REVIEW ARTICLE

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Systematic review of robotic ventral hernia repair with meta-analysis

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Abstract

Background: Despite being one of the most common operations performed by general surgeons, there is a lack of consensus regarding the recommended approach for ventral hernia repair (VHR). Recent times have seen the rapid development of new techniques, such as robotic ventral hernia repair (RVHR). This systematic review and meta-analysis aims to evaluate the currently available evidence relating to RVHR, in comparison to open VHR (OVHR) and laparoscopic VHR (LVHR).
Methods: A systematic search of the following databases was conducted: PubMed, Embase, Scopus and Web of Science. A meta-analysis was performed for the outcomes of length of stay (LOS), recurrence, operative time, intraoperative complications, wound complications, 30-day readmission, 30-day reoperation, mortality and costs.
Results: A total of 39 studies met inclusion criteria. Overall, RVHR reduced LOS, intra-operative complications, wound complications and readmission compared to OVHR. Compared to LVHR, RVHR was associated with increased operative time and costs, with comparable clinical outcomes.
Conclusion: There is currently a lack of robust evidence to support the robotic approach in VHR. It does not demonstrate major benefits in comparison to LVHR, which is more affordable and accessible. Strong quality, long-term data is required to help with establishing a gold standard approach in VHR.

Introduction

Ventral hernia is a common general surgical problem with significant health, functional, quality-of-life and health economic consequences. While the nature of the surgical problem has not changed for decades, the way that the surgeon approaches ventral hernia repair (VHR) has evolved dramatically.

Despite still being one of the commonest operations performed by surgeons, there remains a lack of consensus regarding the recommended "gold standard" method of VHR. Recent times have seen the development of a myriad of alternative surgical techniques, such as robotic VHR (RVHR) and extended view totally extraperitoneal hernia repair (eTEP). Rapid development and implementation have been pursued and often without a robust evidence base.

The traditional open ventral hernia repair (OVHR) involves direct repair of the defect through an incision. Open primary suture repair without mesh is typically performed for small primary defects under 2 cm.[1] For larger or incisional hernias, open mesh repair is preferred to reinforce the abdominal wall and reduce recurrence.[2]

Laparoscopic ventral hernia repair (LVHR) was first described in 1993 by LeBlanc and Booth.[3] Due to its minimally invasive nature, requiring smaller incisions and less traumatic tissue handling, it is associated with reduced post-operative pain, recovery time, hospital length of stay (LOS) and wound complications compared to OVHR.[4] Recent times have seen further development of other LVHR techniques beyond intra-peritoneal onlay/underlay mesh (IPOM/IPUM), such as eTEP and mini/less-open sublay (MILOS) repair. There is less long-term prospective data supporting the use of such techniques.

Robotic surgery is purported to offer improved dexterity, precision, three dimensional optics, and surgeon ergonomics.[5] Improved manoeuvrability and degrees-of-freedom may facilitate repair of

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large or complex hernias requiring component separation techniques (CRT), such as transversus abdominis release (TAR).[1,6] Disadvantages include increased costs, reduced accessibility and increased operative time compared to other approaches.[1,7] It is questionable whether the benefits are justified by the costs.[6–8]

Despite a clinical problem that has not changed over recent times, new approaches are rapidly becoming available to the surgeon and patient. An evidence-based review of techniques is required to consolidate the current understanding of best practice, and to facilitate informed decision-making. Through a systematic review of the literature and meta-analysis, this paper serves to evaluate the clinical and economic efficacy of RVHR in comparison with LVHR and OVHR.

Methods

Study design

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[9] The protocol was registered in the PROSPERO International Prospective Registrar of Systematic Reviews (CRD42022340945).

Search strategy

A literature search was conducted of the following databases from inception to 14 October 2022: PubMed, Embase, Scopus and Web of Science. MeSH terms were used in PubMed: (Robotic Surgical Procedures[MeSH] OR robot*[tiab]) AND ("Hernia, Ventral"[MeSH] OR "ventral hernia"[tiab] OR "abdominal wall hernia"[tiab] OR (hernia*[TiAb] AND (ventral[TiAb] OR incisional[TiAb] OR epigastric[TiAb] OR umbilical[TiAb] OR parastomal[TiAb] OR Spiegel*[TiAb] OR Spigel*[TiAb])). There were no restrictions on language. Reference lists of articles were reviewed; no additional studies were found.

Selection criteria

Inclusion criteria were comparative studies including RVHR in adult patients. Exclusion criteria included noncomparative, paediatric and animal studies; descriptions; letters; editorials; commentaries; and other reviews. Abstracts were included if they had sufficient data for analysis. A total of 39 studies proceeded to data extraction (Fig. 1).

Quality assessment

The quality of non-randomized studies was assessed with the aid of the risk of bias in non-randomized studies of interventions (ROBINS-I) tool.[10] The quality of randomized controlled trials (RCTs) was assessed with the aid of cochrane risk-of-bias tool for randomized trials (RoB 2).[11]

Data extraction and analysis

The primary outcomes were length of stay (LOS) and recurrence. Secondary outcomes were operative time, intraoperative complications, wound complications, 30-day readmission, 30-day reoperation, mortality and costs. Clarification was sought from authors regarding unclear or missing data. Binary outcomes were reported in counts and percentages. Continuous variables were recorded as means and standard deviations. Medians and ranges or interquartile ranges were converted to means and standard deviations using algorithms described by Luo *et al*. (2018) and Wan *et al*. (2014).[12,13]

Meta-analysis was performed using Review Manager Software (RevMan) version 5.4. The random-effects analysis model was used. Continuous variables were presented with standard mean differences (SMD) and 95% confidence intervals (CI). Dichotomous variables were presented with risk ratios (RR) and 95% CI. Results were considered statistically significant if $p < 0.05$. Statistical heterogeneity was assessed using I^2 statistic, where I^2 values of 0%–25%, 25%–50% and >50% represented low, moderate, and substantial heterogeneity respectively. Subgroup analysis was conducted for studies comparing robotic TAR (R-TAR) with open TAR (O-TAR). Egger's test in STATA version 18 was used to assess publication bias, deemed to likely be present if $p < 0.05$.

Results

A summary of included study characteristics is displayed in Table 1. Across all 39 included studies, there were 10 273 robotic, 85 723 laparoscopic and 445 270 open cases. There were 29 cohort studies, four RCTs, one case–control study and five abstracts. Studies had moderate to high risk of bias. Following Egger's test, Dauser *et al*. (2021) was removed for analysis of LOS due to risk of publication bias.

Intraoperative outcomes

Operative time

Operative time was reported in 24 studies. The mean operative times for RVHR, LVHR and OVHR were 182.71, 99.91 and 162.51 min, respectively. RVHR is associated with less favourable operative time compared to LVHR (SMD 1.18, 95% CI 0.90–1.47) and OVHR (SMD 0.81, 95% CI 0.56–1.06) (Fig. 2a/i,ii). There was substantial heterogeneity (I^2 87% LVHR; I^2 75% OVHR).

In TAR sub-analysis, mean operative times for R-TAR and O-TAR were 275.20 and 225.99 min, respectively. Operative time was significantly longer in R-TAR than O-TAR (SMD 0.81, 95% CI 0.58–1.04) (Fig. 2a/iii), with low heterogeneity among studies (I^2 12%).

Intraoperative complications

Intraoperative complications were reported in 12 studies. Overall, the intraoperative complication rates in RVHR, LVHR and OVHR were 1.47%, 1.35% and 2.15% respectively. Intraoperative complication rate does not significantly differ between RVHR and LVHR (RR 1.02, 95% CI 0.49–2.14), however it is significantly lower in RVHR than OVHR (RR 0.54, 95% CI 0.30–0.98) (Fig. 2b/i,ii). Overall intraoperative complication rates for R-TAR and O-TAR were 5.19% and 6.93%, respectively. There was no significant difference between R-TAR and O-TAR (RR 0.53, 95%

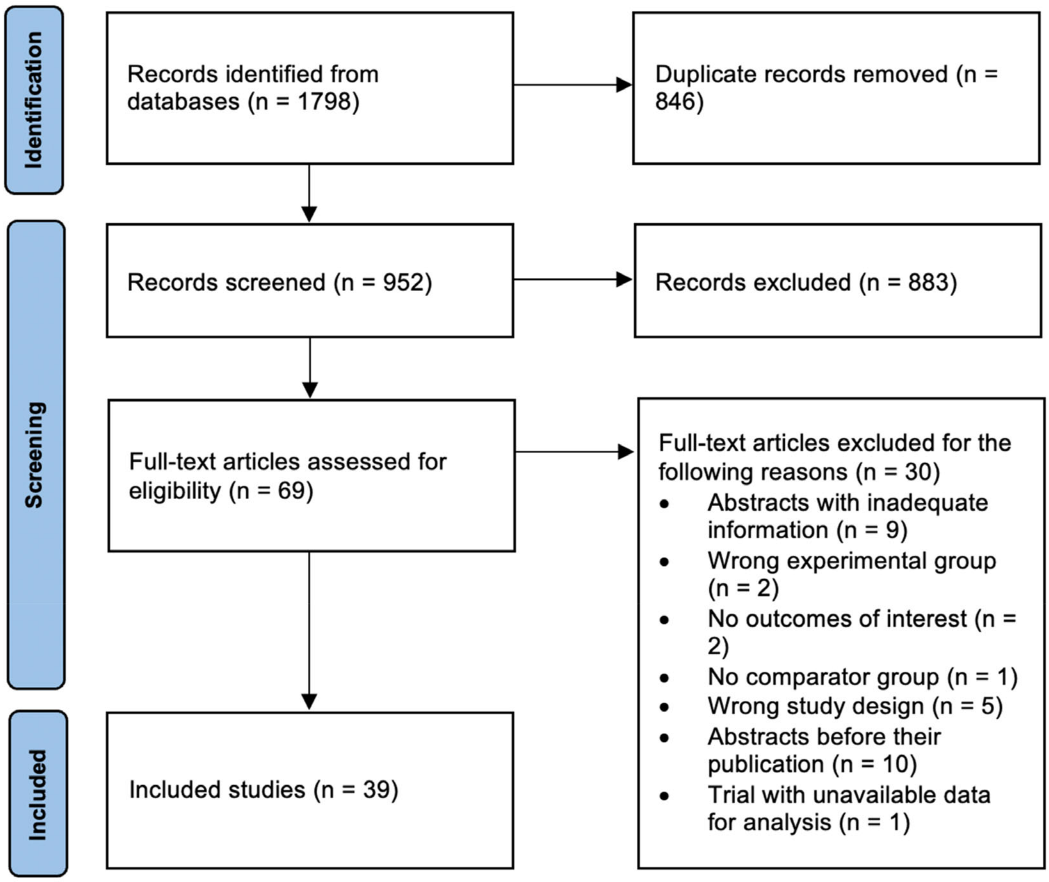

Fig. 1. PRISMA flow diagram.

CI 0.24–1.17) (Fig. 2b/iii). There was low heterogeneity (I^2 0%) for all comparisons.

Post-operative outcomes

Length of stay (LOS)

LOS was reported in 32 studies. Dauser *et al.* (2021) was removed from the analysis due to concerns of publication bias. Mean LOS for RVHR, LVHR and OVHR were 3.16, 3.17 and 7.41 days, respectively. Mean LOS for R-TAR and O-TAR were 2.43 and 6.39 days, respectively. There was no statistical significance in LOS between RVHR and LVHR (SMD −0.05, 95% CI −0.20 to 0.11) (Fig. 3a). LOS was significantly lower in RVHR compared to OVHR (SMD −1.11, 95% CI −1.41 to −0.81) and in R-TAR compared to O-TAR (SMD −1.34, 95% CI −1.85 to −0.82) (Fig. 3b,c). There was substantial heterogeneity among studies (I^2 96% LVHR; I^2 98% OVHR; I^2 65% O-TAR).

Surgical site infection (SSI)

30-day SSI rate was reported in 10 studies. 30-day SSI rates in RVHR, LVHR and OVHR were 1.22%, 1.52%, and 4.13%, respectively. It was not significantly different between RVHR and LVHR (RR 0.45, 95% CI 0.14–1.42) (Fig. 4a/i). It was significantly lower in RVHR than OVHR (RR 0.51, 95% CI 0.27–0.96) (Fig. 4a/ii). There was low heterogeneity (I^2 9% for LVHR; I^2 8% for OVHR).

30-day SSI rates for R-TAR and O-TAR were 4.05% and 6.61%, respectively. There was no significant difference between R-TAR and O-TAR (RR 0.74, 95% CI 0.08–6.99) (Fig. 4a/iii), with substantial heterogeneity (I^2 55%).

Surgical site occurrence (SSO)

30-day SSO rates were reported in nine studies. For comparability, SSO was defined as surgical site events not including infection, such as seroma and haematoma. 30-day SSO rates in RVHR, LVHR and OVHR were 14.11%, 9.05% and 9.89%, respectively. There was no statistically significant difference in SSO when comparing RVHR with LVHR (RR 0.79, 95% CI 0.49–1.27) and OVHR (RR 0.92, 95% CI 0.15–5.56) (Fig. 4b/i,ii). There was moderate heterogeneity (I^2 39%) among studies comparing RVHR and LVHR, and substantial heterogeneity (I^2 76%) among studies comparing RVHR and OVHR.

30-day SSO rates in R-TAR and O-TAR groups were 17.73% and 20.28%, respectively. There was no significant difference between R-TAR and O-TAR (RR 0.81, 95% CI 0.51–1.30) (Fig. 4b/iii), with low heterogeneity among studies (I^2 0%).

Table 1 Summary of study characteristics

Author, Year	Study design	Number of patients				Risk of bias
		RVHR	LVHR	OVHR	Total	
Altieri, 2018[14]	Cohort	679	20 896		21 565	High
Armijo, 2018[15]	Cohort	465	6829	39 505	46 799	Moderate
Ayuso, 2022[16]	Cohort	5942	19 853	180 635	206 430	Moderate
Bittner, 2018[17]	Cohort	26		76	102	Moderate
Carbonell, 2018[18]	Cohort	111		222	333	Moderate
Chen, 2017[19]	Cohort	39	33		72	Moderate
Christoffersen, 2022[20]	Cohort	27	32		59	Moderate
Coakley, 2017[21]	Cohort	351	32 243		32 594	Moderate
Collins, 2022[22]	Cohort	350		759	1109	Moderate
Costa, 2022[23]	RCT	18	19		37	Moderate
Dauser, 2021[24]	Cohort	16		10	26	High
Dewulf, 2022[25]	Case control	90		79	169	Moderate
Dhanani, 2021[8]	RCT	65	59		124	Moderate
Forester, 2021[26]	Cohort	77	300	418	795	High
Gonzalez, 2013[27]	Abstract – cohort	67	67		134	NI
Guzman-Pruneda, 2020[28]	Cohort	42		194	236	High
Halabi, 2022[29]	Cohort	19	17	19	55	High
Halka, 2019[30]	Cohort	49		134	183	Moderate
Han, 2022[31]	Cohort	25		108	133	Moderate
Kakela, 2022[32]	Cohort	19	19		38	Moderate
Khorgami, 2019[33]	Cohort	99	3600		3699	Moderate
Kudsi, 2021[34]	Cohort	35		43	78	High
LaPinska, 2021[35]	Cohort	615	615		1230	Moderate
LeBlanc, 2021[36]	Cohort	159	82	130	371	Moderate
Lu, 2020[37]	Cohort	86	120		206	Moderate
Martin-del-Campo, 2018[38]	Cohort	38		76	114	Moderate
Mehaffey, 2017[39]	Cohort					Moderate
Moore, 2017[40]	Abstract – cohort	84	89		173	NI
Nguyen, 2021[41]	Cohort	27		16	43	Moderate
Olavarria, 2020[6]	RCT	65	59		124	Moderate
Petro, 2021[42]	RCT	39	36		75	Moderate
Prabhu, 2017[43]	Cohort	186	452		638	Moderate
Reeves, 2020[44]	Cohort	13		13	26	Moderate
Roberts, 2019[45]	Abstract – cohort	13		12	25	NI
Song, 2017[46]	Abstract – cohort	96	94	96	286	NI
Switzer, 2019[47]	Abstract – cohort	30		90	120	NI
Walker, 2018[48]	Cohort	142	73		215	Moderate
Warren, 2016[49]	Cohort	53	103		156	High
Zayan, 2019[50]	Cohort	16	33		49	High

NI = insufficient information to make assessment.

SSO requiring procedural intervention (SSOPI)

SSOPI was reported in 11 studies. As there was limited data on SSOPI within a common follow-up period, overall SSOPI rates were compared. SSOPI rates in RVHR, LVHR and OVHR were 2.74%, 2.27% and 6.19%, respectively. There was no significant difference in SSOPI between RVHR and LVHR (RR 0.62, 95% CI 0.27–1.43) (Fig. 4c/i), with substantial heterogeneity among studies (I^2 63%). It was significantly reduced in RVHR compared to OVHR (RR 0.55, 95% CI 0.37–0.83) (Fig. 4c/ii) with low heterogeneity (I^2 0%).

SSOPI rates in R-TAR and O-TAR were 4.42% and 9.06%, respectively. There was no significant difference between R-TAR and O-TAR (RR 0.53, 95% CI 0.22–1.30) (Fig. 4c/iii) with low heterogeneity (I^2 0%).

Readmission within 30 days

30-day readmission was reported in 15 studies. Rates for RVHR, LVHR and OVHR were 3.98%, 3.05% and 7.50%, respectively. There was no significant difference between RVHR and LVHR (RR 0.92, 95% CI 0.56–1.53) (Fig. 5a/i), with substantial heterogeneity (I^2 61%). It was significantly lower in RVHR compared to OVHR (RR 0.65, 95% CI 0.44–0.97) (Fig. 5a/ii), with moderate heterogeneity (I^2 27%).

30-day readmission rates for R-TAR and O-TAR were 3.42% and 11.11%, respectively. It was significantly lower in R-TAR than O-TAR (RR 0.38, 95% CI 0.14–0.98) (Fig. 5a/iii), with low heterogeneity (I^2 0%).

Reoperation within 30 days

30-day reoperation rates were reported in eight studies. Rates in RVHR, LVHR and OVHR were 0.68%, 1.63% and 2.59%, respectively. Figure 5b/i,ii shows no significant difference between RVHR and LVHR (RR 0.47, 95% CI 0.17–1.29) or OVHR (RR 0.56, 95% CI 0.21–1.49), with low heterogeneity (I^2 0%).

Recurrence

One-year recurrence was reported in six studies, with overall rates in RVHR, LVHR and OVHR being 11.17%, 6.67% and 18.15%,

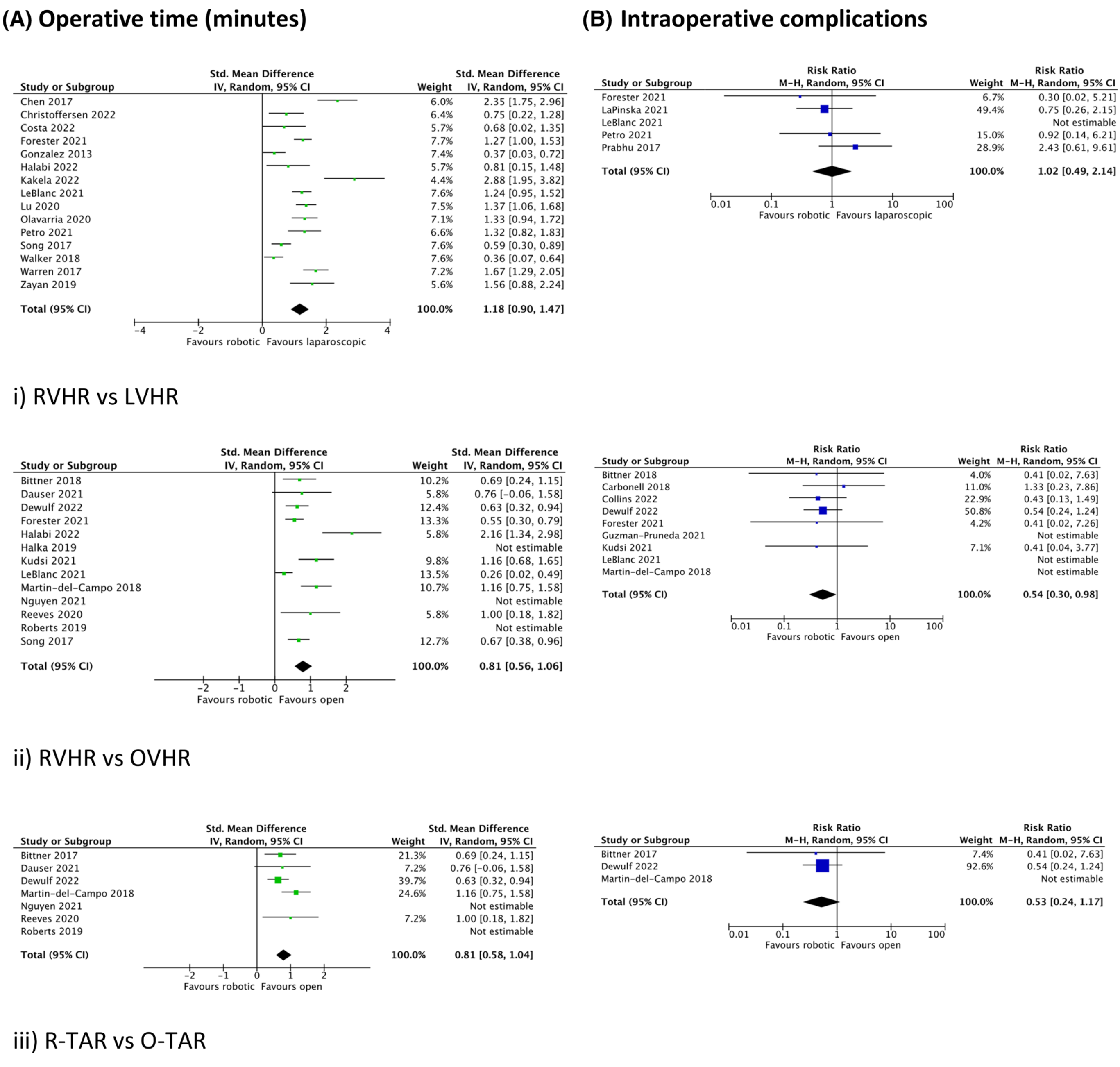

Fig. 2. Forest plots comparing intra-operative outcomes.

respectively. There was no significant difference when comparing RVHR with LVHR (RR 0.63, 95% CI 0.21–1.88) and OVHR (RR 1.18, 95% CI 0.74–1.89) (Fig. 5c/i,ii), with low heterogeneity (I^2 0%).

Mortality

Mortality was reported in 12 studies. Rates in RVHR, LVHR and OVHR were 0.43%, 0.26% and 1.90%, respectively. There is no significant difference in mortality between RVHR and LVHR (RR 0.83, 95% CI 0.55–1.24) or OVHR (RR 0.44, 95% CI 0.18–1.07) (Fig. 6a,b). Heterogeneity was low in studies comparing RVHR with LVHR (I^2 0%) but substantial in studies comparing RVHR with OVHR (I^2 57%).

Total costs

Total costs were reported in nine studies. Mean costs (USD) in RVHR, LVHR and OVHR were $77 468.72, $44 507.07 and $97 450.13, respectively. RVHR was associated with significantly higher costs than LVHR (SMD 11.32, 95% CI 5.35 to 17.28) (Fig. 7a) with substantial heterogeneity (I^2 100%). Costs were not significantly different between RVHR and OVHR (SMD −0.08, 95% CI −0.21 to 0.05) (Fig. 7b), with substantial heterogeneity (I^2 87%).

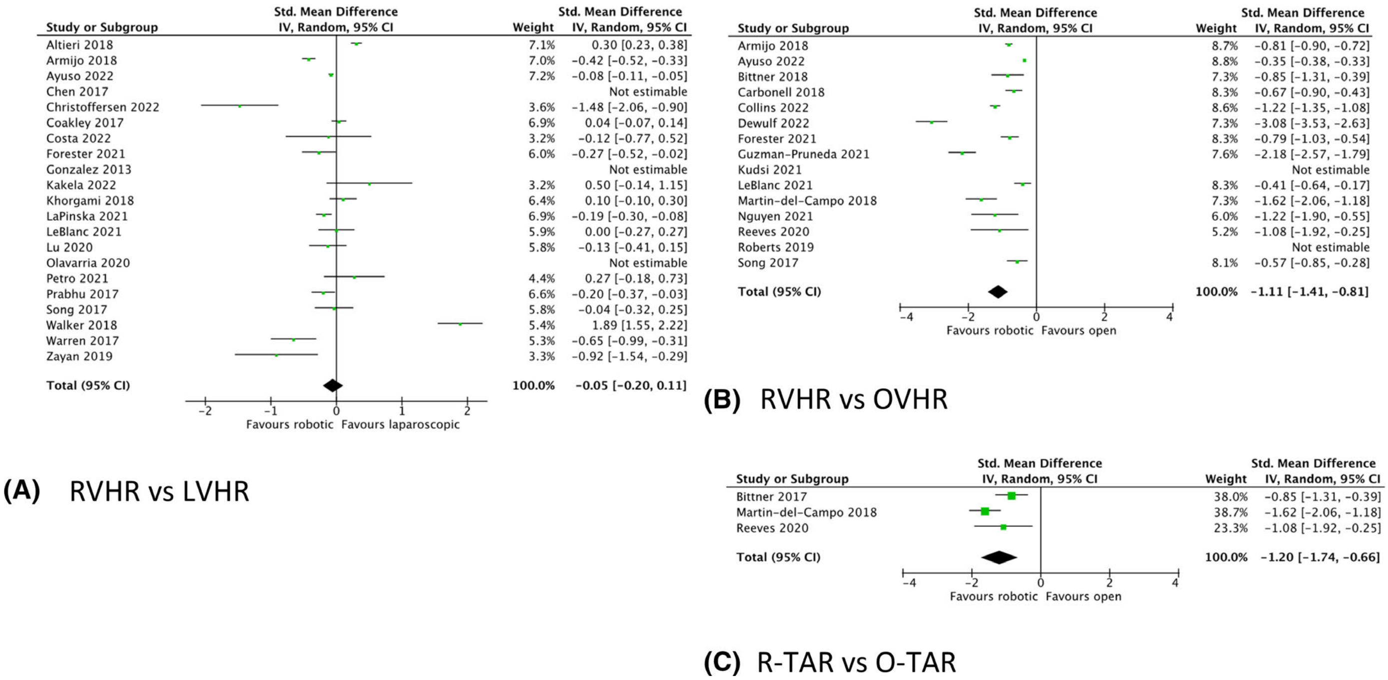

Fig. 3. Forest plots comparing LOS (days).

Discussion

Robotic surgery has garnered significant interest in recent years as it offers the potential of enhanced dexterity, precision, three-dimensional optics, and surgeon ergonomics. This research aimed to evaluate whether these proposed benefits translate to changes in clinical and economical outcomes in VHR. The primary outcomes were hospital LOS and recurrence.

The included studies indicate that RVHR is associated with significantly shorter hospital LOS compared to OVHR, but it is not

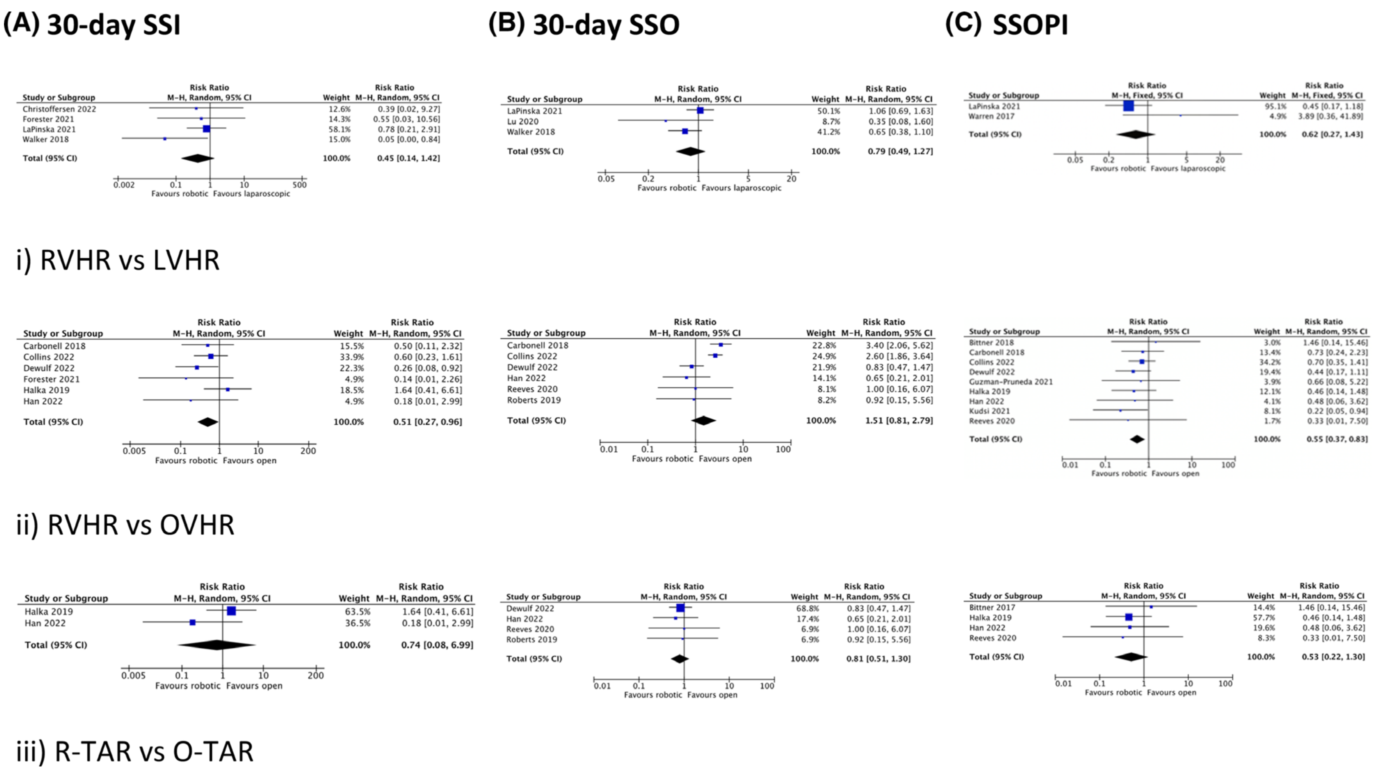

Fig. 4. Forest plots comparing wound complication rates.

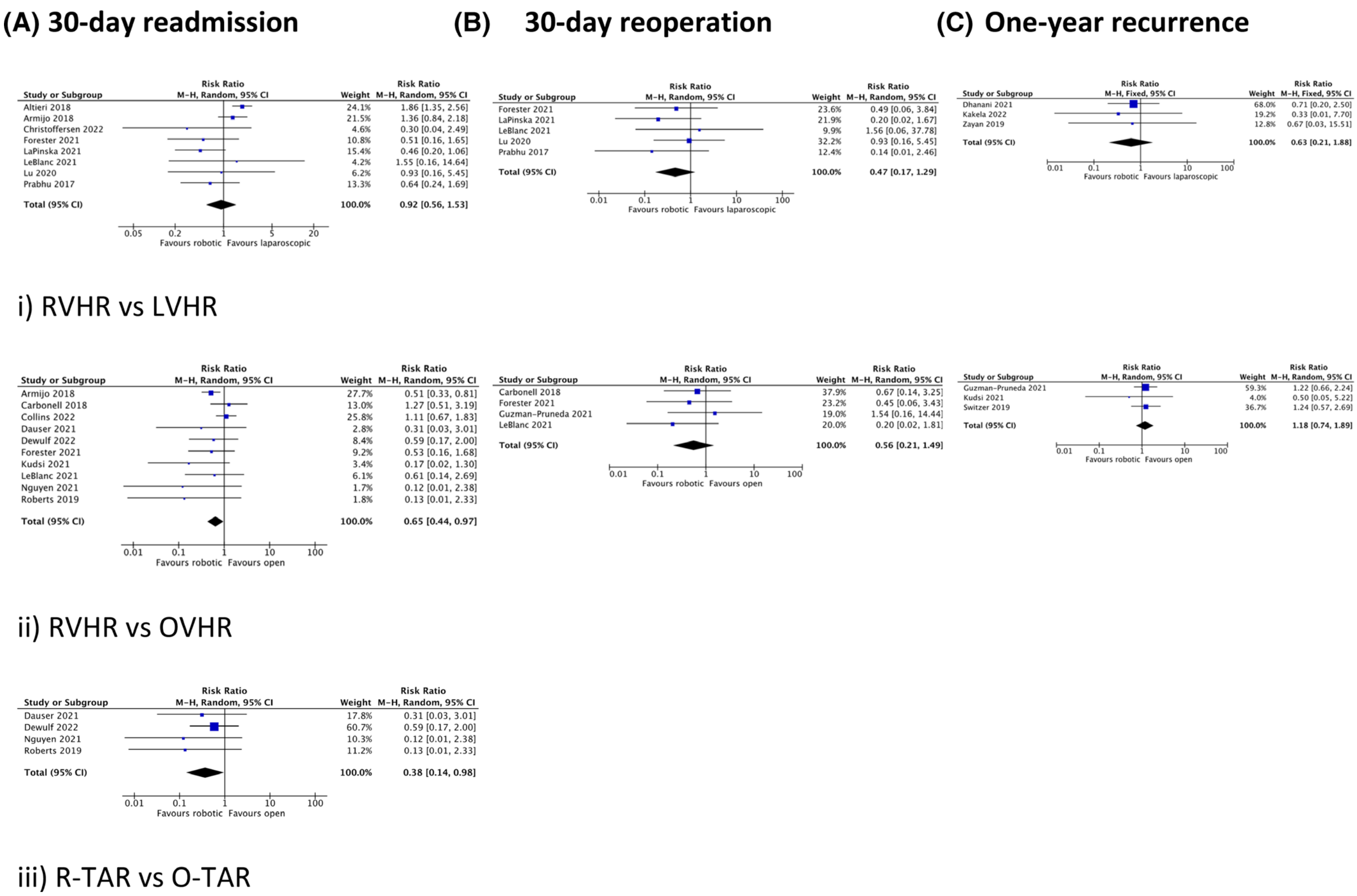

Fig. 5. Forest plots comparing readmission, reoperation and recurrence rates.

significantly different from LVHR. Through reduced trauma and incision size, MIS is associated with reduced postoperative pain, which is a major factor in LOS.[51] Moreover, intraoperative complications would be expected to prolong LOS as they may require monitoring or treatment. Indeed, studies demonstrated that intraoperative complication rate was significantly lower in RVHR than OVHR, but comparable between RVHR and LVHR.

Studies demonstrated that robotic retrorectus VHR had significantly shorter LOS than laparoscopic IPOM.[20,35,43,49,50] Noting that most studies did not show a significant difference in LOS between RVHR and LVHR, these findings may relate to retrorectus mesh placement, rather than the robotic approach itself. Retrorectus mesh placement is technically challenging to achieve in LVHR due to limited degrees of freedom.[52] RVHR facilitates dissection of the retromuscular space for mesh placement, which is thought to reduce the risks of delayed complications such as adhesions, fistula formation and bowel injury, compared with intraperitoneal mesh.[49,52] The laparoscopic eTEP technique facilitates wider dissection for retrorectus mesh placement. However, similar to RVHR, there is lack of high-quality long-term data comparing laparoscopic eTEP

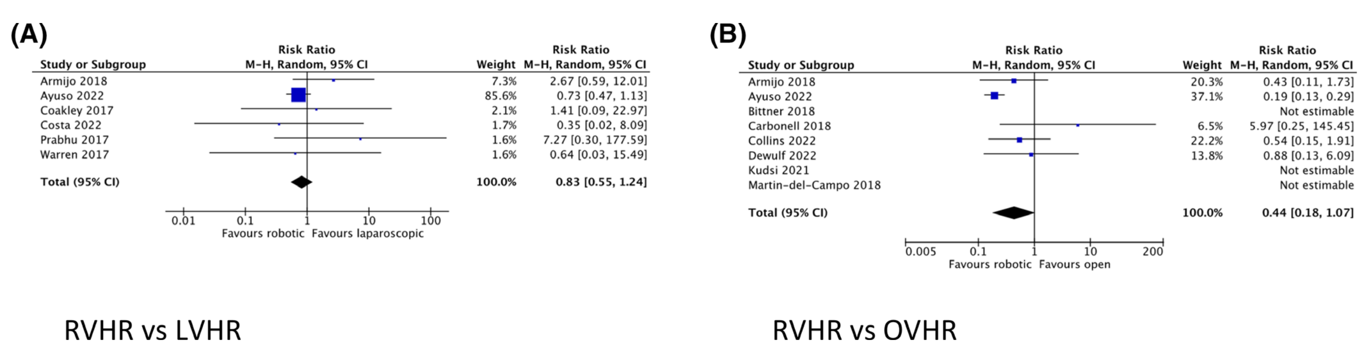

Fig. 6. Forest plots comparing mortality rates.

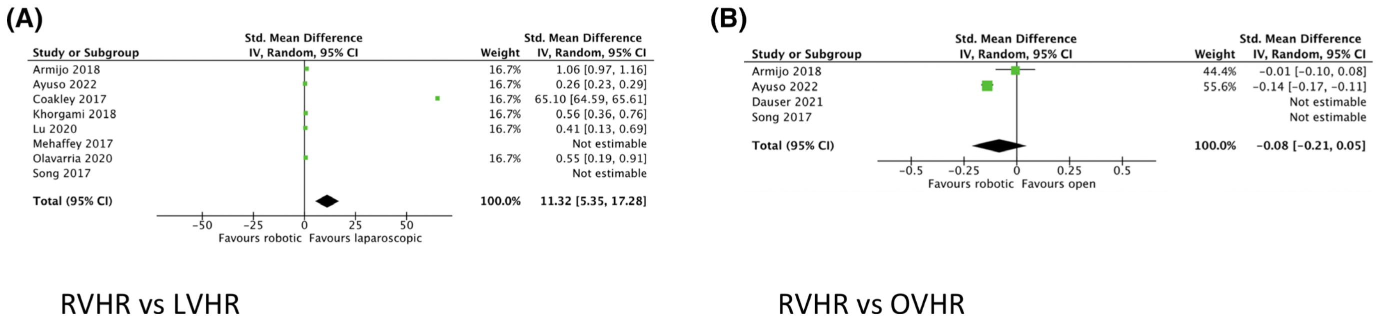

Fig. 7. Forest plots comparing total costs.

with the traditional IPOM/IPUM approach. A systematic review by Li *et al*. (2022) suggested eTEP was associated with reduced LOS, however no significant difference was found in intraoperative and postoperative complications.[53]

Recurrence in hernia surgery is an important outcome as it affects quality of life and may require re-operation. The assessment of recurrence in RVHR is limited, as most available studies have follow-up periods of under 1 year, and recurrence often develops following this period. There were only six studies that reported on one-year recurrence. Such an important outcome measure demands greater scrutiny and is a failing of the current body of work examining hernia outcomes. This can be improved upon with studies following recurrence over longer periods of time.

Through smaller incisions, minimally invasive surgery limits tissue trauma and subsequent opportunity for wound complications. Included studies demonstrate that RVHR significantly reduces SSI and SSOPI rates compared to OVHR, however there is no significant effect on SSO rates. As SSI and SSOPI are more likely to require treatment than SSO, RVHR may have a positive impact in reducing the costs and LOS relating to wound complications, compared to OVHR. However, as RVHR and LVHR are comparable with regards to wound complications, this outcome would not justify increased incorporation of RVHR in clinical practice.

In complex hernia surgery and abdominal wall reconstruction, OVHR remains the standard approach for most surgeons. CRT, such as TAR, are useful in large complex hernia repair as the mobilization of muscle and fascial layers helps to achieve tension-free closure of the hernia defect and improved abdominal wall function following loss of domain.[25,41,44] CRT are seldom conducted laparoscopically due to ergonomic limitations.[54] RVHR offers benefits of MIS, while improving access to planes that would otherwise be restricted in LVHR. The sub-analyses comparing R-TAR and O-TAR indicate that R-TAR is associated with reduced LOS and 30-day readmission rate, at the expense of longer operative time. Intra-operative and wound complications were not significantly different between approaches. However, sub-analyses were limited by the low number of studies available, with under 10 studies evaluating the role of robotic surgery in VHR involving TAR. Future studies could further delineate the role of robotic surgery in large, complex hernia repair and abdominal wall reconstruction.

Most studies report that RVHR incurs higher costs and longer operative times compared to other approaches, being significantly higher than LVHR.[6,15–17,19–21,23–27,29,32–34,36–38,41,42,44,46,48–50] The costs of robotic systems, software, equipment and maintenance outweigh that of laparoscopic and open surgery. These costs may be offset with reduced hospital costs associated with LOS and complications. The validity of the cost analysis is compromised by the variability in reported cost calculations among studies. Moreover, costs would be expected to differ between various countries and economies. Future studies may consider shared specific criteria for comparison of total and constituent costs. This would offer an improved understanding of the economic impact and potential strategies to reduce costs associated with RVHR. Moreover, strategies such as use of recyclable or reusable, instead of disposable, equipment may reduce equipment-related costs.[55] Emerging competitors in the market offer the possibility of increased affordability of robotic systems in the future.

RVHR is associated with significantly increased operative time compared to both LVHR and OVHR. Increased operative time in RVHR may be contributed by the additional steps of docking/undocking equipment, and operator learning curve.[56] It is foreseeable that operative times, and corresponding cost, would reduce with increased training, operator experience, and developments in equipment set-up. This would correspondingly reduce costs associated with operative time. It may be worthwhile to investigate specific factors that increase operative time for RVHR, such as the steps contributing to prolonged duration.

This study was limited by the heterogeneity and lack of high-quality, long-term data evaluating RVHR. The population sizes for robotic groups are substantially lower than other groups, being under one-fifth of the laparoscopic group and under one-twentieth of the open group. This is contributed by the recent uptake and limited accessibility of robotic surgery in VHR. There is a lack of double-blind RCTs, which is particularly challenging to conduct in surgical practice, where the operator cannot be blinded. Studies did not consistently report data on shared outcomes. Ten studies obtained data from Americas Hernia Society Quality Collaborative, which relies on selection of cases by surgeons or centres, presenting risk of selection bias. A potential solution is to form a shared registry for all RVHR cases with common data variables.

There was heterogeneity among studies with regards to the definitions and measurement of outcomes. For instance, some studies defined SSO as that including SSI, whereas others did not.[18,31,48] For the articles where SSO included SSI, SSO was re-calculated to exclude SSI, to improve data comparability. The outcome of recurrence was determined clinically or radiologically in different studies. There were differences in follow-up periods between approaches and between studies, limiting the validity of comparison as complications are more likely to be detected where follow-up periods are longer. Analyses were conducted for outcomes sharing a common follow-up period, such as 30-days post-operatively; however, this was not available in all studies. Another source of heterogeneity is the ventral hernia type included in studies. Several studies focussed on incisional hernias.[23,26,36,43,44] Han *et al*. (2022) focussed on recurrent hernias.[31] Kudsi *et al*. (2021) studied emergent hernia repair.[34] There were inadequate studies to conduct sub-analyses for sub-types.

Confounding factors, such as co-morbidities, were not consistently reported among studies. There was limited data on operative factors such as concomitant procedures, mesh position and fixation, analgesia, and fascial closure. Another limitation is that two-third (26 of 39) of studies were contributed by authors who disclosed financial, personal, academic, or other interests with robotic surgery companies, suggesting potential for bias. Studies may not be generalizable to general surgeons as most cases of RVHR are conducted by experts in hernia or minimally invasive surgery.

Conclusion

RVHR offers benefits compared to OVHR with respect to intraoperative complications, LOS, wound complications and readmission. RVHR is associated with significantly increased operative time and costs compared to LVHR, with comparable clinical outcomes. It is foreseen that operative time and costs would reduce with further development and integration of robotic surgery into clinical practice. Ultimately, strong quality, registry-derived long-term data is required moving forward to assist in identifying a gold standard approach that is efficacious, sustainable and economical.

Author contributions

Study conception and design: ET, JG, JS. Data collection: ET. Data analysis: ET, JS. Manuscript preparation: ET, JG. All authors reviewed and approved the final version of the manuscript.

Conflicts of interest

None declared.

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