to significant heterogeneity, particularly resulting from studies reporting on longer durations of follow-up for this outcome. There was also a noticeable trend that older studies reported non-surgical treatments, whereas newer studies compared surgical treatments that were introduced more recently. Older studies reported postprocedural pain on a VAS less often and used categorical scales instead. In addition, postprocedural pain comparisons were based only on day 1 scores, owing to the lack of data on pain for other days. Pain scores may vary over several days after the procedure and this should be considered when interpreting data on this outcome. The Cochrane Collaboration's risk-of-bias tool 2.0 was used to assess study quality, and overall found it to be adequate, except for measurement of blinding of both participants and personnel (risk of bias due to deviation from intended interventions) and outcome assessors (risk of bias in measurement of outcome).

The findings of the present NMA are similar to those of a previously reported NMA¹⁰¹ of grade III-IV haemorrhoids, which concluded that open and closed haemorrhoidectomy and SH are associated with worse postprocedural pain, bleeding, urinary retention, and bowel incontinence than other non-surgical treatments, but have the advantage of lower rates of symptom recurrence. These results are concordant with a previous metaanalysis¹⁰² comparing conventional with stapled haemorrhoidectomy, which showed the stapled procedure to have better outcomes with regard to operating time, postprocedural pain, duration of hospital stay, and time to return to work, but resulted in a higher recurrence risk. Similarly, a previous meta-analysis¹⁰³ that compared DG-HAL with SH showed no differences between the two treatments in terms of postprocedural complications and recurrence of haemorrhoids. The present study also had equivalent results to an earlier meta-analysis¹⁰⁴ comparing conservative treatment options for haemorrhoids, where IJS and IRC were more likely to require further therapy than RBL, but were less painful. A number of studies^{23,37,48,49,80,99} reported the use of suture ligation or suture mucopexy for the treatment of prolapsing haemorrhoids. Using NMA, it was documented that suture ligation results in relatively lower odds of symptom recurrence than RBL. However, the included studies in this NMA comparing suture ligation are limited in number and quality, and further studies comparing suture ligation with stapled and excisional (open

and closed) haemorrhoidectomy are warranted for grade II–III haemorrhoids.

The limitations of this NMA include the presence of a small number of grade 1 haemorrhoids in studies that compared conservative treatments, such as RBL and IJS. However, the findings of the sensitivity analysis showed that this did not affect the overall results. The inclusion range of the literature also dates back 30 years, which may affect the quality of studies. It was deemed necessary to include older publications, as studies comparing conservative treatments frequently date from older periods, and newer surgical treatments have been published more recently. Other limitations include heterogeneity in the duration of follow-up. Some studies reported follow-up as short as 6 weeks, whereas others had a follow-up of over 2 years, which may have contributed to heterogeneity in the recurrence outcome. Further limitations of an NMA include inconsistencies between direct and indirect comparisons. Although there were few instances of inconsistency in the outcomes measured, the failure to detect inconsistency does not imply consistency. The amount of evidence a treatment carries and the number of available comparisons between treatments determines the diversity and strength of an NMA¹⁰⁵. A major imbalance between the quantity of evidence and treatments available for comparison may affect the power and reliability of the NMA¹⁰⁰. Some treatment comparisons were informed by several RCTs, whereas others were sparsely informed. In the present NMA, treatments analysed in only one study were excluded from the network of that outcome to remove sparsely informed trials and obscure treatments that are not commonly used. The present NMA could not distinguish differences in outcomes between a number of excisional surgical techniques owing to the small number of relevant trials in each network. There was also an inadequate number of studies to reach statistical significance when LigaSureTM and Harmonic[®] scalpel haemorrhoidectomy were compared with other treatments in this NMA.

Further studies comparing treatments for haemorrhoids should assess treatment effectiveness according to standardized and validated patient-reported outcome measures (PROMs)^{2,106}. The use of a PROM such as a haemorrhoid symptom severity score or a health-related quality-of-life scale may provide valuable information about the symptomatic burden of disease and is a useful measure for assessing the recurrence of haemorrhoidal symptoms. Many older studies did not use a PROM for haemorrhoid symptom recurrence; such an assessment is important and necessary for a disease such as haemorrhoids, as some symptoms may persist even though the patient may be unconcerned². Future clinical trials should consider reporting outcomes against a haemorrhoid core outcome set with regard to symptoms, complications, and patient satisfaction¹⁰⁶. A method of standardized reporting of outcomes will enable more reliable comparison of outcomes in meta-analyses. Finally, further higher-quality RCTs are needed to compare interventional treatments for haemorrhoids, particularly in terms of blinding of participants, personnel, and outcome assessors.

A range of treatments is available for grade II–III haemorrhoids, each with its benefits and complication profiles. Conservative, clinic-based procedures are associated with a higher rate of symptom recurrence, but should be considered initially as they carry a lower risk of complications. If they are not successful in resolving symptoms, more invasive treatments with a much greater risk of complications should be offered. The benefits and risks of each treatment should be discussed with the patient before a treatment decision is made. Disclosure. The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at BJS Open online.

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