Use of imaging for pre- and post-operative characterisation of ventral hernia

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Title Page

A Systematic Methodological Review of Reported Perioperative Variables, Postoperative Outcomes and Hernia Recurrence from Randomised Controlled Trials of Elective Ventral Hernia Repair: Clear Definitions and Standardised Datasets are needed.

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A Systematic Methodological Review of Reported Perioperative Variables, Postoperative Outcomes and Hernia Recurrence from Randomised Controlled Trials of Elective VH Repair: Clear Definitions and Standardised Datasets are needed.

Abstract

Background This systematic review assesses the perioperative variables and post-operative outcomes reported by randomised controlled trials (RCTs) of VH repair. This review focuses particularly on definitions of hernia recurrence and techniques used for detection.

Objective Our aim is to identify and quantify the inconsistencies in perioperative variable and postoperative outcome reporting, so as to justify future development of clear definitions of hernia recurrence and a standardised dataset of such variables.

Methods The PubMed database was searched for elective VH repair RCTs reported January 1995 to March 2016 inclusive. Three independent reviewers performed article screening, and two reviewers independently extracted data. Hernia recurrence, recurrence rate, timing and definitions of recurrence, and techniques used to detect recurrence were extracted. We also assessed reported post-operative complications, standardised operative outcomes, patient reported outcomes, pre-operative CT scan hernia dimensions, intra-operative variables, patient co-morbidity, and hernia morphology.

Results 31 RCTs (3367 patients) were identified. Only 6 (19.3%) defined hernia recurrence and methods to detect recurrence were inconsistent. Sixty-four different clinical outcomes were reported across the RCTs, with wound infection (30 trials, 96.7%), hernia recurrence (30, 96.7%), seroma (29, 93.5%), length of hospital stay (22, 71%) and haematoma (21, 67.7%) reported most frequently. Fourteen (45%), 11 (35%) and 0 trials reported CT measurements of hernia defect area, width and loss of domain respectively. No trial graded hernias using generally accepted scales.

Conclusion VH RCTs report peri- and post-operative variables inconsistently, and with poor definitions. A standardised minimum dataset, including definitions of recurrence, is required.

Background

In an ageing population[1] with an increasing prevalence of both obesity[2] and abdominal surgery, the incidence of ventral hernia (VH) is increasing[3,4]. The projected number of VH repairs performed in 2016 in the United States approaches 400,000[3]. Recurrence rates after repair are high, reaching 10 to 40%[5],[6]. Incidence of large complex VH is also increasing and significant loss of domain coupled with comorbidity means these patients present the sternest surgical challenge[7]. Despite innovation[8–10] there is no consensus regarding optimal reconstructive techniques[11,12].

Currently, the VH literature consists primarily of case series and large observational studies. This level 4 evidence[13] suggests the cause of postoperative complications and hernia recurrence are complex and multifactorial. To date, research has focussed largely on surgical technique[12],[14] and patient co-morbidity[15,16] with limited focus on hernia morphology. Although several hernia grading scales have been produced[17–21], in an attempt to predict post-operative outcomes, few have been externally validated and, if so, with limited success[22–24]. Comparative trials and observational studies seldom define hernia recurrence and if they do, many use different definitions for recurrence as well as a variety of techniques to detect recurrence. Standardised definitions and validated datasets for VH repair studies would make reported data consistent, allowing for greater accuracy of trial comparison and meta-analysis.

In this systematic review, we analysed randomised controlled trials (RCTs) of adult patients undergoing elective VH repair. All VH repair RCTs were included irrespective of the intervention and comparator groups. We analysed all perioperative variables and post-operative outcomes reported, paying particular attention to the different methods used to detect and define hernia recurrence. Our objective was to demonstrate the inconsistencies in variable and outcome reporting by RCTs and the necessity for standardised trial datasets as well as clear definitions of hernia recurrence and recurrence detection methods.

Methods

Reporting and Registration

This systematic review was reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[25]. Ethical permission is not required by our centre for systematic reviews of available primary literature. A protocol was developed and registered with PROSPERO, the international prospective register of systematic reviews (CRD42016043071).

Inclusion and exclusion criteria

Inclusion criteria for studies

We aimed to identify RCTs that described clinical outcomes in patients following VH repair between 1st January 1995 and 31st March 2016 inclusive. We excluded trials with less than 10 patients in an individual study arm since such data are likely to be weak. Only RCTs written in English were included.

Target condition

The target condition was surgical VH repair. All different VH morphologies were eligible as were all VH working group (VHWG) grades[17]. Studies describing femoral and/or inguinal hernias (i.e. groin hernia) were excluded. Emergency VH repair was excluded as was primary closure after damage control laparotomy. However, patients having elective VH repair after primary closure from damage control laparotomy were eligible as were RCTs of elective VH repair with bridging repair (i.e. failure to establish primary fascial closure). RCTs of parastomal hernia repairs were excluded. Trials with concomitant bowel resection were included (since this is often intended) and as long as the primary objective of surgical repair was VH repair. We excluded trials with either concomitant tumour removal or bariatric surgery.

Participants

Adult participants having a surgical VH repair. We excluded paediatric studies (defined as 18 years or less) since these are not representative of 'typical' CVH patients.

Follow up

We stipulated no minimum length of follow-up.

Comparison

There was no restriction placed on any study arm comparator (e.g. operative technique, mesh type, position of mesh).

Search strategy and string

A surgical research fellow, SGP, searched the PubMed database from 1st January 1995 to 31st March 2016 inclusive limiting the search using the following terms: "adult 19+", "human studies" and to those written in English. Our search string identified and combined the two following criteria to identify relevant articles:

- To identify studies of VH disease including complex disease we used the MESH terms "hernia", "abdominal hernia", "umbilical hernia" and "VH" were used. These were combined with keywords: "abdominal wall reconstruction"; "herniorrhaphy"; "ventral defect" and "entero-cutaneous fistula".
- To identify studies of surgical techniques used for VH repair we used the MESH terms: "general surgery"; "reconstructive surgical procedures" and "surgical mesh". This was combined with keywords: "pneumoperitoneum", "botox", "botulinium", "two-stage", "two step", "staged repair", "component

separation", "transversus abdominis", "retro-rectus", "bridging", "bridge repair", "silo", "open" and "laparoscopic".

Our complete search string is shown in online resource 1.

Citation management and screening

SGP stored identified citations in an Excel spreadsheet (Microsoft Excel for Mac 2011 Version 14.5.9, Microsoft Corporation, Washington, USA), up-loading these subsequently into a reference manager able to access online original articles directly (Mendeley Desktop Version 1.17 for Windows XP and Mac OS X, London, UK). After the search filters were applied and duplicates were excluded, the citations were divided into two equal groups. The titles of the first-half of the citations were screened by SGP and the second-half by CW. The researchers screened for comparative studies of VH disease. They discarded articles that were 'clearly unsuitable' for the review (e.g. subject not VH) and retained any regarded as 'uncertain' or 'definitely possible'. These two latter groups were combined and researchers, SGP, CW and RB, then independently screened the titles and abstracts of the 'uncertain' and 'definitely possible' results with the aim of identifying all comparative studies. Any discrepancies were settled by face-to-face discussion amongst the three researchers. A third hand search of the full text by SGP, CW and RB, then divided the selected comparative studies into respective methodological designs; case-control studies, cohort studies and RCTs. Any article where uncertainty persisted was discussed with senior members, AW and SH, face-to-face. An exclusion log was kept at all stages. The PRISMA diagram (fig 1.) shows the flow of article selection.

Data extraction

SGP and JB extracted data independently from all RCTs selected for the review, which were cross-checked subsequently face-to-face. Data were entered by the researchers into an Excel datasheet and categorised into broad groups as follows: study design; hernia morphology; pre-operative patient factors including comorbidities; intraoperative variables and clinical outcomes, including complication rates and hernia recurrence.

Study demographics and risk of bias

Information extracted for RCT study design included: the study setting (multi-centre vs. single centre), the country of publication, the date of publication and the number of patients in each study arm. Researchers, SGP and JB, used the Cochrane Collaboration's tool to assess the risk of bias[26]. Any differences in opinion were discussed face-to-face and settled by discussion with senior authors if required.

Hernia morphology

For hernia morphology, we intended to record dimensions of the hernia defect, including area, loss of domain, the ventral hernia working group (VHWG)

grade[17] and the CDC wound classification[27]. We recorded whether the study included patients with either primary or incisional VHs, or both, and if so the proportion of these two hernia types. However, we anticipated that many trials would not report these details of hernia morphology and grade, and recorded when these items were not reported. Similarly, we recorded the number of previous attempts at hernia repair where documented. We noted prior surgical site infection in patients undergoing repair since this is known to predispose to subsequent recurrence[15].

Pre-operative patient characteristics and co-morbidities

Baseline patient characteristics extracted were mean patient age and the proportion of male to females. Comorbidity data included the mean and standard deviation of body mass index (BMI), the proportion of patients with chronic obstructive pulmonary disease (COPD), diabetes, steroid use, and the proportion of each American Society of Anaesthesiologists (ASA) grade (and mean ASA grade) in each study group. Proportion by smoking status, arteriopath status (previous diagnosis of ischaemic heart disease (IHD), peripheral vascular disease (PVD), cerebrovascular accidents (CVAs)) and a diagnosis of benign prostatic hypertrophy (BPH) were also noted.

Intra-operative variables

We recorded the mode of surgery used (e.g. laparoscopic or open), the type of mesh where used, the anatomical layer within the abdominal wall into which the mesh was implanted (i.e. intraperitoneal, pre-peritoneal, retro-rectus, inlay or onlay), operative duration, intra-operative blood loss, and the experience of the principal surgeon where documented.

Reported Clinical Outcomes

Hernia recurrence

Our outcomes of primary interest were; hernia recurrence, the post-operative recurrence rates, the timing of recurrence, the definitions for VH recurrence used, and the test method(s) used to diagnose recurrence (for example clinical examination, CT scan, US scan) were recorded. These data were analysed to investigate whether the method used to detect recurrence influenced recurrence rate. As we were aware of no generally accepted imaging definition of VH recurrence, we anticipated considerable inter-observer variability for reporting recurrence.

We did not pre-specify the definition of post-operative hernia recurrence. We did not restrict by timing of recurrence, the definitions for VH recurrence used, or the test method(s) used to diagnose recurrence.

Secondary outcomes

Post-operative complications

All post-operative complications described were recorded. Complications were grouped into intraoperative, early postoperative, late post-operative, and general or standardised outcomes. Early postoperative complications were sub-grouped into local wound complications (wound infection, seroma formation, wound dehiscence, skin necrosis) and systemic complications (hospital acquired pneumonia, myocardial infarction, pulmonary embolism). Early post-operative complications were defined as those occurring within 30 days of surgery and late post-operative complications as those occurring thereafter. Late complications were extracted for the timespan presented in the paper.

Standardised outcomes

Where reported, we recorded all standardised post-operative outcome measures used. We anticipated that RCTs would use a variety of outcome measures such as length of hospital stay, 30-day re-operation rate and 30-day re-admission rate. If trial complications were measured using a standardised post-operative complication scale, the value was recorded.

Patient reported outcome measures

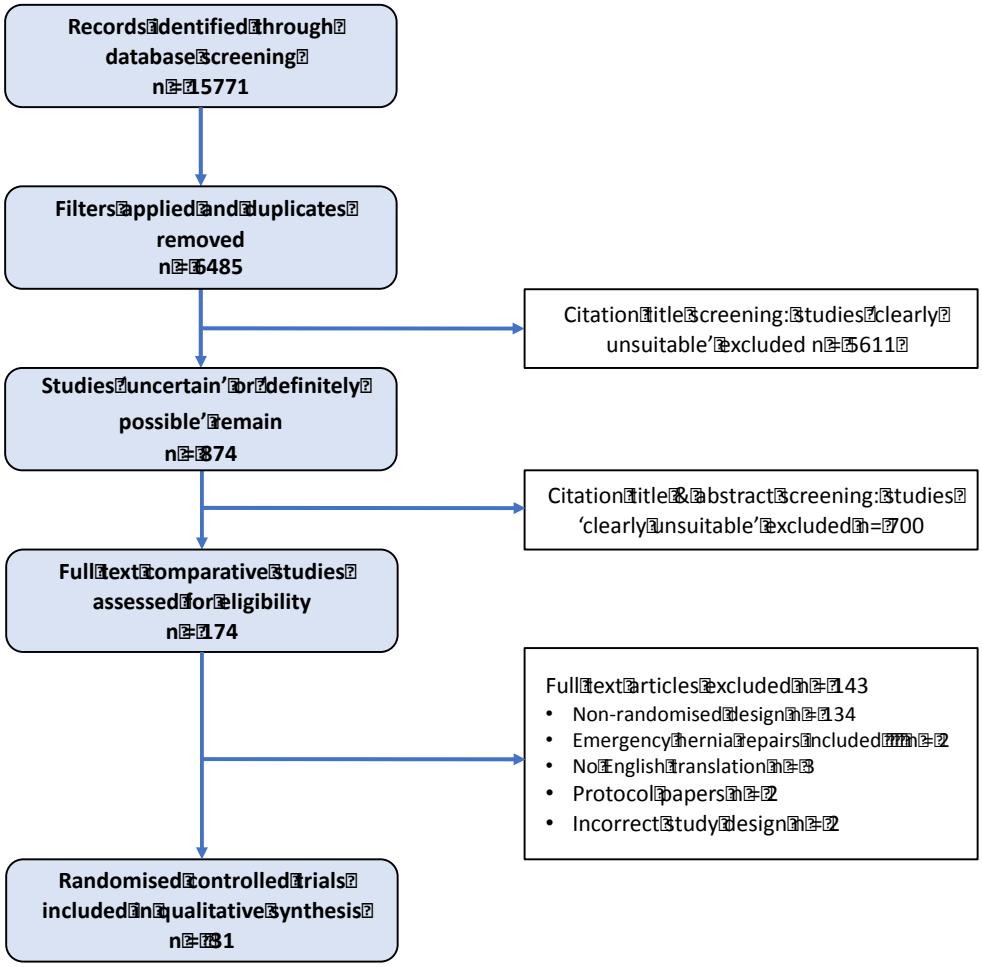
We foresaw that some trials may use standardised patient reported outcome measures (PROMs) to measure operative success. These may include visual analogue scales for pain or overall health status. They may also report the time to first bowel movement or the time taken to return to normal activities. All such outcomes were recorded, along with the timing of the assessment.

Results

Search results

Our initial search retrieved 15771 results (fig 1.). After applying search filters [studies published between 1st January 1995 to 31st March 2016, human trials only, participants aged ≥19, studies written in English], we excluded 9286 studies, resulting in 6485 papers for our initial review. After screening the citation titles, we ultimately categorised 874 studies as 'definitely possible' or 'uncertain'. This fell to 174 comparative studies after title and abstract screening. The full text of all 174 articles was assessed for details of study methodology. This identified 31 RCTs included in the present systematic review.

Figure 1. PRISMA diagram showing selection of RCTs for this review



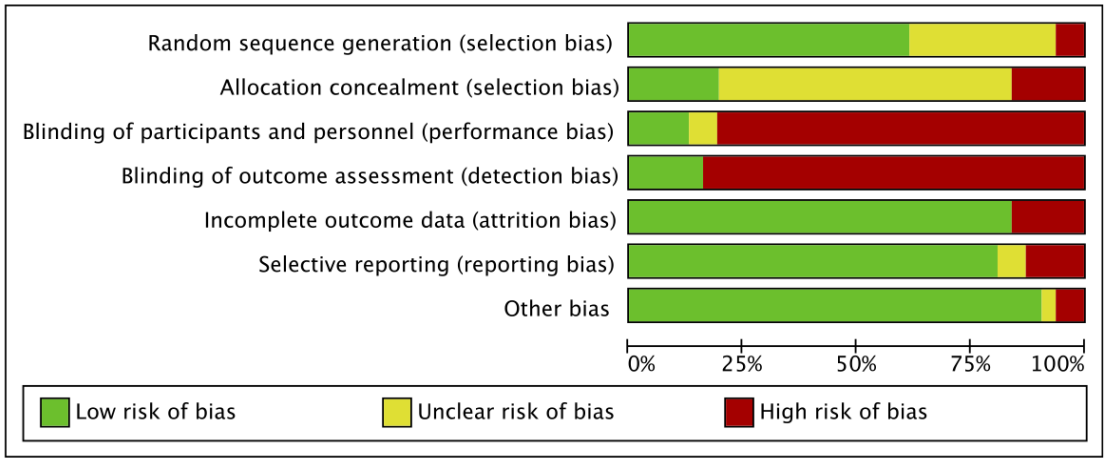
Study demographics

Study demographics and design characteristics are shown in Table 1. The 31 RCTs included 3,367 patients with a mean of 109 patients, range 24 to 337. One study[28] appears twice since it divided patients into simple and complex hernia groups, creating two individual trials (suture vs mesh repair and prosthetic mesh vs auto-dermal graft repair). Five RCTs were carried out in both the Netherlands[29–33] and Spain[34–38]. Thirteen RCTs were multi-centre and 18 were single centre. Over the past 20 years the number of RCTs performed increased, with 8 published between 1995 to 2005 versus 23 published from 2005 to 2016. There were 3 groups where RCTs compared the same interventions: Eleven studies compared laparoscopic versus open repair; 5 studies[28,30,36,39,40] compared suture versus mesh repair and 3 studies[37,41,42] compared tack versus suture mesh fixation in laparoscopic VH repair.

Table 1. Demographic and characteristics of the 31 RCTs included in the Systematic Review.

Included Studies - Demographics		
Characteristic	**Subgroup**	**No. of RCTs**
-Country of Publication	Netherlands[29–33] Spain[34–38]	5
	India[41–43] Eygpt[44–46]	3
	Pakistan[40],[47] Turkey[39],[48] Italy[49,50]Germany [28],[51]	2
	Sweden[52] USA[53] Australia(54) Lithuania[55] France[56] Belgium[57] Denmark[58]	1
-Multi vs Single-centre	Multi centre[28-30],[32-34],[40],[49],[51-53],[57-58]	13
	Single centre[31],[35-39],[41-46],[48-50],[54-56]	18
-Year of Publication	1995-2005[28],[30],[32],[35-36],[39],[46]	7
	2006-2016[29],[31],[33-34],[37-38],[40-45],[47-58]	24
Included Studies		
Characteristic	**Subgroup**	**No. of RCTs**
-Trial Groups	Laparoscopic vs. Open[29],[34-35],[43],[47-50],[52-54]	11
	Open mesh vs. suture[28],[30],[36],[39-40]	5
	Laparoscopic mesh fixation; Tacks vs. Sutures[31],[37],[41-42]	3
	• Open VH repair:	
	Onlay vs. Sublay[44],[55]	2
	Light weight vs. Heavy weight mesh[32]	1
	Medium weight vs. Medium weight mesh[51]	1
	*Autograft vs. Prosthetic mesh**[28*]	1
	Component separation vs. Prosthetic mesh[33]	1
	Onlay vs. Underlay[45]	1
	Intraperitoneal vs. Onlay [bridging][46]	1
	Ventralex patch vs Biomesh composite mesh[56]	1
	• Laparoscopic VH repair:	
	Double crown tack vs. suture and tack mesh fixation[31],[57]	2
	Double crown tack vs. fibrin sealant mesh fixation[58]	1
	Light weight mesh vs. Medium weight mesh[38]	1
	Total	32*
	*Large hernias from Korenkov et al. (a suture vs. mesh RCT) were analysed as a separate category. This makes this total 32 rather than 31.	
-Hernia type	Primary hernias only[36],[39-40],[44-45],[47]	6
	Incisional hernias only[28-30],[32-34],[38],[46],[49-53],[55]	14
	Primary and incisional hernias[31],[35],[37],[41-43],[48],[54],[56-58]	11
-Primary outcomes	Hernia recurrence[28],[49],[54],[56]	4
	Quality of life/ Health questionnaires[32],[34],[51-52]	4
	Pain [measured using visual analogue scores][29],[31],[57],[58]	4
	Pain and hernia recurrence [two primary outcomes][38]	1
	Mesh shrinkage[37]	1
	Total complications rates[53]	1
	Unclear[30],[33],[35-36],[39-48],[50],[55]	16
-Risk of Bias: Cochrane Collaboration's tool	High risk of bias[28-50],[52-58]	30
	Low risk of bias[51]	1

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



Risk of bias and study design

Thirty RCTs were assessed as at high risk of bias with just one[51] considered at low risk. Figure 2 shows that this high level of bias is mostly due to the failed blinding of trial participants, personnel (surgeons) and outpatient assessors. Only two trials[32],[51] achieved blinding for both these criteria.

Hernia morphology

Twenty-three of 30 (76.6%) RCTs used hernia dimensions as an inclusion criteria and one RCT[28] divided hernias into simple and complex categories using a 10cm defect width cutpoint. Seven trials had no selection criteria that used hernia dimension. The exact nature of dimension inclusion criteria varied across trials, ranging from hernias with a width of less than 4cm[39], to hernias with a width of greater than 10cm[28,46]. Fourteen trials (45.2%) recorded the average defect surface area, which ranged from 3.4cm^2 to 141.2cm^2, with a mean of 43.1cm^2. Eleven trials (35.5%) recorded the average or median hernia width within each comparison group, which ranged from 3.6cm to 17cm with a mean of 7.5cm. None of the RCTs reported loss of domain or used loss of domain for patient selection (Table 2.).

As anticipated, no RCT recorded either VHWG grade or CDC wound classification of included hernias. Indeed, no RCT used a VH grading scale of any description. Six trials (19.3%) included primary VHs only, 14 trials (45.2%) included incisional hernias only, and 11 trials (35.5%) included both primary and incisional hernias. Ten of these 11 trials, including both primary and incisional VHs, reported the proportion of primary to incisional hernias, with a mean of 32 primary to 41 incisional hernias (range 31:7[58] to 18:65[57]). Seven of the 25 trials (28%) analysing incisional hernias included the ratio of primary incisional hernias to recurrent incisional hernias (mean of 84.1 primary to 28.3 incisional hernias, range 160:3[49] to 24:30[28]). Only two trials [30,47] reported the number of patients with previous ventral wound infection.

Table 2. Summarising the hernia morphology data reported.

Hernia dimension	*No. of RCTs reporting variable*
Average hernia defect surface area	14[30-31],[35],[37-38],[41],[43],[50],[52-57]
Average hernia defect width	11[28,29],[32-34],[38],[40],[44],[49-50],[52]
Loss of Domain	0

Pre-operative patient characteristics and co-morbidities

Table 3 summarises the patient characteristics and comorbidities reported.
The pre-operative patient characteristics and comorbidities reported differed between trials. While many reported basic patient demographics of age, gender and BMI, few went beyond this to report patient comorbidities, including smoking status, diabetic status and steroid use.

Table 3. Preoperative patient characteristics and comorbidities reported.

Patient characteristic/comorbidities	*No. of RCTs reporting variable*
Age [mean]	30[28-39],[41-58]
Gender [male/female ratio]	29[28-39],[41-50],[52-58]
Obesity [as a ratio >/< 35 or mean [SD]]	23[28-34],[37-38],[41-45],[48-50],[51-53],[55-58]
No. patients ASA 3	10[29],[31],[36-37],[39],[45],[49],[51-53]
COPD	8[28],[34],[38],[43],[45],[51-53]
Smoking status	8[28],[30],[45],[51-53],[56-57]
No. patients with Diabetes	7[34],[38],[44],[51-53],[56]
No. patients ASA 1	7[29],[31],[45],[49],[51-53]
No. patients ASA 2	7[29],[31],[45],[49],[51-53]
SF-36 QoL questionnaire[59]	3[32],[51],[52]
No. patients using steroids	3[28],[51],[53]
No. of arteriopaths [IHD/PVD/CVA]	3[28],[44],[52]
No. patients ASA 4	3[29],[49],[51]
Average ASA score	2[34],[55]
Liver cirrhosis / Childs-Pugh A	1[44]
SF-12 QoL questionnaire[59]	1[56]

Intra-operative variables

Table 4 shows that intraoperative variables were reported with increased frequency compared to pre-operative variables and patient comorbidities. Mode of surgery, type of mesh implanted (prosthetic, composite, biosynthetic or biologic) and anatomical layer were recorded in all 31 RCTs. Operation duration, intra-operative blood loss and the experience of the principal operating surgeon were all reported less frequently.

Table 4. Intra-operative variables reported.

Intra-operative variable	**No. of RCTs reporting variable**
Mode of Surgery [laparoscopic/open]	31[28-58]
Category of mesh used	31[28-58]
Anatomical layer of mesh placement	31[28-58]
Duration of operation	27[28-31],[33-45],[48-50],[52-58]

Experience of the principal surgeon	14[29],[31],[33-34],[36],[46-47],[49],[52-55],[57-58]
Intra-operative blood loss	3[29],[33],[43]

Clinical outcomes

Sixty-four different clinical outcomes were reported overall, with little consistency between trials, even when reporting similar intervention groups and primary outcomes. Indeed, 16 (51.6%) RCTs stated no primary outcome explicitly (Table 1). Of the 15 RCTs (48.4%) stating a primary outcome; 4[28,49,54,56] used hernia recurrence and 4[32,34,51,52] employed quality of life. Three trials[32],[51,52] used the SF-36 questionnaire[59] and 1 trial[34] used the EQ-5D questionnaire[60]. Four trials[29,31,57,58] used pain as their primary outcome, assessed via visual analogue scales (VASs). One trial stated both pain and recurrence as two separate primary outcomes, with no statistical accounting for co-primary outcomes[38]. The remaining two trials used mesh shrinkage[37] or standardised complication rates[53] as their primary outcomes respectively. Multiple different primary outcomes led to many different clinical and patient reported outcomes (as shown in online resource 2).

Length of follow-up was reported in all studies and averaged 24.5 months (range 1 month to 64 months). Fifteen of 31 (48%) trials had follow-up of at least 24 months. One trial[52] did not report hernia recurrence rate. Of the 30 trials reporting hernia recurrence, 1 RCT[36] reported recurrence at 5 years post repair, 4 RCTs[29-30],[41],[56] reported recurrence at 3 years, 15 RCTs at 2 years, 13 RCTs at 1 year, 5 RCTs[37],[41],[43],[50-51] at 6 months and 1 RCT[34] at 3 months. Six (20%) of 30 RCTs defined recurrence: definitions are shown in table 5. Only three trials used the same definition. Eight (29%) of 30 trials did not specify the method used to detect recurrence. Twelve trials (43%) used clinical examination alone to detect recurrence. Ten (33%) trials used imaging if recurrence was in doubt, or to confirm a recurrence suspected clinically. Five (50%) of these 10 trials[29,31,33,43,57] used either CT or USS to detect recurrence, 3 (30%) trials[30,42,58] used USS alone and 2 (20%) trials[38,46] used CT alone. Recurrence rates increased when imaging was used. Trials using clinical examination had a 4% median recurrence rate whereas trials using USS or CT, USS alone, or CT alone had median recurrence rates of 7%, 9% and 7% respectively. Trials that did not specify test methods for recurrence had a mean re-herniation rate of 7%. The method used to detect hernia recurrence did not depend on the size or type of hernia included in the trial (as shown in online resource 3). Patient reported outcomes used the SF-36[59], SF-12[59], EQ-5D[60], and GIQL[62] questionnaires as well as VASs, to assess pain and overall health status. These were also carried out at varying time intervals. The Calvien-Dindo[61] scale for post-operative complications was used in 9 of the trials to classify complication severity.

Table 5. Six definitions of hernia recurrence encountered in the systematic review.

Reference:	Definition
Arroyo et al.[36] (2001)	'the presence of a defect on the central part of the midline aponeurosis around the umbilicus, where the operation had been performed

	previously.'
Bensaadi et al.[56] (2014) Lal et al.[40] (2012)	'a defect of the midline aponeurosis around the umbilicus at the site where the operation was performed.' 'the presence of a defect on the central part of the midline aponeurosis where the operation had been performed previously.'
Luijendijk et al.[30] (2000)	'any fascial defect that was palable or detected by ultrasound examination and was located within 7cm of the site of hernia repair.'
Pring et al.[54] (2008)	'a clinically detectable defect, associated with the protrusion of viscera on straining'.
Muysoms et al.[57] (2013)	'Patients were considered free from recurrence if at clinical examination, no hernia was felt in an upright position during valsalva manoeuver.'

Discussion

This systematic review has analysed the reported perioperative variables and postoperative outcomes from randomised controlled trials of elective VH repair, performed over the last twenty years. Important findings include the general absence of: a standardised pre-operative patient variable dataset; a universally accepted definition of recurrence; standardised test methods to detect recurrence; standardised assessment times for the key primary and secondary outcomes, and standardised evaluation tools for post-operative pain and quality of life. This lack of standardisation limits the validity of trial comparisons made by meta-analyses and comparison of trials by practicing surgeons. Our review provides evidence-based justification for urgent investment in a core perioperative and clinical outcome dataset applicable to trials of VH surgery. This should be developed and validated with key stakeholders to improve the quality of outcome reporting in this rapidly developing field. A group such as COMET needs identification and encouragement to help develop and endorse this work[63].

As VH research evolves, academics are searching increasingly for outcome predictors. Potentially reliable predictors can be identified from the primary literature only when they are reported. Our review has found that randomised controlled trials are focusing on surgical technique and failing to report variables that would normally be regarded as important predictors. For example, many pre-operative patient comorbidities and, in particular, measures of hernia morphology (e.g. hernia width and area) were omitted from most reports. Loss of domain was not reported by any trial. Because current evidence is contradictory, with some studies suggesting that hernia width does correlate with recurrence[64] whereas others do not[65,66], future trials need to report apparently important predictors to facilitate subsequent analysis. Investigators should also grade hernias using appropriate scales, for example the VHWG scale[17] and the CDC wound classification scale[27] as these scales themselves may prove to be outcome predictors. Our review demonstrates that a trial dataset with multiple pre-operative patient variables (diabetes, COPD, BMI, hernia grade etc), including pre-operative CT scan dimensions (hernia defect area, hernia width, loss of domain etc) and intra-operative variables (operation

time, anatomical plane of mesh insertion, reconstructive technique etc) is required.

While 8 of the 30 trials (26.7%) reporting hernia recurrence didn't even define how recurrence was detected, the remaining trials used differing recurrence detection methods ranging from undefined clinical examination to undefined imaging methods. This introduces bias depending on the differing examination and imaging methods used. There was much variation in the timing of assessment for hernia recurrence. This observed lack of consensus regarding assessment timing, test methods for recurrence, and definitions of recurrence limits data availability and consistency, and impairs meta-analysis. To achieve standardisation a clear definition of VH recurrence is required. Imaging is likely the most precise method with which to determine recurrence, but a radiological definition of recurrence is required that incorporates measures of clinically important and unimportant reherniation. Currently, there is considerable variability in recurrence reporting for CT scans[67]. Our review suggests that the use of imaging does increase reported recurrence rates, which would be anticipated since subclinical recurrences will be identified.

RCT dataset designers should also consult the recommendations made by Muysoms et al. following a consensus meeting in Palmero, Italy in 2012[68]. This work gives detailed advice on how to carry out statistically sound research (interventional studies, observational studies, systematic review, and meta-analysis) in abdominal wall repair. Of particular relevance, this article advises using the EuraHS definition for hernia recurrence[69]; "*a protrusion of the contents of the abdominal cavity or preperitoneal fat through a defect in the abdominal wall at the site of a previous repair of an abdominal wall hernia*", which we support, although (as stated above) a future definition of recurrence that includes radiological detection maybe more accurate but requires development. Muysoms et al. recommend using the EHS hernias classifications scales and measuring post-operative complications using the Clavien-Dindo classification system but do not define or list any other peri-operative or post-operative outcome variables that sound be measured. Importantly, they do allow for variability in the method used for recurrence detection and the time to outpatient assessment, which we feel this should be standardised, especially in RCTs. To standardise trial outcomes, a dataset with clear definitions and follow up assessment times is warranted.

A standardised dataset should include tools to assess chronic pain and quality of life (QoL). When comparing different surgical techniques, chronic pain and QoL are important patient-centred endpoints, as patients frequently place more emphasis on these outcomes than the operative surgeon. In this review, simple visual analogue scales were used commonly to assess pain. However, these analogue scales, and the timings of assessment were not standardised. A future dataset must standardise pain assessment. QoL was measured using many different questionnaires (SF-36[59], SF-12[59], EuroQoL[60] and GIQL[62]). These questionnaires are commonly used and they allow for health economic analysis across different disease states. However, they are not disease specific, and may miss important patient reported outcomes specific to hernia surgery.

Due to the unique set of complications arising from VH surgery, the importance of chronic pain and QoL, a hernia-specific patient reported outcome assessment tool, such as the Carolinas Comfort Scale[70] or the EuraHS-QoL questionnaire[69], should be used.

When constructing a VH perioperative variable and postoperative outcome dataset for randomised control trials, workers should also consult the VH databases currently being used in America[71], Europe[69], Denmark[72] and Spain[73]. These databases collect data prospectively from large cohorts of patients and will generate sizeable observational studies. These databases have been constructed by VH experts with multiple peri-operative and post-operative data-points, many of which should be included in an RCT dataset.

As well as focusing on standardised definitions and datasets, academic surgeons carrying out RCTs should make concerted efforts to reduce trial bias. Thirty of the 31 included trials were assessed as at high risk of bias. Many of the included trials performed poorly in 3 out of the 7 domains of the Cochrane Collaboration's tool for risk of bias[26]. Many trials failed to specify how participant group allocation was concealed, failed to blind participant and surgeon from the allocated treatment, and there was no blinding in the outpatient assessment clinic. Traditionally, surgical trials are usually at high risk of bias due to the impossibility of blinding the primary surgeon. However, if visible skin changes to the participant do not differ between the treatment groups [e.g. open VH repair with onlay vs. sublay mesh], it is possible to blind both the participant and an independent assessor. In addition, concealment of treatment allocation should follow the standards set by the Cochrane Collaboration. In surgery, the allocated treatment should only be revealed to an independent surgeon after the participant is under general anaesthetic and after the participant has been consented to take part in the trial and both possible treatments.

Further bias can arise in RCTs due to commercial funding and readers should be aware of this. We accept there are difficulties in achieving non-commercial funding for RCTs in hernia research and that without proper funding scrupulous methodology can be challenging due to the high work load. Eight out of 31 one of the trials received commercial funding[31,32],[37],[51],[54],[56–58], one trial received non-commercial funding[53] and one trial received both commercial and non-commercial funding[52]. In the remaining 21 trials the funding method was not specified. The practical difficulty of obtaining non-commercial funding can only be addressed by researchers, who whilst applying for funding must clearly explain the technical difficulties faced by reconstructive surgeons and the high prevalence of morbidity suffered by patients after hernia repair; namely chronic pain and recurrence. If researchers face difficulties with funding or carryout research with commercial funding, little can be done apart from carrying out research to highest possible standards. We note that any data is better than no data, as supported by Lilford et al[74].

Conclusion

So far systematic reviews of elective VH RCTs have focused on comparing the outcomes of open versus laparoscopic VH repair[75],[76],[77]. This review is the first to assesses the methodology of VH RCTs. The results show that the perioperative variables and postoperative outcomes reported by RCTs of VH repair lack definition and consistency. To solve this, a defined minimum dataset of variables and outcomes is required. Since operative success is determined by the presence or absence of hernia recurrence, recurrence is therefore the prime outcome and requires standard clinical and radiological definitions, together with a minimum period of follow-up. For a clinical definition, we recommend using the European definition for hernia recurrence[69], and that a radiological definition requires development. Such measures will standardise and therefore improve outcome reporting in this rapidly expanding and important field, increasing data homogeneity and the value of subsequent meta-analysis.

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A Systematic Methodological Review of Reported Perioperative Variables, Postoperative Outcomes and Hernia Recurrence from Randomised Controlled Trials of Elective VH Repair: Clear Definitions and Standardised Datasets are needed.

Abstract

Background This systematic review assesses the perioperative variables and post-operative outcomes reported by randomised controlled trials (RCTs) of VH repair. This review focuses particularly on definitions of hernia recurrence and techniques used for detection.

Objective Our aim is to identify and quantify the inconsistencies in perioperative variable and postoperative outcome reporting, so as to justify future development of clear definitions of hernia recurrence and a standardised dataset of such variables.

Methods The PubMed database was searched for elective VH repair RCTs reported January 1995 to March 2016 inclusive. Three independent reviewers performed article screening, and two reviewers independently extracted data. Hernia recurrence, recurrence rate, timing and definitions of recurrence, and techniques used to detect recurrence were extracted. We also assessed reported post-operative complications, standardised operative outcomes, patient reported outcomes, pre-operative CT scan hernia dimensions, intra-operative variables, patient co-morbidity, and hernia morphology.

Results 31 RCTs (3367 patients) were identified. Only 6 (19.3%) defined hernia recurrence and methods to detect recurrence were inconsistent. Sixty-four different clinical outcomes were reported across the RCTs, with wound infection (30 trials, 96.7%), hernia recurrence (30, 96.7%), seroma (29, 93.5%), length of hospital stay (22, 71%) and haematoma (21, 67.7%) reported most frequently. Fourteen (45%), 11 (35%) and 0 trials reported CT measurements of hernia defect area, width and loss of domain respectively. No trial graded hernias using generally accepted scales.

Conclusion VH RCTs report peri- and post-operative variables inconsistently, and with poor definitions. A standardised minimum dataset, including definitions of recurrence, is required.

Background

In an ageing population[1] with an increasing prevalence of both obesity[2] and abdominal surgery, the incidence of ventral hernia (VH) is increasing[3,4]. The projected number of VH repairs performed in 2016 in the United States approaches 400,000[3]. Recurrence rates after repair are high, reaching 10 to 40%[5],[6]. Incidence of large complex VH is also increasing and significant loss of domain coupled with comorbidity means these patients present the sternest surgical challenge[7]. Despite innovation[8–10] there is no consensus regarding optimal reconstructive techniques[11,12].

Currently, the VH literature consists primarily of case series and large observational studies. This level 4 evidence[13] suggests the cause of postoperative complications and hernia recurrence are complex and multifactorial. To date, research has focussed largely on surgical technique[12],[14] and patient co-morbidity[15,16] with limited focus on hernia morphology. Although several hernia grading scales have been produced[17–21], in an attempt to predict post-operative outcomes, few have been externally validated and, if so, with limited success[22–24]. Comparative trials and observational studies seldom define hernia recurrence and if they do, many use different definitions for recurrence as well as a variety of techniques to detect recurrence. Standardised definitions and validated datasets for VH repair studies would make reported data consistent, allowing for greater accuracy of trial comparison and meta-analysis.

In this systematic review, we analysed randomised controlled trials (RCTs) of adult patients undergoing elective VH repair. All VH repair RCTs were included irrespective of the intervention and comparator groups. We analysed all perioperative variables and post-operative outcomes reported, paying particular attention to the different methods used to detect and define hernia recurrence. Our objective was to demonstrate the inconsistencies in variable and outcome reporting by RCTs and the necessity for standardised trial datasets as well as clear definitions of hernia recurrence and recurrence detection methods.

~~Currently, rigorous level 1 research is relatively lacking. We anticipated that RCTs of VH repair use a variety of comparison groups, report different preoperative and intraoperative variables, and study multiple clinical outcomes. Consequently, we hypothesised that the published RCTs' report highly heterogeneous data. Our objective was to investigate this hypothesis by systematic review, paying particular attention to the definitions and methods used to report hernia recurrence.~~

Commented [SP1]: PICOS added

Methods

Reporting and Registration

This systematic review was reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[25]. Ethical permission is not required by our centre for systematic reviews of available

primary literature. A protocol was developed and registered with PROSPERO, the international prospective register of systematic reviews (CRD42016043071).

Inclusion and exclusion criteria

Inclusion criteria for studies

We aimed to identify RCTs that described clinical outcomes in patients following VH repair between 1st January 1995 and 31st March 2016 inclusive. We excluded trials with less than 10 patients in an individual study arm since such data are likely to be weak. Only RCTs written in English were included.

Target condition

The target condition was surgical VH repair. All different VH morphologies were eligible as were all VH working group (VHWG) grades[17]. Studies describing femoral and/or inguinal hernias (i.e. groin hernia) were excluded. Emergency VH repair was excluded as was primary closure after damage control laparotomy. However, patients having elective VH repair after primary closure from damage control laparotomy were eligible as were RCTs of elective VH repair with bridging repair (i.e. failure to establish primary fascial closure). RCTs of parastomal hernia repairs were excluded. Trials with concomitant bowel resection were included (since this is often intended) and as long as the primary objective of surgical repair was VH repair. We excluded trials with either concomitant tumour removal or bariatric surgery.

Participants

Adult participants having a surgical VH repair. We excluded paediatric studies (defined as 18 years or less) since these are not representative of 'typical' CVH patients.

Follow up

We stipulated no minimum length of follow-up.

Comparison

There was no restriction placed on any study arm comparator (e.g. operative technique, mesh type, position of mesh).

Search strategy and string

A surgical research fellow, SGP, searched the PubMed database from 1st January 1995 to 31st March 2016 inclusive limiting the search using the following terms: "adult 19+", "human studies" and to those written in English. Our search string identified and combined the two following criteria to identify relevant articles:

- To identify studies of VH disease including complex disease we used the MESH terms “hernia”, “abdominal hernia”, “umbilical hernia” and “VH” were used. These were combined with keywords: “abdominal wall reconstruction”; “herniorrhaphy”; “ventral defect” and “entero-cutaneous fistula”.
- To identify studies of surgical techniques used for VH repair we used the MESH terms: “general surgery”; “reconstructive surgical procedures” and “surgical mesh”. This was combined with keywords: “pneumoperitoneum”, “botox”, “botulinium”, “two-stage”, “two step”, “staged repair”, “component separation”, “transversus abdominis”, “retro-rectus”, “bridging”, “bridge repair”, “silo”, “open” and “laparoscopic”.

Our complete search string is shown in online resource 1.

Citation management and screening

SGP stored identified citations in an Excel spreadsheet (Microsoft Excel for Mac 2011 Version 14.5.9, Microsoft Corporation, Washington, USA), up-loading these subsequently into a reference manager able to access online original articles directly (Mendeley Desktop Version 1.17 for Windows XP and Mac OS X, London, UK). After the search filters were applied and duplicates were excluded, the citations were divided into two equal groups. The titles of the first-half of the citations were screened by SGP and the second-half by CW. The researchers screened for comparative studies of VH disease. They discarded articles that were ‘clearly unsuitable’ for the review (e.g. subject not VH) and retained any regarded as ‘uncertain’ or ‘definitely possible’. These two latter groups were combined and researchers, SGP, CW and RB, then independently screened the titles and abstracts of the ‘uncertain’ and ‘definitely possible’ results with the aim of identifying all comparative studies. Any discrepancies were settled by face-to-face discussion amongst the three researchers. A third hand search of the full text by SGP, CW and RB, then divided the selected comparative studies into respective methodological designs; case-control studies, cohort studies and RCTs. Any article where uncertainty persisted was discussed with senior members, AW and SH, face-to-face. An exclusion log was kept at all stages. The PRISMA diagram (fig 1.) shows the flow of article selection.

Data extraction

SGP and JB extracted data independently from all RCTs selected for the review, which were cross-checked subsequently face-to-face. Data were entered by the researchers into an Excel datasheet and categorised into broad groups as follows: study design; hernia morphology; pre-operative patient factors including comorbidities; intraoperative variables and clinical outcomes, including complication rates and hernia recurrence.

Study demographics and risk of bias

Information extracted for RCT study design included: the study setting (multi-centre vs. single centre), the country of publication, the date of publication and the number of patients in each study arm. Researchers, SGP and JB, used the

Cochrane Collaboration's tool to assess the risk of bias[26]. Any differences in opinion were discussed face-to-face and settled by discussion with senior authors if required.

Hernia morphology

For hernia morphology, we intended to record dimensions of the hernia defect, including area, loss of domain, the ventral hernia working group (VHWG) grade[17] and the CDC wound classification[27]. We recorded whether the study included patients with either primary or incisional VHs, or both, and if so the proportion of these two hernia types. However, we anticipated that many trials would not report these details of hernia morphology and grade, and recorded when these items were not reported. Similarly, we recorded the number of previous attempts at hernia repair where documented. We noted prior surgical site infection in patients undergoing repair since this is known to predispose to subsequent recurrence[15].

Pre-operative patient characteristics and co-morbidities

Baseline patient characteristics extracted were mean patient age and the proportion of male to females. Comorbidity data included the mean and standard deviation of body mass index (BMI), the proportion of patients with chronic obstructive pulmonary disease (COPD), diabetes, steroid use, and the proportion of each American Society of Anaesthesiologists (ASA) grade (and mean ASA grade) in each study group. Proportion by smoking status, arteriopath status (previous diagnosis of ischaemic heart disease (IHD), peripheral vascular disease (PVD), cerebrovascular accidents (CVAs)) and a diagnosis of benign prostatic hypertrophy (BPH) were also noted.

Intra-operative variables

We recorded the mode of surgery used (e.g. laparoscopic or open), the type of mesh where used, the anatomical layer within the abdominal wall into which the mesh was implanted (i.e. intraperitoneal, pre-peritoneal, retro-rectus, inlay or onlay), operative duration, intra-operative blood loss, and the experience of the principal surgeon where documented.

Reported Clinical Outcomes

Hernia recurrence

Our outcomes of primary interest were; hernia recurrence, the post-operative recurrence rates, the timing of recurrence, the definitions for VH recurrence used, and the test method(s) used to diagnose recurrence (for example clinical examination, CT scan, US scan) were recorded. These data were analysed to investigate whether the method used to detect recurrence influenced recurrence rate. As we were aware of no generally accepted imaging definition of VH recurrence, we anticipated considerable inter-observer variability for reporting recurrence.

We did not pre-specify the definition of post-operative hernia recurrence. We did not restrict by timing of recurrence, the definitions for VH recurrence used, or the test method(s) used to diagnose recurrence.

Secondary outcomes

Post-operative complications

All post-operative complications described were recorded. Complications were grouped into intraoperative, early postoperative, late post-operative, and general or standardised outcomes. Early postoperative complications were sub-grouped into local wound complications (wound infection, seroma formation, wound dehiscence, skin necrosis) and systemic complications (hospital acquired pneumonia, myocardial infarction, pulmonary embolism). Early post-operative complications were defined as those occurring within 30 days of surgery and late post-operative complications as those occurring thereafter. Late complications were extracted for the timespan presented in the paper.

Standardised outcomes

Where reported, we recorded all standardised post-operative outcome measures used. We anticipated that RCTs would use a variety of outcome measures such as length of hospital stay, 30-day re-operation rate and 30-day re-admission rate. If trial complications were measured using a standardised post-operative complication scale, the value was recorded.

Patient reported outcome measures

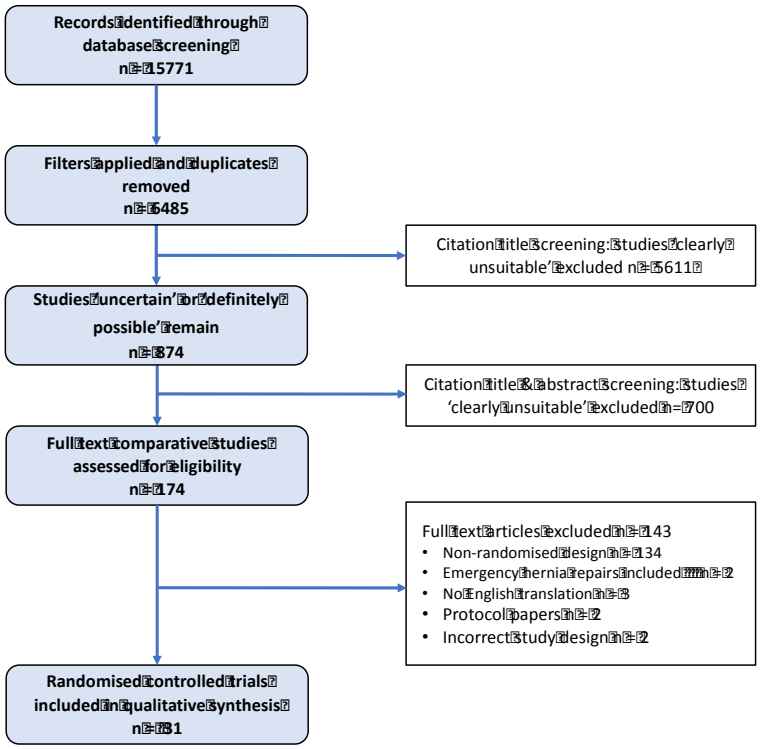
We foresaw that some trials may use standardised patient reported outcome measures (PROMs) to measure operative success. These may include visual analogue scales for pain or overall health status. They may also report the time to first bowel movement or the time taken to return to normal activities. All such outcomes were recorded, along with the timing of the assessment.

Results

Search results

Our initial search retrieved 15771 results (fig 1.). After applying search filters [studies published between 1st January 1995 to 31st March 2016, human trials only, participants aged ≥19, studies written in English], we excluded 9286 studies, resulting in 6485 papers for our initial review. After screening the citation titles, we ultimately categorised 874 studies as 'definitely possible' or 'uncertain'. This fell to 174 comparative studies after title and abstract screening. The full text of all 174 articles was assessed for details of study methodology. This identified 31 RCTs included in the present systematic review.

Figure 1. PRISMA diagram showing selection of RCTs for this review



Study demographics

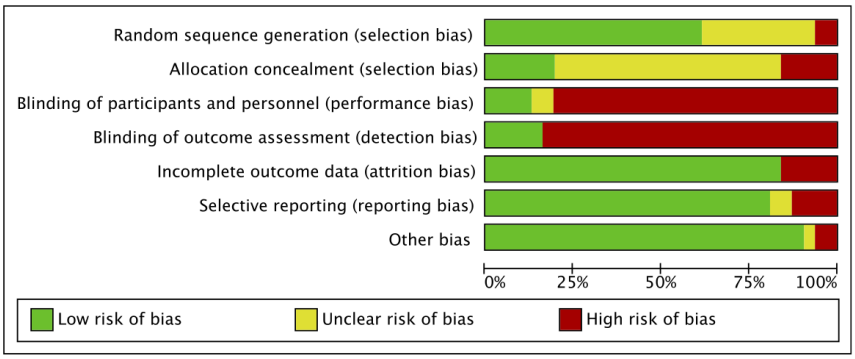
Study demographics and design characteristics are shown in Table 1. The 31 RCTs included 3,367 patients with a mean of 109 patients, range 24 to 337. One study[28] appears twice since it divided patients into simple and complex hernia groups, creating two individual trials (suture vs mesh repair and prosthetic mesh vs auto-dermal graft repair). Five RCTs were carried out in both the Netherlands[29–33] and Spain[34–38]. Thirteen RCTs were multi-centre and 18 were single centre. Over the past 20 years the number of RCTs performed increased, with 8 published between 1995 to 2005 versus 23 published from 2005 to 2016. There were 3 groups where RCTs compared the same

interventions: Eleven studies compared laparoscopic versus open repair; 5 studies[28,30,36,39,40] compared suture versus mesh repair and 3 studies[37,41,42] compared tack versus suture mesh fixation in laparoscopic VH repair.

Table 1. Demographic and characteristics of the 31 RCTs included in the Systematic Review.

Included Studies - Demographics		
Characteristic	**Subgroup**	**No. of RCTs**
-Country of Publication	Netherlands[29–33] Spain[34–38]	5
	India[41–43] Eygpt[44–46]	3
	Pakistan[40],[47] Turkey[39],[48] Italy[49,50]Germany [28],[51]	2
	Sweden[52] USA[53] Australia(54) Lithuania[55] France[56] Belgium[57] Denmark[58]	1
-Multi vs Single-centre	Multi centre[28-30],[32-34],[40],[49],[51-53],[57-58]	13
	Single centre[31],[35-39],[41-46],[48-50],[54-56]	18
-Year of Publication	1995-2005[28],[30],[32],[35-36],[39],[46]	7
	2006-2016[29],[31],[33-34],[37-38],[40-45],[47-58]	24
Included Studies		
Characteristic	**Subgroup**	**No. of RCTs**
-Trial Groups	Laparoscopic vs. Open[29],[34-35],[43],[47-50],[52-54]	11
	Open mesh vs. suture[28],[30],[36],[39-40]	5
	Laparoscopic mesh fixation; Tacks vs. Sutures[31],[37],[41-42]	3
	• Open VH repair:	
	Onlay vs. Sublay[44],[55]	2
	Light weight vs. Heavy weight mesh[32]	1
	Medium weight vs. Medium weight mesh[51]	1
	*Autograft vs. Prosthetic mesh**[28*]	1
	Component separation vs. Prosthetic mesh[33]	1
	Onlay vs. Underlay[45]	1
	Intraperitoneal vs. Onlay [bridging][46]	1
	Ventralex patch vs Biomesh composite mesh[56]	1
	• Laparoscopic VH repair:	
	Double crown tack vs. suture and tack mesh fixation[31],[57]	2
	Double crown tack vs. fibrin sealant mesh fixation[58]	1
	Light weight mesh vs. Medium weight mesh[38]	1
	Total	32*
	*Large hernias from Korenkov et al. (a suture vs. mesh RCT) were analysed as a separate category. This makes this total 32 rather than 31.	
-Hernia type	Primary hernias only[36],[39-40],[44-45],[47]	6
	Incisional hernias only[28-30],[32-34],[38],[46],[49-53],[55]	14
	Primary and incisional hernias[31],[35],[37],[41-43],[48],[54],[56-58]	11
-Primary outcomes	Hernia recurrence[28],[49],[54],[56]	4
	Quality of life/ Health questionnaires[32],[34],[51-52]	4
	Pain [measured using visual analogue scores][29],[31],[57],[58]	4
	Pain and hernia recurrence [two primary outcomes][38]	1
	Mesh shrinkage[37]	1
	Total complications rates[53]	1
	Unclear[30],[33],[35-36],[39-48],[50],[55]	16
-Risk of Bias: Cochrane Collaboration's tool	High risk of bias[28-50],[52-58]	30
	Low risk of bias[51]	1

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



Risk of bias and study design

Thirty RCTs were assessed as at high risk of bias with just one[51] considered at low risk. Figure 2 shows that this high level of bias is mostly due to the failed blinding of trial participants, personnel (surgeons) and outpatient assessors. Only two trials[32],[51] achieved blinding for both these criteria.

Hernia morphology

Twenty-three of 30 (76.6%) RCTs used hernia dimensions as an inclusion criteria and one RCT[28] divided hernias into simple and complex categories using a 10cm defect width cutpoint. Seven trials had no selection criteria that used hernia dimension. The exact nature of dimension inclusion criteria varied across trials, ranging from hernias with a width of less than 4cm[39], to hernias with a width of greater than 10cm[28,46]. Fourteen trials (45.2%) recorded the average defect surface area, which ranged from 3.4cm^2 to 141.2cm^2, with a mean of 43.1cm^2. Eleven trials (35.5%) recorded the average or median hernia width within each comparison group, which ranged from 3.6cm to 17cm with a mean of 7.5cm. None of the RCTs reported loss of domain or used loss of domain for patient selection (Table 2.).

As anticipated, no RCT recorded either VHWG grade or CDC wound classification of included hernias. Indeed, no RCT used a VH grading scale of any description. Six trials (19.3%) included primary VHs only, 14 trials (45.2%) included incisional hernias only, and 11 trials (35.5%) included both primary and incisional hernias. Ten of these 11 trials, including both primary and incisional VHs, reported the proportion of primary to incisional hernias, with a mean of 32 primary to 41 incisional hernias (range 31:7[58] to 18:65[57]). Seven of the 25 trials (28%) analysing incisional hernias included the ratio of primary incisional hernias to recurrent incisional hernias (mean of 84.1 primary to 28.3 incisional hernias, range 160:3[49] to 24:30[28]). Only two trials [30,47] reported the number of patients with previous ventral wound infection.

Table 2. Summarising the hernia morphology data reported.

Hernia dimension	*No. of RCTs reporting variable*
Average hernia defect surface area	14[30-31],[35],[37-38],[41],[43],[50],[52-57]
Average hernia defect width	11[28,29],[32-34],[38],[40],[44],[49-50],[52]
Loss of Domain	0

Pre-operative patient characteristics and co-morbidities

Table 3 summarises the patient characteristics and comorbidities reported.
The pre-operative patient characteristics and comorbidities reported differed between trials. While many reported basic patient demographics of age, gender and BMI, few went beyond this to report patient comorbidities, including smoking status, diabetic status and steroid use.

Table 3. Preoperative patient characteristics and comorbidities reported.

Patient characteristic/comorbidities	*No. of RCTs reporting variable*
Age [mean]	30[28-39],[41-58]
Gender [male/female ratio]	29[28-39],[41-50],[52-58]
Obesity [as a ratio >/< 35 or mean [SD]]	23[28-34],[37-38],[41-45],[48-50],[51-53],[55-58]
No. patients ASA 3	10[29],[31],[36-37],[39],[45],[49],[51-53]
COPD	8[28],[34],[38],[43],[45],[51-53]
Smoking status	8[28],[30],[45],[51-53],[56-57]
No. patients with Diabetes	7[34],[38],[44],[51-53],[56]
No. patients ASA 1	7[29],[31],[45],[49],[51-53]
No. patients ASA 2	7[29],[31],[45],[49],[51-53]
SF-36 QoL questionnaire[59]	3[32],[51],[52]
No. patients using steroids	3[28],[51],[53]
No. of arteriopaths [IHD/PVD/CVA]	3[28],[44],[52]
No. patients ASA 4	3[29],[49],[51]
Average ASA score	2[34],[55]
Liver cirrhosis / Childs-Pugh A	1[44]
SF-12 QoL questionnaire[59]	1[56]

Intra-operative variables

Table 4 shows that intraoperative variables were reported with increased frequency compared to pre-operative variables and patient comorbidities. Mode of surgery, type of mesh implanted (prosthetic, composite, biosynthetic or biologic) and anatomical layer were recorded in all 31 RCTs. Operation duration, intra-operative blood loss and the experience of the principal operating surgeon were all reported less frequently.

Table 4. Intra-operative variables reported.

Intra-operative variable	**No. of RCTs reporting variable**
Mode of Surgery [laparoscopic/open]	31[28-58]
Category of mesh used	31[28-58]
Anatomical layer of mesh placement	31[28-58]
Duration of operation	27[28-31],[33-45],[48-50],[52-58]

Experience of the principal surgeon	14[29],[31],[33-34],[36],[46-47],[49],[52-55],[57-58]
Intra-operative blood loss	3[29],[33],[43]

Clinical outcomes

Sixty-four different clinical outcomes were reported overall, with little consistency between trials, even when reporting similar intervention groups and primary outcomes. Indeed, 16 (51.6%) RCTs stated no primary outcome explicitly (Table 1). Of the 15 RCTs (48.4%) stating a primary outcome; 4[28,49,54,56] used hernia recurrence and 4[32,34,51,52] employed quality of life. Three trials[32],[51,52] used the SF-36 questionnaire[59] and 1 trial[34] used the EQ-5D questionnaire[60]. Four trials[29,31,57,58] used pain as their primary outcome, assessed via visual analogue scales (VASs). One trial stated both pain and recurrence as two separate primary outcomes, with no statistical accounting for co-primary outcomes[38]. The remaining two trials used mesh shrinkage[37] or standardised complication rates[53] as their primary outcomes respectively. Multiple different primary outcomes led to many different clinical and patient reported outcomes (as shown in online resource 2).

Length of follow-up was reported in all studies and averaged 24.5 months (range 1 month to 64 months). Fifteen of 31 (48%) trials had follow-up of at least 24 months. One trial[52] did not report hernia recurrence rate. Of the 30 trials reporting hernia recurrence, 1 RCT[36] reported recurrence at 5 years post repair, 4 RCTs[29-30],[41],[56] reported recurrence at 3 years, 15 RCTs at 2 years, 13 RCTs at 1 year, 5 RCTs[37],[41],[43],[50-51] at 6 months and 1 RCT[34] at 3 months. Six (20%) of 30 RCTs defined recurrence: definitions are shown in table 5. Only three trials used the same definition. Eight (29%) of 30 trials did not specify the method used to detect recurrence. Twelve trials (43%) used clinical examination alone to detect recurrence. Ten (33%) trials used imaging if recurrence was in doubt, or to confirm a recurrence suspected clinically. Five (50%) of these 10 trials[29,31,33,43,57] used either CT or USS to detect recurrence, 3 (30%) trials[30,42,58] used USS alone and 2 (20%) trials[38,46] used CT alone. Recurrence rates increased when imaging was used. Trials using clinical examination had a 4% median recurrence rate whereas trials using USS or CT, USS alone, or CT alone had median recurrence rates of 7%, 9% and 7% respectively. Trials that did not specify test methods for recurrence had a mean re-herniation rate of 7%. The method used to detect hernia recurrence did not depend on the size or type of hernia included in the trial (as shown in online resource 3). Patient reported outcomes used the SF-36[59], SF-12[59], EQ-5D[60], and GIQL[62] questionnaires as well as VASs, to assess pain and overall health status. These were also carried out at varying time intervals. The Calvien-Dindo[61] scale for post-operative complications was used in 9 of the trials to classify complication severity.

Table 5. Six definitions of hernia recurrence encountered in the systematic review.

Reference:	Definition
Arroyo et al.[36] (2001)	'the presence of a defect on the central part of the midline aponeurosis around the umbilicus, where the operation had been performed

	previously.'
Bensaadi et al.[56] (2014)	'a defect of the midline aponeurosis around the umbilicus at the site where the operation was performed.'
Lal et al.[40] (2012)	'the presence of a defect on the central part of the midline aponeurosis where the operation had been performed previously.'
Luijendijk et al.[30] (2000)	'any fascial defect that was palable or detected by ultrasound examination and was located within 7cm of the site of hernia repair.'
Pring et al.[54] (2008)	'a clinically detectable defect, associated with the protrusion of viscera on straining'.
Muysoms et al.[57] (2013)	'Patients were considered free from recurrence if at clinical examination, no hernia was felt in an upright position during valsalva manoeuver.'

Discussion

This systematic review has analysed the reported perioperative variables and postoperative outcomes from randomised controlled trials of elective VH repair, performed over the last twenty years. Important findings include the general absence of: a standardised pre-operative patient variable dataset; a universally accepted definition of recurrence; standardised test methods to detect recurrence; standardised assessment times for the key primary and secondary outcomes, and standardised evaluation tools for post-operative pain and quality of life. This lack of standardisation limits the validity of trial comparisons made by meta-analyses and comparison of trials by practicing surgeons. Our review provides evidence-based justification for urgent investment in a core perioperative and clinical outcome dataset applicable to trials of VH surgery. This should be developed and validated with key stakeholders to improve the quality of outcome reporting in this rapidly developing field. A group such as COMET needs identification and encouragement to help develop and endorse this work[63].

As VH research evolves, academics are searching increasingly for outcome predictors. Potentially reliable predictors can be identified from the primary literature only when they are reported. Our review has found that randomised controlled trials are focusing on surgical technique and failing to report variables that would normally be regarded as important predictors. For example, many pre-operative patient comorbidities and, in particular, measures of hernia morphology (e.g. hernia width and area) were omitted from most reports. Loss of domain was not reported by any trial. Because current evidence is contradictory, with some studies suggesting that hernia width does correlate with recurrence[64] whereas others do not[65,66], future trials need to report apparently important predictors to facilitate subsequent analysis. Investigators should also grade hernias using appropriate scales, for example the VHWG scale[17] and the CDC wound classification scale[27] as these scales themselves may prove to be outcome predictors. Our review demonstrates that a trial dataset with multiple pre-operative patient variables (diabetes, COPD, BMI, hernia grade etc), including pre-operative CT scan dimensions (hernia defect area, hernia width, loss of domain etc) and intra-operative variables (operation

time, anatomical plane of mesh insertion, reconstructive technique etc) is required.

While 8 of the 30 trials (26.7%) reporting hernia recurrence didn't even define how recurrence was detected, the remaining trials used differing recurrence detection methods ranging from undefined clinical examination to undefined imaging methods. This introduces bias depending on the differing examination and imaging methods used. There was much variation in the timing of assessment for hernia recurrence. This observed lack of consensus regarding assessment timing, test methods for recurrence, and definitions of recurrence limits data availability and consistency, and impairs meta-analysis. To achieve standardisation a clear definition of VH recurrence is required. Imaging is likely the most precise method with which to determine recurrence, but a radiological definition of recurrence is required that incorporates measures of clinically important and unimportant reherniation. Currently, there is considerable variability in recurrence reporting for CT scans[67]. Our review suggests that the use of imaging does increase reported recurrence rates, which would be anticipated since subclinical recurrences will be identified.

RCT dataset designers should also consult the recommendations made by Muysoms et al. following a consensus meeting in Palmero, Italy in 2012[68]. This work gives detailed advice on how to carry out statistically sound research (interventional studies, observational studies, systematic review, and meta-analysis) in abdominal wall repair. Of particular relevance, this article advises using the EuraHS definition for hernia recurrence[69]; "*a protrusion of the contents of the abdominal cavity or preperitoneal fat through a defect in the abdominal wall at the site of a previous repair of an abdominal wall hernia*", which we support, although (as stated above) a future definition of recurrence that includes radiological detection maybe more accurate but requires development. Muysoms et al. recommend using the EHS hernias classifications scales and measuring post-operative complications using the Clavien-Dindo classification system but do not define or list any other peri-operative or post-operative outcome variables that sound be measured. Importantly, they do allow for variability in the method used for recurrence detection and the time to outpatient assessment, which we feel this should be standardised, especially in RCTs. To standardise trial outcomes, a dataset with clear definitions and follow up assessment times is warranted.

A standardised dataset should include tools to assess chronic pain and quality of life (QoL). When comparing different surgical techniques, chronic pain and QoL are important patient-centred endpoints, as patients frequently place more emphasis on these outcomes than the operative surgeon. In this review, simple visual analogue scales were used commonly to assess pain. However, these analogue scales, and the timings of assessment were not standardised. A future dataset must standardise pain assessment. QoL was measured using many different questionnaires (SF-36[59], SF-12[59], EuroQoL[60] and GIQL[62]). These questionnaires are commonly used and they allow for health economic analysis across different disease states. However, they are not disease specific, and may miss important patient reported outcomes specific to hernia surgery.

Due to the unique set of complications arising from VH surgery, the importance of chronic pain and QoL, a hernia-specific patient reported outcome assessment tool, such as the Carolinas Comfort Scale[70] or the EuraHS-QoL questionnaire[69], should be used.

When constructing a VH perioperative variable and postoperative outcome dataset for randomised control trials, workers should also consult the VH databases currently being used in America[71], Europe[69], Denmark[72] and Spain[73]. These databases collect data prospectively from large cohorts of patients and will generate sizeable observational studies. These databases have been constructed by VH experts with multiple peri-operative and post-operative data-points, many of which should be included in an RCT dataset.

As well as focusing on standardised definitions and datasets, academic surgeons carrying out RCTs should make concerted efforts to reduce trial bias. Thirty of the 31 included trials were assessed as at high risk of bias. Many of the included trials performed poorly in 3 out of the 7 domains of the Cochrane Collaboration's tool for risk of bias[26]. Many trials failed to specify how participant group allocation was concealed, failed to blind participant and surgeon from the allocated treatment, and there was no blinding in the outpatient assessment clinic. Traditionally, surgical trials are usually at high risk of bias due to the impossibility of blinding the primary surgeon. However, if visible skin changes to the participant do not differ between the treatment groups [e.g. open VH repair with onlay vs. sublay mesh], it is possible to blind both the participant and an independent assessor. In addition, concealment of treatment allocation should follow the standards set by the Cochrane Collaboration. In surgery, the allocated treatment should only be revealed to an independent surgeon after the participant is under general anaesthetic and after the participant has been consented to take part in the trial and both possible treatments.

Further bias can arise in RCTs due to commercial funding and readers should be aware of this. We accept there are difficulties in achieving non-commercial funding for RCTs in hernia research and that without proper funding scrupulous methodology can be challenging due to the high work load. Eight out of 31 one of the trials received commercial funding[31,32],[37],[51],[54],[56–58], one trial received non-commercial funding[53] and one trial received both commercial and non-commercial funding[52]. In the remaining 21 trials the funding method was not specified. The practical difficulty of obtaining non-commercial funding can only be addressed by researchers, who whilst applying for funding must clearly explain the technical difficulties faced by reconstructive surgeons and the high prevalence of morbidity suffered by patients after hernia repair; namely chronic pain and recurrence. If researchers face difficulties with funding or carryout research with commercial funding, little can be done apart from carrying out research to highest possible standards. We note that any data is better than no data, as supported by Lilford et al[74].

Conclusion

So far systematic reviews of elective VH RCTs have focused on comparing the outcomes of open versus laparoscopic VH repair[75],[76],[77]. This review is the first to assesses the methodology of VH RCTs. The results show that the perioperative variables and postoperative outcomes reported by RCTs of VH repair lack definition and consistency. To solve this, a defined minimum dataset of variables and outcomes is required. Since operative success is determined by the presence or absence of hernia recurrence, recurrence is therefore the prime outcome and requires standard clinical and radiological definitions, together with a minimum period of follow-up. For a clinical definition, we recommend using the European definition for hernia recurrence[69], and that a radiological definition requires development. Such measures will standardise and therefore improve outcome reporting in this rapidly expanding and important field, increasing data homogeneity and the value of subsequent meta-analysis.

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Figure

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Figure 1. PRISMA diagram showing selection of RCTs for this review

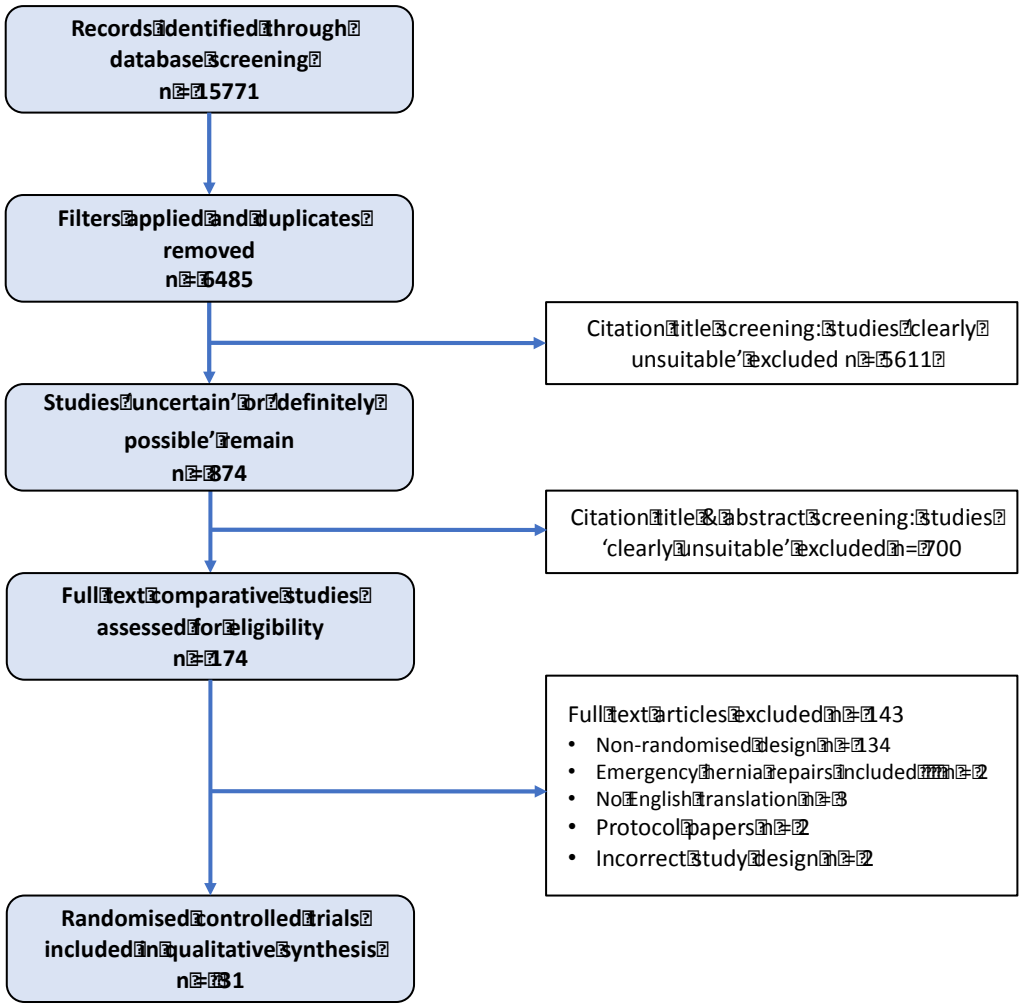

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

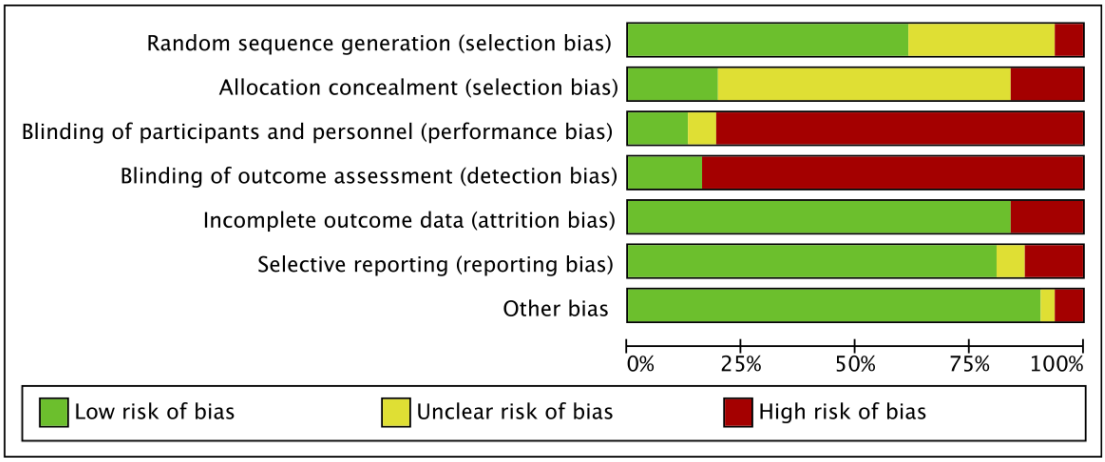

Table 1. Demographic and characteristics of the 31 RCTs included in the Systematic Review.

Included Studies - Demographics		
Characteristic	**Subgroup**	**No. of RCTs**
-Country of Publication	Netherlands[29–33] Spain[34–38]	5
	India[41–43] Eygpt[44–46]	3
	Pakistan[40],[47] Turkey[39],[48] Italy[49,50]Germany [28],[51]	2
	Sweden[52] USA[53] Australia[54] Lithuania[55] France[56] Belgium[57] Denmark[58]	1
-Multi vs Single-centre	Multi centre[28-30],[32-34],[40],[49],[51-53],[57-58]	13
	Single centre[31],[35-39],[41-46],[48-50],[54-56]	18
-Year of Publication	1995-2005[28],[30],[32],[35-36],[39],[46]	7
	2006-2016[29],[31],[33-34],[37-38],[40-45],[47-58]	24
Included Studies		
Characteristic	**Subgroup**	**No. of RCTs**
-Trial Groups	Laparoscopic vs. Open[29],[34-35],[43],[47-50],[52-54]	11
	Open mesh vs. suture[28],[30],[36],[39-40]	5
	Laparoscopic mesh fixation; Tacks vs. Sutures[31],[37],[41-42]	3
	• Open ventral hernia repair:	
	Onlay vs. Sublay[44],[55]	2
	Light weight vs. Heavy weight mesh[32]	1
	Medium weight vs. Medium weight mesh[51]	1
	*Autograft vs. Prosthetic mesh**[28*]	1
	Component separation vs. Prosthetic mesh[33]	1
	Onlay vs. Underlay[45]	1
	Intraperitoneal vs. Onlay [bridging][46]	1
	Ventralex patch vs Biomesh composite mesh[56]	1
	• Laparoscopic ventral hernia repair:	
	Double crown tack vs. suture and tack mesh fixation[31],[57]	2
	Double crown tack vs. fibrin sealant mesh fixation[58]	1
	Light weight mesh vs. Medium weight mesh[38]	1
	Total	32*
	*Large hernias from Korenkov et al. (a suture vs. mesh RCT) were analysed as a separate category. This makes this total 32 rather than 31.	
-Hernia type	Primary hernias only[36],[39-40],[44-45],[47]	6
	Incisional hernias only[28-30],[32-34],[38],[46],[49-53],[55]	14
	Primary and incisional hernias[31],[35],[37],[41-43],[48],[54],[56-58]	11
-Primary outcomes	Hernia recurrence[28],[49],[54],[56]	4
	Quality of life/ Health questionnaires[32],[34],[51-52],	4
	Pain [measured using visual analogue scores][29],[31],[57],[58]	4
	Pain and hernia recurrence [two primary outcomes][38]	1
	Mesh shrinkage[37]	1
	Total complications rates[53]	1
	Unclear[30],[33],[35-36],[39-48],[50],[55]	16

-Risk of Bias: Cochrane Collaboration's tool	High risk of bias[28-50],[52-58]	30
	Low risk of bias[51]	1

Table 2. Summarising the hernia morphology data reported.

Hernia dimension	No. of RCTs reporting variable
Average hernia defect surface area	14[30-31],[35],[37-38],[41],[43],[50],[52-57]
Average hernia defect width	11[28,29],[32-34],[38],[40],[44],[49-50],[52]
Loss of Domain	0

Table 3. Preoperative patient characteristics and comorbidities reported.

Patient characteristic/comorbidities	**No. of RCTs reporting variable**
Age [mean]	30[28-39],[41-58]
Gender [male/female ratio]	29[28-39],[41-50],[52-58]
Obesity [as a ratio >/< 35 or mean [SD]]	23[28-34],[37-38],[41-45],[48-50],[51-53],[55-58]
No. patients ASA 3	10[29],[31],[36-37],[39],[45],[49],[51-53]
COPD	8[28],[34],[38],[43],[45],[51-53]
Smoking status	8[28],[30],[45],[51-53],[56-57]
No. patients with Diabetes	7[34],[38],[44],[51-53],[56]
No. patients ASA 1	7[29],[31],[45],[49],[51-53]
No. patients ASA 2	7[29],[31],[45],[49],[51-53]
SF-36 QoL questionnaire[59]	3[32],[51],[52]
No. patients using steroids	3[28],[51],[53]
No. of arteriopaths [IHD/PVD/CVA]	3[28],[44],[52]
No. patients ASA 4	3[29],[49],[51]
Average ASA score	2[34],[55]
Liver cirrhosis / Childs-Pugh A	1[44]
SF-12 QoL questionnaire[59]	1[56]

Table 4. Intra-operative variables reported.

Intra-operative variable	**No. of RCTs reporting variable**
Mode of Surgery [laparoscopic/open]	31[28-58]
Category of mesh used	31[28-58]
Anatomical layer of mesh placement	31[28-58]
Duration of operation	27[28-31],[33-45],[48-50],[52-58]
Experience of the principal surgeon	14[29],[31],[33-34],[36],[46-47],[49],[52-55],[57-58]
Intra-operative blood loss	3[29],[33],[43]

Table 5. Six definitions of hernia recurrence encountered in the systematic review.

Reference:	Definition
Arroyo et al.[36]	'the presence of a defect on the central part of the midline aponeurosis around the umbilicus, where the operation had been performed previously.'
Bensaadi et al.[56]	'a defect of the midline aponeurosis around the umbilicus at the site where the operation was performed.'
Lal et al.[40]	'the presence of a defect on the central part of the midline aponeurosis where the operation had been performed previously.'
Luijendijk et al.[30]	'any fascial defect that was palable or detected by ultrasound examination and was located within 7cm of the site of hernia repair.'
Pring et al.[54]	'a clinically detectable defect, associated with the protrusion of viscera on straining'.
Muysoms et al.[57]	'Patients were considered free from recurrence if at clinical examination, no hernia was felt in an upright position during valsalva manoeuver.'

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