



Review

Optimal surgical management in kidney and pancreas transplantation to minimise wound complications: A systematic review and meta-analysis



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ABSTRACT

Background: Immunosuppression in transplant patients increases the risk of wound complications. However, an optimal surgical approach to kidney and pancreas transplantation can minimise this risk.

Materials and methods: We performed a systematic review and meta-analysis to examine factors contributing to incisional hernia formation in kidney and pancreas transplant recipients. Bias appraisal of studies was conducted via the Newcastle-Ottawa scale. We considered recipient factors, surgical methods, and complications of repair.

Results: The rate of incisional hernia formation in recipients of kidney and pancreas transplants was 4.4% (CI 95% 2.6–7.3, $p < 0.001$). Age above or below 50 years did not predict hernia formation ($Q(1) = 0.09$, $p = 0.77$). Body mass index (BMI) above 25 (10.8%, CI 95% 3.2–30.9, $p < 0.001$) increased the risk of an incisional hernia. Mycophenolate mofetil (MMF) use significantly reduced the risk of incisional hernia from 11.9% (CI 95% 4.3–28.7, $p < 0.001$) to 3.8% (CI 95% 2.5–5.7, $p < 0.001$), $Q(1) = 4.25$, $p = 0.04$. Sirolimus significantly increased the rate of incisional hernia formation from 3.7% (CI 95% 1.7–7.1, $p < 0.001$) to 18.1% (CI 95% 11.7–27, $p < 0.001$), $Q(1) = 13.97$, $p < 0.001$. While paramedian (4.1% CI 95% 1.7–9.4, $p < 0.001$) and Rutherford-Morrison incisions (5.6% CI 95% 2.5–11.7, $p < 0.001$) were associated with a lower rate of hernia compared to hockey-stick incisions (8.5% CI 95% 3.1–21.2, $p < 0.001$) these differences were not statistically significant ($Q(1) = 1.38$, $p = 0.71$). Single layered closure (8.1% CI 95% 4.9–12.8, $p < 0.001$) compared to fascial closure (6.1% CI 95% 3.4–10.6, $p < 0.001$) did not determine the rate of hernia formation [$Q(1) = 0.55$, $p = 0.46$].

Conclusions: Weight reduction and careful immunosuppression selection can reduce the risk of a hernia. Rutherford-Morrison incisions along with single-layered closure represent a safe and effective technique reducing operating time and costs.

1. Introduction

Transplantation remains the gold standard of management for end-stage renal disease and type 1 diabetes [1]. Despite advances in surgical technique and immunosuppressive therapy, fundamental surgical issues are associated with preventable morbidity, hospitalization, readmission, and reoperation [2]. The significant burden related to immunosuppressant use remains a challenging balance between the increased risk of infection and wound complications against the need to prevent rejection in patients [3].

Wound dehiscence and infections are common surgical post-transplant complications [4], and incisional hernia can lead to longer-term

complications. Incisional herniation of the abdomen has been linked to significantly reduced quality of life through its impact on occupation, activities of daily living, mobility, perceived pain and psychological well-being [5]. The Global Burden of Disease study, conducted in 2010, reports that the surgical morbidity associated with a hernia resulted in the loss of 792,000 disability-adjusted life years [6].

In transplant recipients, the association between factors thought to precipitate incisional hernia formation have been explored. These factors include increased recipient age or body mass index [7], an immunosuppressive regimen that includes sirolimus or mycophenolate mofetil (MMF) [8], Rutherford-Morrison transplant incision [9] and single layered closure [10]. In this meta-analysis, we aimed to assess

Abbreviations: BMI, Body mass index; CENTRAL, Cochrane register of randomized controlled trials; MMF, Mycophenolate mofetil; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, Randomised controlled trial; SPK, Simultaneous pancreas-kidney transplantation

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the risk and factors contributing to incisional hernia formation in kidney and pancreas transplant recipients by synthesizing the evidence available in the literature. We also reviewed the evidence for methods of repair to reduce the morbidity associated with this complication.

2. Materials and Methods

2.1. Criteria for considering studies in this review

All studies examined were case reports or retrospective reviews that reported on incisional herniation after kidney alone, kidney and pancreas and pancreas alone transplants abdominal organ transplants (study $n = 25$). The studies included in the meta-analysis were only the studies reporting incisional or ventral hernias, as these were more likely to be due to the transplantation surgery.

2.2. Primary outcome measures

Event rates of incisional hernia formation reported numerically or as odds ratios in the relevant studies were used for synthesis and analysis. We also examined rates of recurrence of a hernia following repair with herniorrhaphy with resorbable or non-resorbable mesh and laparoscopic techniques.

2.3. Moderating factors

We considered multiple moderating factors in this review. These included recipient factors such as age and BMI. We also considered surgical factors at the time of transplantation such as the type of incision and single-layered or multi-layered closure. The medical factors we examined included whether the immunosuppressive regimen included sirolimus or MMF.

2.4. Search methods for the identification of studies

2.4.1. Initial search

The search strategy followed guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions [11] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12].

Electronic databases including MEDLINE via PubMed/, EMBASE and Cochrane register of randomized controlled trials (CENTRAL) were searched using combinations of the terms ‘hernia’ and ‘transplant’ and their variations from inception to May 2017. We mapped terms to MeSH terms. In addition to these electronic searches, we examined each report’s citation list for additional studies.

2.4.2. Data collection

The search strategy involved screening titles and abstracts for duplicates and identifying ineligible studies. Using full copies of the papers, two researchers (SS and HT) independently assessed whether studies met the inclusion criteria, and we resolved disagreements through discussion. Relevant statistics were then extracted from the eligible studies and included in the meta-analysis.

Aspects relating to study quality were assessed, using the Newcastle-Ottawa Quality Assessment Scale [13] including how participants were selected, comparability of groups and assessment and follow-up of outcomes. This information is presented in a table describing features of the included studies (see Table 1).

2.5. Statistical analysis

The Comprehensive Meta-Analysis [14] program was used to calculate an overall event rate from the individual event rates within each study. This event rate provides an estimate of the rate of occurrence of an event within a group. Heterogeneity across studies was assessed

using the Q-statistic [15]. A significant Q-statistic indicates different effect sizes across studies, indicating potential differences in methodology or study population across studies.

We inspected the funnel plot for symmetry to determine whether any publication bias was present. This technique determines whether there was a significant risk of bias, and controls for that risk by imputing values to correct for the bias [16]. We verified these results against the Begg test [16] to ensure there was no publication bias. We constructed plots utilizing software packages GraphPad Prism [17] and R Statistical Package [18].

3. Results

3.1. Study characteristics

26 relevant articles met our inclusion criteria for systematic review from a total of 3011 articles (see Fig. 1). 22 were retrospective reviews of kidney transplantation, two included simultaneous pancreas-kidney (SPK) transplantation, and one article was pancreas alone transplantation. Two articles were prospective reviews including one randomised controlled trial comparing wound complications in patients receiving sirolimus and tacrolimus [19].

Of the 26 relevant articles, 17,821 recipients of kidney and pancreas transplantation were included in the present review. This included 17,574 kidney transplants, 66 SPK transplants, and 181 pancreas transplants. Of these patients, 2538 had a Rutherford-Morrison incision, 2198 had a hockey-stick incision, 712 had a paramedian incision, 156 had a midline incision. 341 patients had single layered closure, while 4838 had multi-layered closure. 1629 patients received MMF and 2914 did not receive MMF. 1125 patients received sirolimus while 6120 did not. Broggi et al. [10] reported data in the form of an odds ratio rather than raw numbers and these patients have not been included in these numeric descriptors.

3.2. Bias appraisal

The studies included in the present meta-analysis were well reported (see Table 2). Overall, patients from both the hernia and control groups were drawn from transplant populations from hospitals and thus were highly representative. Presence of an incisional hernia was assessed either by a surgeon in theatre, in follow-up clinics or from secure medical records for all papers. However, many studies did not report whether patients had experienced previous hernias or if the hernias were present before the transplant. Outcomes were identified by medical personnel prospectively or found in the medical records for most studies. Follow-up was poorly reported in the studies. There was no statement about attrition rates in many of the retrospective studies, and this should be reported explicitly in all future studies.

3.3. Rate of incisional hernia formation and recipient characteristics

The overall rate of incisional hernia formation in recipients of kidney and pancreas transplants was 4.4% (CI 95% 2.6–7.3, $p < 0.001$), see Fig. 2. We inspected the funnel plot and found no evidence of asymmetry, indicating there was no publication bias. The classic fail-safe N statistic showed an additional 3418 studies would be required to invalidate this result.

We then compared studies based on whether they reported on a mean recipient age of < 50 years or > 50 years. We found incisional hernia occurred in both groups at a similar rate [$Q(1) = 0.09$, $p = 0.77$], that is 5.6% (CI 95% 2.7–11.4, $p < 0.001$) in < 50 years and 4.7% (CI 95% 1.911.3, $p < 0.001$) in > 50 years groups, see Fig. 3A.

We separated studies based on whether the mean BMI was in the normal range or not. Individuals with a normal BMI had a 4% (CI 95% 0.3–34.5, $p < 0.001$) rate of incisional hernia formation, while those

Table 1
Summary of studies considered in this systematic review and meta-analysis.

Reference	Organ	Incision	Closure	Immunosuppression	Total Recipients	Hernia No.	Design
Mehrsai [32]	Kidney				230	1	Retrospective
Sheriffdeen [33]	Kidney				481	3	Prospective
Dean [19]	Kidney	Pararectus	Single	Prednisone, MMF and 59 received tacrolimus while 64 received sirolimus	123	8	Prospective
Humar [21]	Kidney	Hockey-stick	Fascial	Cyclosporine, azathioprine, and prednisone (MMF final year)	2013	73	Retrospective
Pliszczynski [34]	Kidney			Cyclosporine with or without sirolimus	593	154	Retrospective
Nanni [28]	Kidney	Hockey stick or oblique incision	Single		100	10	Retrospective
Singh [35]	Kidney			Cyclosporine, MMF, and prednisone	68	3	Retrospective
Mahdavi [36]	Kidney	Paramedian incision	Fascial	Cyclosporine, azathioprine, and prednisolone (recently MMF)	589	16	Retrospective
Mazzucchi [37]	Kidney	Rutherford-Morrison	Fascial	Cyclosporine, azathioprine, and MMF	371	14	Retrospective
Luc [38]	Kidney				n/a	61	Retrospective
Neeff [39]	Kidney	Rutherford-Morrison		Cyclosporine or tacrolimus, MMF, and prednisone	100	4	Retrospective
Varga B [40]	Kidney	Rutherford-Morrison	Fascial	MMF, prednisone and cyclosporine or tacrolimus	1067	28	Retrospective
Biolini [41]	Kidney			Cyclosporine, azathioprine, and prednisone	1685	19	Retrospective
Knight [26]	Kidney	Rutherford-Morrison	Fascial	Sirolimus, cyclosporine, and prednisone	263	34	Retrospective
Chang [42]	Kidney	Midline laparotomy right or left lower quadrant			3289	42	Retrospective
Benavides [43]	Kidney			Sirolimus, cyclosporine, and prednisone	350	46	Retrospective
Filocamo [27]	Kidney	Midline and hockey-stick			168	18	Retrospective
Marconi [22]	Kidney				1233	29	Retrospective
Ooms [44]	Kidney				1564	50	Retrospective
Broggi [10]	Kidney	Rutherford-Morrison	Odds ratios for single	Odds ratios for many combinations provided in text	225	45	Retrospective
Li [45]	Kidney (1 SPK)				2499	41	Retrospective
Antonopoulos [46]	Kidney and SPK	Rutherford-Morrison	Fascial	Cyclosporine, azathioprine/MMF, and prednisone	462	13	Retrospective
Smith [47]	Kidney and SPK				2, 742	See note ^a .	Retrospective
Yannam [20]	Kidney and Pancreas				n/a	93	Retrospective
Genzini [48]	Pancreas				171	4	Retrospective
Piros [49]	SPK	Midline	Fascial	Sirolimus, cyclosporine, and prednisone	23	8	Retrospective

^a Data was presented in a form that we could not use for analysis.

with a raised BMI had a 10.8% (CI 95% 3.2–30.9, $p < 0.001$) rate, see Fig. 3B. This difference was not statistically significant [$Q(1) = 0.539$, $p = 0.46$].

3.4. Immunosuppression

We examined whether the use of MMF precipitated a hernia and found contrary evidence. The rate of hernia formation in studies reporting the use of MMF was 3.8% (CI 95% 2.5–5.7, $p < 0.001$). In studies that did not use MMF in their immunosuppressive protocol, the rate was significantly higher [$Q(1) = 4.25$, $p = 0.04$] at 11.9% (CI 95% 4.3–28.7, $p < 0.001$).

We found that the use of sirolimus significantly predicted a highly significant increase in hernia rates [$Q(1) = 13.97$, $p < 0.001$]. In studies where sirolimus was used the hernia rate increased to as high as 18.1% (CI 95% 11.7–27, $p < 0.001$) and in the same studies where it was not used the rate was 3.7% (CI 95% 1.7–7.1, $p < 0.001$), see Fig. 4.

3.5. Incision and method of closure

The type of surgical incision used at transplantation appeared to play a role in the rate of incisional hernia formation, but these differences were not statistically significant [$Q(1) = 1.38$, $p = 0.71$]. Paramedian (4.1% CI 95% 1.7–9.4, $p < 0.001$) and Rutherford-Morrison (5.6% CI 95% 2.5–11.7, $p < 0.001$) incisions were associated with the lowest rates of hernia formation. Hockey stick incisions were associated with a higher rate of hernia formation (8.5% CI 95%

3.1–21.2, $p < 0.001$). The data for midline incisions were too variable to be interpreted (10.2% CI 95% 0.5–71.1, $p = 0.17$), see Fig. 5A.

There was no evidence that method of closure played a role in predicting the rate of incisional hernia formation [$Q(1) = 0.55$, $p = 0.46$]. Both single-layer closure (8.1% CI 95% 4.9–12.8, $p < 0.001$) and layered fascial closure (6.1% CI 95% 3.4–10.6, $p < 0.001$) were associated with similar rates of hernia formation (see Fig. 5B).

3.6. Repair

Of the 577 patients who experienced an incisional hernia and were considered for repair, 42 underwent primary repair via herniorrhaphy, and 179 underwent mesh repair. 36 patients had laparoscopic repair of the hernia with mesh. We conducted a meta-analysis to examine the rate of recurrence following repair and found the rate of recurrence after mesh repair was 14.8% (CI 95% 8.8–23.9, $p < 0.001$). The rate of recurrence after the primary repair was 23.7% (CI 95% 6.0–60.0, $p = 0.15$), but this result was not statistically significant due to high variability (see Fig. 6).

Other complications reported on in the 221 patients undergoing herniorrhaphy (with or without mesh) included two cases of seroma, five abdominal wall abscesses, three hematomas and eight mesh infections. We were not able to conduct a meta-analysis to compare the complication rates in laparoscopic repair as only one study reported on this [20]. Outcomes from this study, however, report conversion to open repair in five cases, three seromas, three recurrences and no mesh-related infections in the 36 patients.

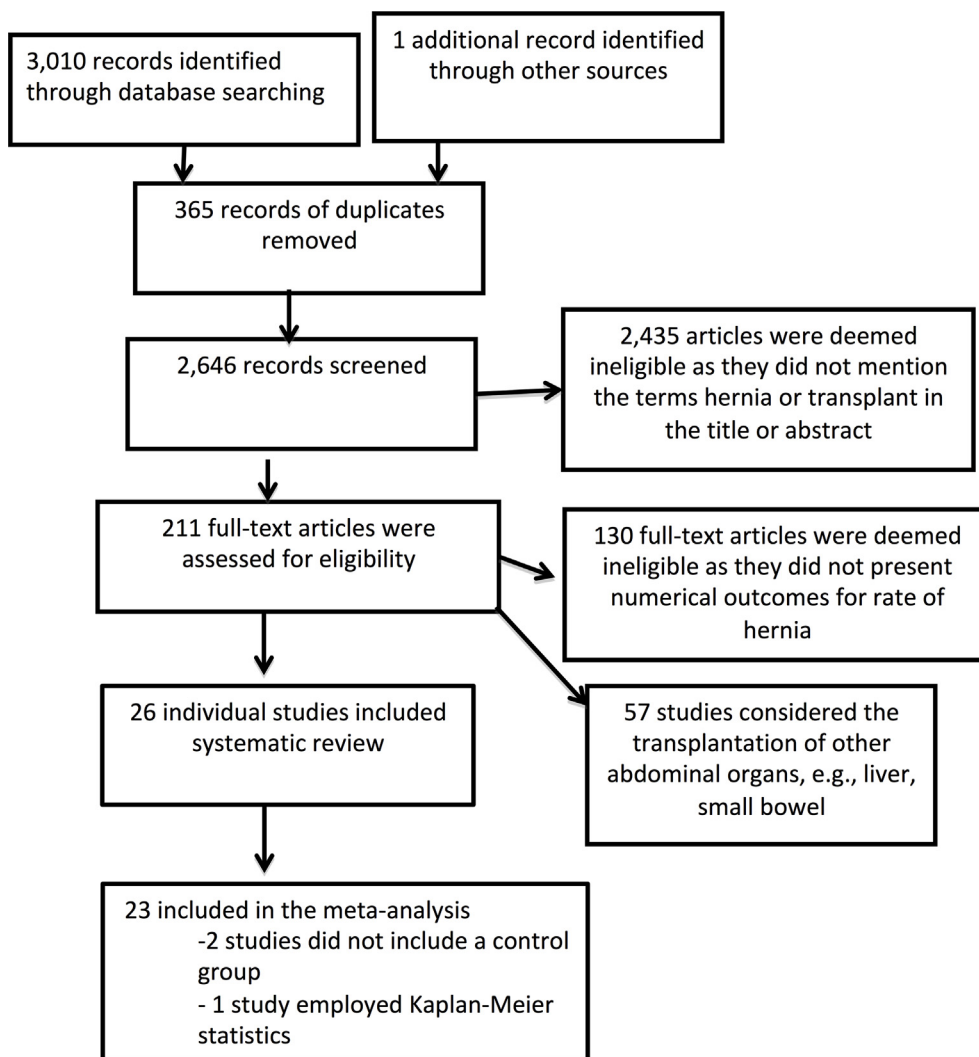


Fig. 1. CONSORT diagram of results at each stage of the search.

4. Discussion

Results of the present work indicate the rate of incisional hernia formation in recipients of kidney and pancreas transplants is extremely low at 4.4%, despite the use of immunosuppression. Age below or above 50 years does not appear to predict an increased rate of hernia formation, but evidence suggests BMI above the normal range may play some role. The use of immunosuppressive agent sirolimus increases the risk of incisional hernia formation significantly. Despite the findings in previous work [21] suggesting wound complications secondary to the use of MMF, we found no evidence that MMF raises the risk of hernia formation and in fact, our study demonstrates the contrary. This study informs surgical practice regarding effective incision and closure methods, which include the Rutherford-Morrison incision with a single-layered method of closure.

Previous work has suggested donor factors such as age [22] and BMI may influence the rate of hernia formation. While we were unable to compare age > 70 years in the present meta-analysis due to a lack of literature, previous work has demonstrated a significantly higher rate of hernia formation in this age group. We found evidence that BMI above the normal range may be associated with an increased rate of hernia formation. This finding is in line with numerous studies that have shown obesity to be linked with problems with delayed wound healing and a risk factor for hernia formation [23–25].

In line with previous studies, we found an increased rate of

incisional hernia formation secondary to the use of sirolimus, but not MMF [8,19]. Sirolimus is prescribed for its unique actions as an immunosuppressant, but it impairs signal transduction of fibroblast and endothelial growth factors, resulting in a greater incidence of wound-related complications [26]. At least in the initial post-transplant period, it appears that caution with the use of sirolimus is warranted. While previous work has suggested, MMF may also be associated with problems in wound healing [21] the present study found no evidence of increased incisional hernia.

The present work illustrates the optimal practice of transplant surgeons. Previous studies have compared incisional hernia rates between patients with different types of incisions [27,28]. Nanni et al. [28] suggest that incisional hernia formation occur four times as often in hockey-stick incisions relative to Rutherford-Morrison, while Filocamo et al. [27] suggest incisional hernia occurrence is five times as common in hockey-stick relative to midline incisions. Our results suggest that the Rutherford-Morrison and paramedian incisions are associated with lower rates of incisional hernia formation than the hockey-stick incision, which may be explained by the longer incision length and direction. The differences we detected in the 2358 patients, however, were not as significant as those shown in previous surgical studies, which may reflect the multicenter expertise and the overall low rate of hernia formation in transplant patients.

Further, closure method with single or multi-fascial closure does not appear to influence the rate of hernia formation. The recently published

Table 2
Newcastle-Ottawa Scale assessment of Quality of Individual studies.

Selection	Comparability				Outcome		
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Assessment of outcome	Follow up was long enough for outcomes to occur	Adequacy of follow up of cohorts
Antonopoulos [46]	*	*	*	*	*	*	*
Benavides [43]	*	*	*	*	*	*	*
Birolini [41]	*	*	*	*	*	*	*
Broggi [10]	*	*	*	*	*	*	*
Chang [42]	*	*	*	*	*	*	*
Dean [19]	*	*	*	*	**	*	*
Filocamo [27]	*	*	*	*	*	*	*
Genzini [48]	*	*	*	*	*	*	*
Humar [21]	*	*	*	*	*	*	*
Knight [26]	*	*	*	*	*	*	*
Li [45]	*	*	*	*	*	*	*
Luc [38]	*	*	*	*	*	*	*
Mahdavi [36]	*	*	*	*	*	*	*
Marconi [22]	*	*	*	*	*	*	*
Mazzucchi [37]	*	*	*	*	*	*	*
Mehrsai [32]	*	*	*	*	*	*	*
Nanni [28]	*	*	*	*	*	*	*
Neeff [39]	*	*	*	*	*	*	*
Ooms [7]	*	*	*	*	*	*	*
Piros [49]	*	*	*	*	*	*	*
Pliszczynski [34]	*	*	*	*	*	*	*
Sheriffdeen [33]	*	*	*	*	*	*	*
Singh [35]	*	*	*	*	**	*	*
Smith [47]	*	*	*	*	*	*	*
Varga [40]	*	*	*	*	*	*	*
Yannam [20]	*	*	*	*	*	*	*

article by Broggi et al. [10] suggests the single-layered parietal closure increases the odds of hernia formation by 2.89 times. It is unclear, however, how many patients in this group underwent single-layered parietal closure. In the 341 patients included in the present work that underwent single layered closure, we found no evidence of increased rate of incisional hernia formation. We suggest that when expertly

performed, this single-layered closure is a safe and efficient technique that reduces operative time and risk for patients. Further studies reporting on complications following varying incision types and types of closure would be of benefit in clarifying this.

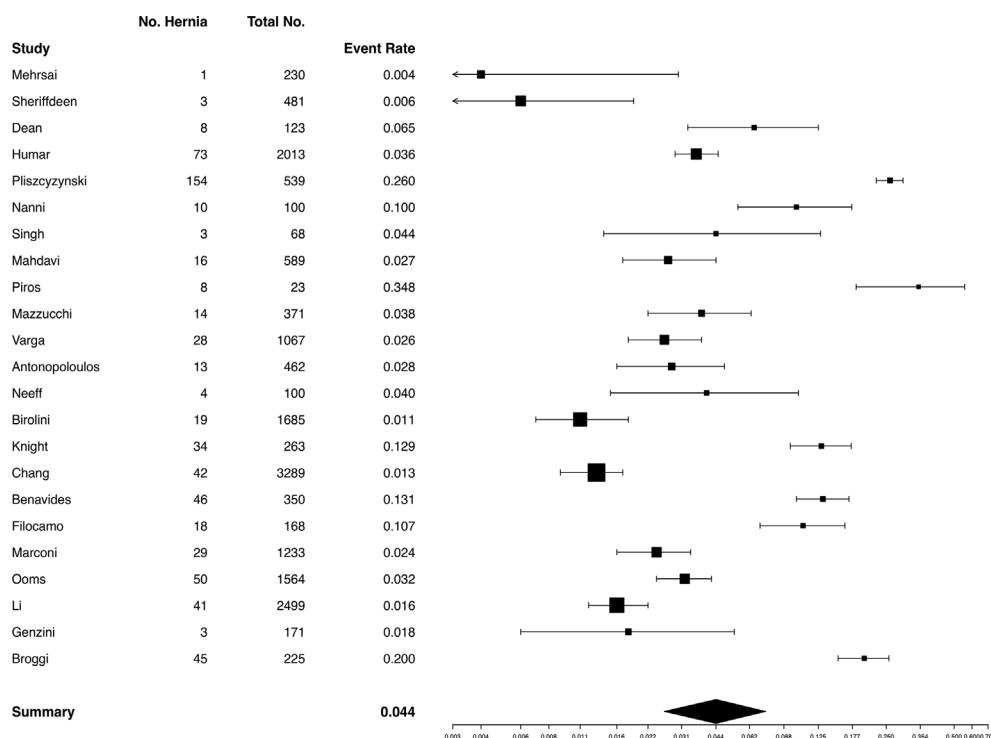


Fig. 2. Forest plot of hernia rates in included studies of kidney and pancreas transplantation.

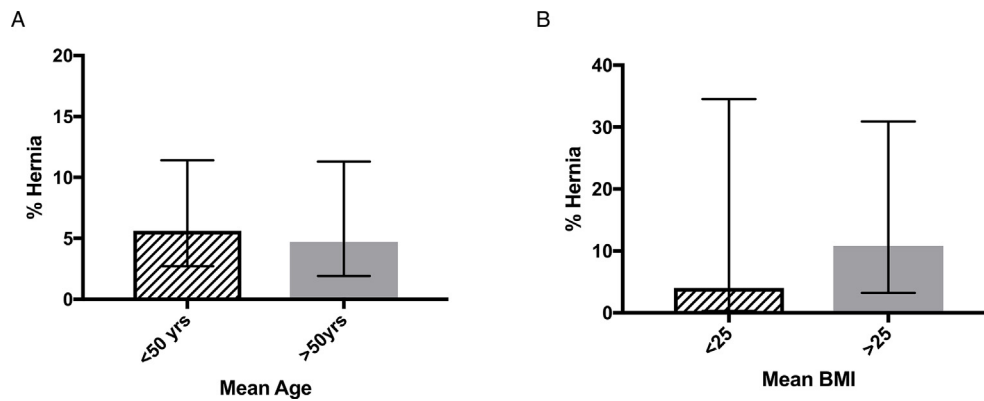


Fig. 3. A) mean recipient age; B) mean recipient BMI and rate of incisional hernia formation in kidney and pancreas transplant recipients.

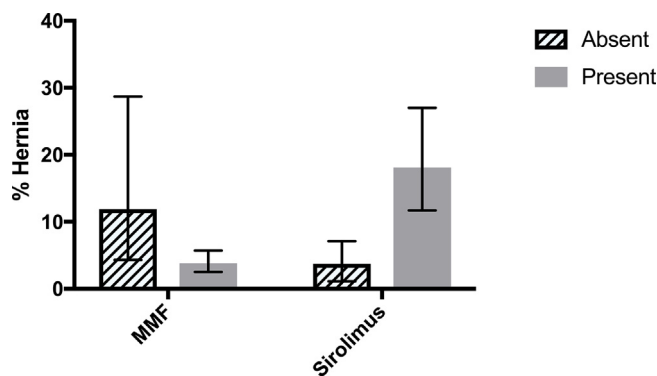


Fig. 4. Immunosuppression and rate of incisional hernia formation in kidney and pancreas transplant recipients.

4.1. Future directions

Future studies examining the rates of hernia recurrence after laparoscopic repair with and without mesh, relative to primary repair, and complications such as seroma, hematoma, infection and recurrence of hernias would allow for further meta-analysis directly comparing methods of repair.

There is evidence to suggest certain patient groups with very high risks of developing incisional hernias may benefit from prophylactic mesh placement [29]. In a multicenter, double-blind and randomised controlled trial of patients with BMI > 27kg/m² undergoing elective midline laparotomy, Jairam AP et al. [30] showed the incisional hernia rate was 30% for primary closure, 13% for onlay mesh reinforcement and 18% for sublay mesh reinforcement at 2-year follow-up³¹ [31]. To the authors' knowledge, there are currently no studies on the use of prophylactic mesh placement in the higher-risk transplant patients such as those with high BMI, on sirolimus and undergoing hockey stick incision for their transplant procedure.

4.2. Limitations

The main limitation of the present work was the lack of power due to limited numbers of patients in subgroups used for comparison. More studies reporting on hernias in pancreas recipients would enable analysis in this group. Further availability of high-quality literature reporting specific surgical outcomes and complications of transplant recipients would clarify the present findings. The details of comorbid factors such as renal function, time on dialysis, severity of diabetes mellitus, metabolic syndrome or congestive heart failure could clarify groups at highest risk. This evidence would strengthen recommendations regarding the optimal medical and surgical management of patients receiving renal and pancreas transplantation.

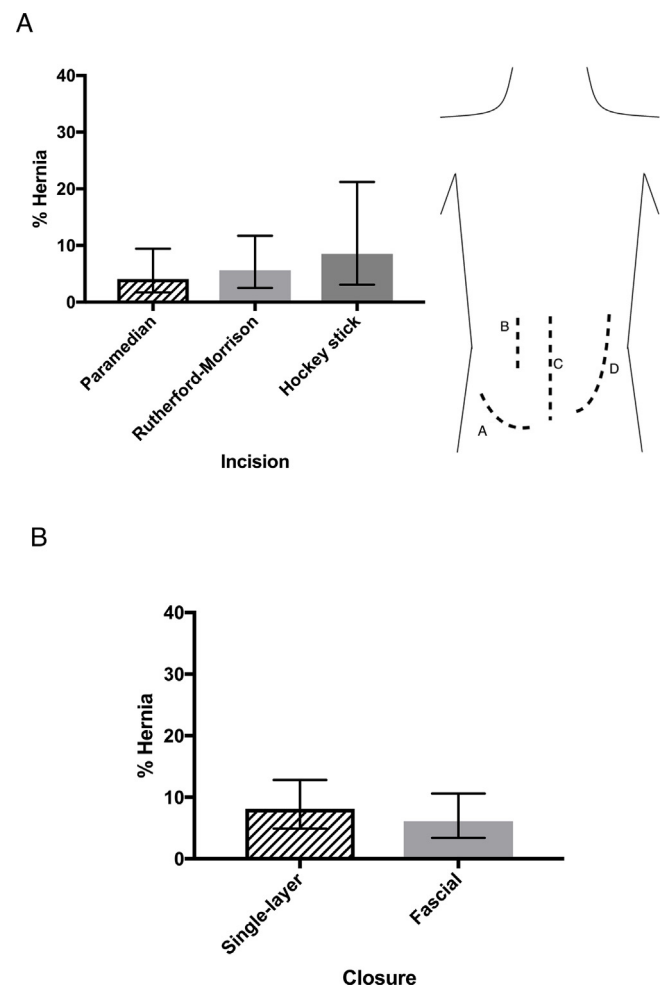


Fig. 5. A; incision type (A: Rutherford-Morrison, B: Paramedian, C: Midline, D: Hockey-Stick) and B; closure type and rate of incisional hernia formation in kidney and pancreas transplant recipients.

5. Conclusions

The findings of the present work inform the most appropriate surgical practice for patients undergoing kidney and pancreas transplants. Optimally, patients should make efforts to reduce weight into the healthy range before undergoing transplantation. Careful selection of immunosuppression with sirolimus sparing especially in the early post-transplant period can minimize the risk of incisional hernia formation. Major transplant units currently favor the Rutherford-Morrison incision

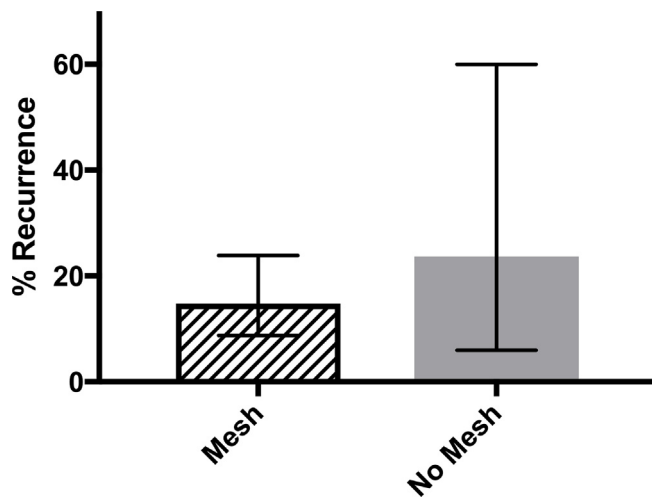


Fig. 6. Recurrence rate of an incisional hernia after open repair with and without mesh in kidney and pancreas transplant recipients.

as a method of surgical incision, and the present evidence indicates this is a safe and efficient method for transplantation. There is no evidence that single-layered closure is associated with a higher rate of incisional hernia formation and when expertly performed can reduce operative time.

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Ethical approval

Ethical approval was not necessary for this type of study.

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Author contribution

Sara Shahrestani-study design, data collection, analysis and writing.
 Hanh Minh Tran-study design, data collection, and writing.
 Henry Pleass-study design, data analysis and writing.
 Wayne J Hawthorne-study design, data analysis and writing.

Conflicts of interest

There are no conflicts of interest to declare.

Trial registry number

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