MEDDOCS Open Access Publisher

ISSN: 2640-1258

Journal of Abdominal Wall Reconstruction

Open Access | Research Article

Abdominal Wall Hernia Repair with Composite Meshes: Systematic Review and Meta-Analysis of Mesh-Related Complications

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Received: Feb 21, 2023

Accepted: Mar 23, 2023

Published Online: Mar 30, 2023

Journal: Journal of Abdominal Wall Reconstruction

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Composite mesh; Abdominal wall hernia; Ventralex; Composix; Dipromed

Abstract

Introduction: Umbilical and epigastric hernias are frequent clinical conditions with expected low complications. This systematic review and meta-analysis aimed to analized the complications associated to the intraperitoneal bicomponent meshes as Ventralex· Bard Composix Kugel· / FLaPp· / CMC· produced respectively by Bard and Dipromed SRL. These prostheses are the most frequently used composite meshes.

Methods: This systematic review and meta-analysis were reported according to the recommendations of the 2020 updated Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines, and the Cochrane handbook for systematic reviews of interventions. One hundred and eighteen papers from 2000 to 2022 were screened and collected, and the final analysis was performed on 24 studies.

Results: Since in some cases the time of occurrence of bowel obstruction/occlusion, seroma, and recurrence was not specified in the analyzed studies, two versions of the meta-analysis were conducted for these complications: version#1: we counted only those cases for which there is the clear indication about the time of occurrence of the complication; version#2: we counted all cases of complication, also without any indication about the time of occurrence. In the case of Composix mesh: 10 studies were included for a total of 389 patients considered: 1 case of enterocutaneous fistula and 1 case of foreign body sensation, no adhesion cases

Cite this article: Montori G, Rosati S, Ortenzi M, Mazzarolo G, Licitra E, et al Abdominal Wall Hernia Repair with Composite Meshes: Systematic Review and Meta-Analysis of Mesh-Related Complications. J Abdom Wall Reconstr. J Abdom Wall Reconstr. 2023; 6(1): 1012.

or chronic pain or small bowel obstruction or mortality, the pooled incidence of seroma emerged from version#2 is 1.50% (95% CI: 0.01% - 4.40%), about recurrence the pooled incidence is 0.11% (95% CI: 0.00% - 1.45%). In the case of Ventralex mesh: 14 studies were used in the meta-analysis for assessing the incidence of each mesh- related complication, for a total of 2181 patients considered. No cases of adhesion, enterocutaneous istula, small bowel obstruction, or mortality. The pooled incidence of seroma that emerged from version#2 is 0.00% (95% CI: 0.00% - 0.00%). The pooled incidence of foreign body sensation is 0.00% (95% CI: 0.00% - 0.43%). The pooled incidence of recurrence for version#2 is 0.58% (95% 53 CI: 0.00% - 2.06%).

Conclusions: In conclusion, data reported in this meta-analysis won't compare different types of meshes commonly used in surgical practice to evaluate the complications mesh-related. However, due to the different language in complications classification, version#2 appeared more comprehensive and nearer to reality. Including studies with stronger study designs and longer follow up (more than 2 years), it is possible to find complications like recurrence and foreign body sensation which probably take longer to appear.

Background

Umbilical and epigastric hernias are frequent clinical conditions with expected low complication rates (about 3.5 %) after surgical repair [1]. To date, it is globally accepted that the use of meshes to reinforce the abdominal wall is the gold standard in the treatment of abdominal wall hernias [2,3].

The interest to identify the ideal mesh (biocompatible, with the lowest possible complication rate after surgery, and easy to use and economical) pushes the market towards highly competitive devices. Composite meshes are frequently used in surgery, especially in intraperitoneal laparoscopic repair, as they can be placed comfortably in an intra-peritoneal position, avoiding the dissection of the retromuscolar space. Current literature reports that the concept and the design of composite meshes appear to be very convincing [1].

Despite several publications and studies, no clear consensus about the definition of complications that can occur, also regarding the cause of these complications (mesh type, surgical technique, or other conditions) can be found in the literature to date. This lack of evidence makes it difficult to speak a common language in different clinical articles and compare different studies. In this study, we want to try to evaluate the complications rates of the bicomponent meshes that we used more frequently in our clinical practice (FLaPp· / CMC·), to make an overview of the safety profile of these meshes to better guide the using choice. This systematic review and meta-analysis aimed to evaluate the complications related to the use of this specific type of meshes. Bicomponent meshes are mesh composed by a dual layer having a synthetic parietal side in polypropylene to promote a strong repair and a visceral surface, that repels tissue ingrowth and decreases adhesion formation. The two layers are initially separated and are sewn together. In the search literature we found 4 meshes that meet these criteria and are similar in use, composition, and structure: Ventralex· Bard Composix Kugel· / FLaPp· / CMC·. The two first are performed by Bard®, and the other 2 meshes are performed by Dipromed SRL. These prostheses are the most frequently used composite meshes (made of Polypropylene -PP- and expanded polytetrafluoroethylene -ePTFE-), particularly in open intraperitoneal Onlay mesh position (IPOM). For this reason, we evaluated the most frequent mesh-related complication that can occur and the safety profile of these meshes.

Materials and methods

This systematic review and meta-analysis were conducted according to recommendations of the 2020 update Preferred Reporting Items for Systematic reviews and Metanalyses (PRISMA) guidelines [2,3], and the Cochrane handbook for systematic reviews of interventions [4,5]. The risk of bias in each included study was assessed according to the ROBINS-I tool [6] for observational studies and was not performed for the single included Randomized Controlled Trial (RCT). The inclusion criteria for the PICO search strategy are exposed in **Table 1**.

Table 1: Search terms and keywords used in the literature research. (1) Needed for the assessment of safety and performances. (2) Needed for the assessment of state of the art.

Principal Search Terms	Additional Search Terms or Filters (used if required to focus the search)
CMC[1]	Full text
FLAPP[1]	Last 20 years
PCMC[1]	Last 5 years
UCMC[1]	Human study
Hernia[2]	
Incisional hernia[2]	
Mesh infection[2]	
Bulging[2]	
Mesh adhesions[2]	
intestinal fistula[2]	
mesh detachment[2]	
ventral laparoscopy[2]	
incisional hernia and abdominal wall hernia[2]	
hernioplasty[2]	

Types of meshes

We analyzed four types of composite meshes: Bard Ventralex hernia patch® and Bard Composix Kugel·, / FLaPp· / CMC·. Meshes characteristics were reported below. The last three mesh types were similar in characteristics and were put in the same group of analysis.

Ventralex hernia patch® (Bard) is a composite polytetraXuoroethylene (ePTFE)/polypropylene mesh, which is placed behind the hernia defect. The PP side of the patch promotes tissue ingrowth and the incorporation of the patch into the abdominal wall. The ePTFE side of the patch, which is placed in contact with the viscera, gives a permanent barrier and minimizes tissue attachment. The mesh has also two PP straps that facilitate placement, positioning, and fixation.

Composix KugelTM patch® (Bard Davol, Inc.), the mesh is a self-expanding, non-absorbable prosthesis with an intestinal side in expanded polytetrafluoroethylene (ePTFE) and two layers of monofilament polypropylene (PP) for the abdominal wall side. A Peripheral Polyethylene Terephthalate (PET) memory recoil ring is located within the two PP layers. The PP layers have

additional ''pockets'' to support the ideal placement of the mesh. The abdominal side of the mesh has a sewn edge covering the 1.05-mm thick PET memory recoil ring which is held together by welds. The ring keeps the mesh optimally expanded; larger meshes have a second, concentrically placed inner ring. The PP mesh surface facilitates the ingrowth of granulation tissue and provides stability as a replacement for the abdominal wall.

FLaPp® mesh (Free Lateral Polypropylene Prosthesis–Dipromed SRL, San Mauro Torinese, Torino, Italy), is obtained by joining a PP monofilament mesh layer for the abdominal wall side, and a non- absorbable PP film with anti-adherent properties for viscera side. The advantages are related to the easy positioning, even in pluri-operated patients or after previous implant removal [23].

Clear Composite Mesh (CMC, DIPROMED SRL San Mauro Torinese, Turin, Italy) has two PP layers, a microporous light mesh, and a thin transparent film. The parietal side is microporous and is made of PP monofilament to optimize tissue growth. The visceral side is made of non-porous, smooth, transparent PP film to prevent the formation of adhesions on the intestinal side. This mesh has a visceral side with anti-erosive and anti-adhesive functions and a ventral macroporous side allowing the growth of fibroblasts [31]. As reported in preclinical studies, the CMC can be colonized by fibroblasts on the side facing the abdominal wall (without strong foreign body reaction), whereas no cell growth occurs on the side facing the viscera and the temporary inflammation avoiding adhesion with intraabdominal viscera. Its elasticity and anisotropy index were more like those of natural tissue [32].

Outcomes measures

The search was conducted according to PICO criteria **(Table 2)**. The populations of the study were chosen based on the most recent guidelines of the European Hernia Society (EHS) [33] we decided to include the following mesh complications: Adherences/adhesions, Enterocutaneous fistula, Seroma (if occurred at least 3 months after surgery), Foreign body sensation, Chronic pain not due to fixation, Bowel obstruction/occlusion (if occurred at least 1 month after surgery), Recurrence (if occurred at least 3 months after surgery), Mortality.

Table 2: PICO process used for the search strategy of the device.

Acronym	P	I	C	O
Description	Problem /Patient / Population	Intervention / Indicator	Compare / Control	Outcome
Query	Who are the users, patients or population being affected?	What is the management strategy (e.g. surgical intervention, screening, rehabilitation, drug co- administration etc.) for the identified population?	Is there a control group and/ or alternative treatment option that should be taken into consideration?	What are the patient relevant outcomes of the studied intervention?
Answer for the device	Patients with abdominal hernia or abdominal defects, such as Incisional hernia	Hernia repair and reinforcement of the abdominal wall using surgical mesh	Alternative methods can be used but reinforcements using surgical mesh is the golden standard	complications, morbidity, (as recurrence rate, seroma rate, chronic pain rate, foreign body sensation, adhesions, enterocutaneous fistula, bowel obstruction) mortality

Literature search strategy

A computerized search in PUBMED, EMBASE, MEDLINE database, Cochrane Collaboration and library, NICE (UK National Institute for Clinical Excellence), Clinical Trials.gov, EU Clinical Trials Register(https://www.clinicaltrialsregister.eu/ctr-search/search), was performed. Articles from 2000 to 2022 were included. The primary search strategy identified 118 studies.

CMC/FLAPP/PCMC/UCMC/hernia/incisional hernia/mesh infection/bulging/mesh adhesions/intestinal fistula/mesh detachment/ventral laparoscopy/incisional hernia/abdominal wall hernia/keratoplasty combined with AND/OR. Search restrictions imposed were the following: human study, full text available. The dates were selected to allow comprehensive published abstracts of clinical trials, comparative studies, randomized controlled trials, systematic reviews, meta-analyses, large case series, original articles, and case reports. Literature selection is reported in the following

PRISMA flow chart **(Figure 1)**. The commune characteristic of the meshes are that are a bicompenent mesh. According to that in the search strategy we found 4 meshes that met this criteria and included in the study: Ventralex, Composix Kugel®, FLaPp®, CMC®.

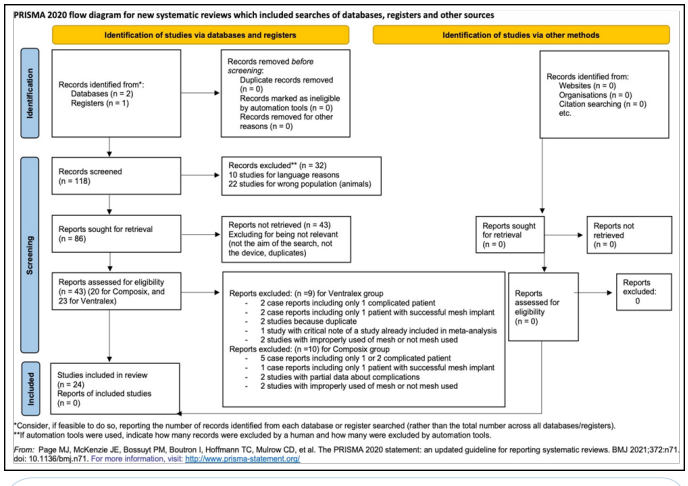

Figure 1: PRISMA flow chart.

Studies identified by the primary search strategy were selected based on title, abstract, and full-text review by two independent reviewers (S.R. and G.M.). A second revision of the full text and a second screening was performed by other two independent reviewers (F.A. and G.M). As reported in PRISMA, articles in other languages than English, animal, and preclinical studies, or in which no clear mesh was defined or no clear complications were defined, were excluded from the meta-analysis.

Statistical analysis

Meta-analysis of proportions with a random-effect model was used to analyze the pooled incidence of clinical complications after hernia repair. Studies heterogeneity was assessed using two different tests: a) the Q statistic, under the null hypothesis H0 that all studies are homogeneous (a p-value <0.05 was considered statistically significant); b) the I2 statistic, expressed in percentage scale where 0% identifies homogeneous studies and 100% represents completely heterogeneous studies. In case of detected heterogeneity, the moderator analysis was performed: studies were divided into subgroups according to surgical technique (open surgery vs laparoscopy), publication year (2012-2022 vs 2001-2011), and journal quartile (https://www.scimagojr.com/, Q1-Q2 vs Q3-Q4-NA), and an independent meta-analysis was conducted on each subgroup. It was not possible to use moderator variables related to the population characteristics (for example patients' age, comorbidity, hernia size, and so on…) since these data were not available for all studies. A qualitative analysis of publication bias was conducted to remove studies that are biased concerning the considered outcome (i.e. complication incidence). Finally, a set of measures were calculated to identify potential outliers that may distort the conclusions of the meta-analysis: studentized deleted residuals, DFFITS values, Cook's distance, and COVRATIO values [35]. Moreover, a qualitative identification of borderline cases, which could influence the homogeneity of the studies, was performed. Studies identified as outliers were removed and meta-analysis was repeated, whereas borderline studies were kept. All these studies (outliers and borderline) were analyzed and discussed separately to understand possible causes that could make them different from the rest. Meta-analysis and related statistics were implemented in RStudio environment (version 2022.02.3).

Results

We included 14 studies for Ventralex mesh [7-20] and 10 for Bard Composix Kugel® / FLaPp® / CMC® mesh [21-30]. For Ventralex mesh, seven were retrospective studies [7-13], one randomized controlled trial (RCT) (14a), and five were prospective studies [15-20]. For Composix/FLaPp/CMC mesh, all studies were retrospective [21-30]. One meta-analysis for each mesh-related complication was conducted. All the studies retrieved from the systematic review were analyzed to identify the incidence of each mesh-related complication. When a complication was attributable to other causes than the mesh, it was not counted for the estimation of the incidence. Since in some cases the time of occurrence of bowel obstruction/occlusion, seroma, and recurrence was not specified in the analyzed studies, two versions of the meta-analysis were conducted for these complications:

- version#1: we counted only those cases for which there is a clear indication about the time of occurrence of the complication
- version#2: we counted all cases of complication, also without any indication about the time of occurrence

No quantitative tests were applied to evaluate the publication bias because there is no evidence that proportional data adequately adjusts for these tests [34].

Meta-Analysis for Composix Meshes

The analysis of Composix meshes included Composix Bard mesh, FLaPp, and CMC, which were considered similar prostheses. Ten studies were included in the meta-analysis for assessing the incidence of each mesh-related complication, for a total of 389 patients considered. Details about the complication incidence reported in each study are shown in **Table 3**. Meta-analysis results for each complication are reported in the following sections and presented using a forest plot in which studies are sorted in descending order concerning their weight (that is proportional to the number of included patients).

Table 3: Details about the complication incidences reported in the studies considered for the meta-analysis on the Composix meshes.

AUTHORS	YEAR	CITATION	#PATIENTS	ADHERENCES/ ADHESIONS	ENTERO- CUTANEOUS FISTULA	SEROMA (version#1)	SEROMA (version#2)	FOREING BODY SENSATION	CHRONIC PAIN	BOWEL OBSTRUCTION/ OCCLUSION (version#1)	BOWEL OBSTRUCTION/ OCCLUSION (version#2)	RECURRENCE (version#1)	RECURRENCE (version#2)	MORTALITY
Wiegering A	2013	Hernia. 2013 Ag	21	0	0	0	3	1	0	0	0	2	2	0
Lasses Martínez B	2017	Hernia. 2017 Apr	48	0	0	0	0	0	0	0	0	9	9	0
Munegato G	2017	Updates Surg. 2017 Dec	29	0	0	0	0	0	0	0	0	0	0	0
Agresta F	2017	Updates Surg. 2017 Dec	29	0	0	0	0	0	0	0	0	0	0	0
Liu FD	2011	Plast Reconstr Surg. 2011 Aug	14	0	0	0	3	0	0	0	0	0	0	0
Ferrara R	2007	Chir Ital. 2007 Sep-Oct	17	0	0	0	0	0	0	0	0	0	0	0
Biondi A	2010	Ann Ital Chir. 2010 May-Jun	28	0	0	0	0	0	0	0	0	0	0	0
Gillian GK	2002	JSLS. 2002 Oct-Dec	100	0	0	0	3	0	0	0	0	0	0	0
Cobb WS	2003	Am Surg. 2003 Sep	95	0	1	0	4	0	0	0	0	2	2	0
McKay R	2006	Surg Laparosc Endosc Percutan Tech. 20	8	0	0	0	0	0	0	0	0	0	0	0

Adherences/Adhesions

None of the considered studies reported evidence of adherences or adhesions due to the mesh.

Enterocutaneous Fistula

In all studies analyzed [21-30], only 1 case of enterocutaneous fistula out of 389 patients was reported. The meta-analysis results are presented in the forest plot in **Figure 2**. As it emerges from the I2 statistic and the p-value of the Q statistic, studies are homogeneous (I2=0%, p-value=1). The pooled incidence of enterocutaneous fistula is 0.00% (95% CI: 0.00% - 0.42%).

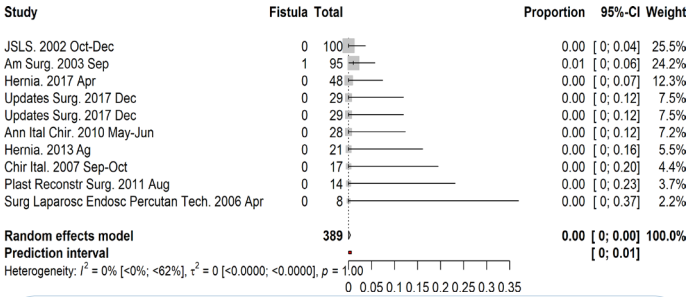

Figure 2: Forest plot of the proportional meta-analysis of enterocutaneous fistula incidence for Composix meshes.

Seroma

The two versions of the meta-analysis reported different incidence values. In particular, in version#1 none of the considered studies reported evidence of seroma due to the mesh. In version#2, a total of 13 cases of seroma (without indication of the time of occurrence) were reported, and results are presented in the forest plot in **Figure 3**. The I2 statistic shows that studies are moderately heterogeneous (I2=45%), also the p-value of the Q statistic is at the limit of significance (p-value=0.06). No outliers were detected using the above-mentioned metrics, while one borderline study was identifiable (25a). None of the moderator variables were able to explain the heterogeneity. The pooled incidence of that emerged from version#2 is 1.50% (95% CI: 0.01% - 4.40%).

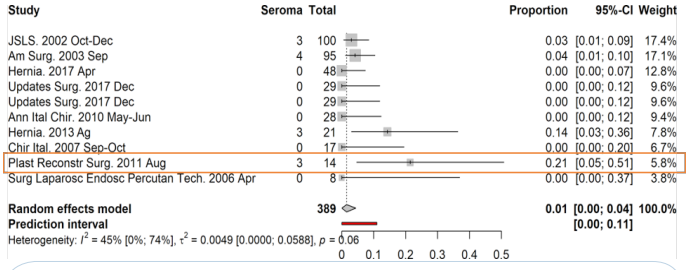

Figure 3: Forest plot of the proportional meta-analysis of seroma incidence (version#2) for composix meshes. Borderline study is highlighted with the orange rectangle.

Foreign Body Sensation

Only 1 case of foreign body sensation out of 389 patients was reported in the considered studies [21-30]. The meta-analysis results are presented in the forest plot in **Figure 4**. As it emerges from the I2 statistic and the p-value of the Q statistic, studies are homogeneous (I2=0%, p-value=0.91). The pooled incidence of foreign body sensation is 0.00% (95% CI: 0.00%-0.25%).

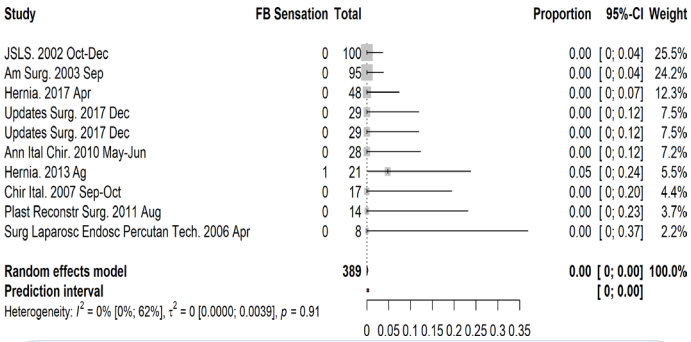

Figure 4: Forest plot of the proportional meta-analysis of foreign body sensation incidence for composix meshes.

Chronic pain

None of the considered studies reported evidence of chronic pain due to the mesh.

Bowel obstruction/Occlusion

None of the considered studies reported evidence of bowel obstruction/occlusion due to the mesh, for both meta-analysis versions.

Recurrence

The incidence of recurrence is the same for all studies in both versions of the meta-analysis (13 cases out of 389 patients) [21-30]. Thus, only one meta-analysis was performed, whose results are presented in the forest plot in **Figure 5a**. Studies are heterogeneous (I2=66%, p-value<0.01). One outlier study was detected using the above-mentioned metrics [22] that was removed from the meta-analysis. No borderline studies were identified. After outlier removal, the studies resulted in homogeneity (I2=0%, p-value=0.51), and the forest plot is shown in **Figure 5b**. The pooled incidence of recurrence is 0.11% (95% CI: 0.00% - 1.45%).

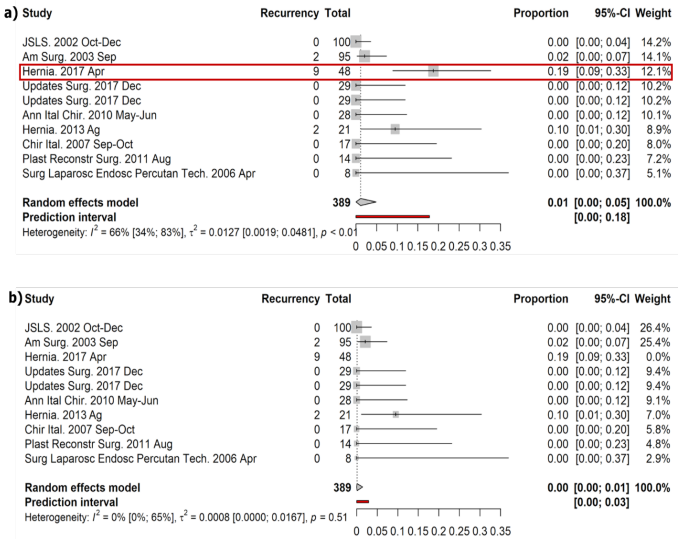

Figure 5: (a and b): Forest plot of the proportional meta-analysis recurrence incidence for Composix meshes before (panel a) and after (panel b) outlier removal. Outlier study is highlighted with the red rectangle.

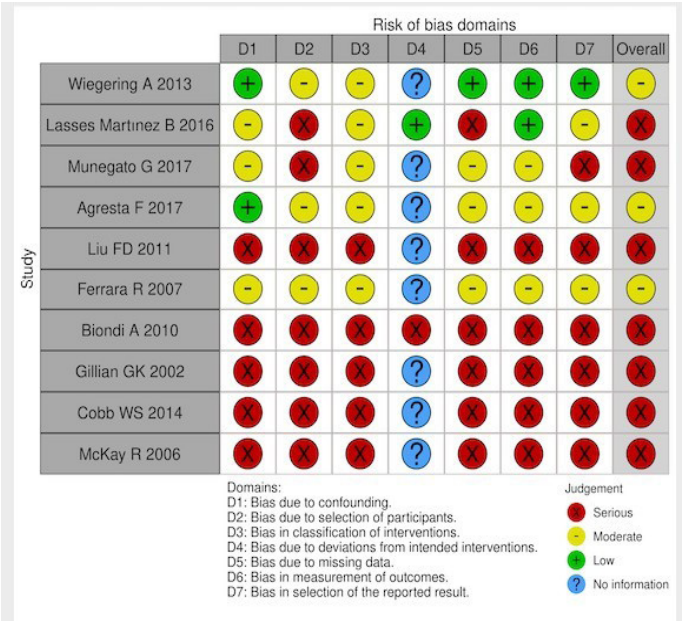

Figure 6: ROBINS-I for observational studies analyzed in case of Composix meshes.

Mortality

None of the considered studies reported evidence of mortality due to the mesh.

Risk of bias evaluation

In **Figure 6** where reported the ROBINS-I conducted for observational studies analyzed [21-30]. The majority of studies have many biases about comorbidities, follow-up duration, ages, recurrence, and hernia dimension.

Meta-Analysis for Ventralex Meshes

Fourteen studies were used in the meta-analysis for assessing the incidence of each mesh-related complication, for a total of 2181 patients considered [7-20]. Details about the complication incidences reported in these studies are shown in **Table 4**. Meta-analysis results for each complication are reported in the following sections and presented using a forest plot in which studies are sorted in descending order concerning their weight (that is proportional to the number of included patients).

Table 4: Details about the complication incidences reported in the studies considered for the meta- analysis on the Ventralex meshes.

AUTHORS	YEAR	CITATION	#PATIENTS	ADHERENCES/ ADHESIONS	ENTERO- CUTANEOUS FISTULA	SEROMA (version#1)	SEROMA (version#2)	FOREING BODY SENSATION	CHRONIC PAIN	BOWEL OBSTRUCTION/ OCCLUSION (version#1)	BOWEL OBSTRUCTION/ OCCLUSION (version#2)	RECURRENCE (version#1)	RECURRENCE (version#2)	MORTALITY
Nicolau AE	2019	Chirurgia (Bucur). 2019 Jan-Feb	28	0	0	0	0	0	0	0	0	0	0	0
Neinstein RM	2015	Plast Reconstr Surg. 2015 Apr	11	0	0	0	0	0	0	0	0	0	0	0
Porrero JL	2019	Hernia. 2019 Feb	1359	0	0	0	0	0	0	0	0	0	52	0
Kalayci M	2019	Ann Ital Chir. 2019	27	0	0	0	0	0	0	0	0	0	0	0
Bensaadi H	2014	Am Surg. 2014 Jan	38	0	0	0	0	6	0	0	0	4	4	0
Popescu RC	2021	JSLS. 2021 Oct-Dec	68	0	0	0	0	0	0	0	0	0	0	0
Martin DF	2008	Hernia. 2008 Aug	88	0	0	0	1	0	0	0	0	0	0	0
Vychnevskaia K	2010	Dig Surg. 2010	101	0	0	0	0	0	0	0	0	0	0	0
Tollens T	2011	Hernia. 2011 Oct	135	0	0	0	0	7	0	0	0	0	0	0
Hadi HI	2006	Hernia. 2006 Oct	51	0	0	0	0	0	0	0	0	0	0	0
Berrevoet F	2011	Am J Surg. 2011 Jan	60	0	0	0	0	0	0	0	0	5	5	0
Tinelli A	2011	Minim Invasive Ther Allied Technol. 2011	51	0	0	0	0	0	0	0	0	0	0	0
Tran H	2011	JSLS. 2011 Jan-Mar	12	0	0	0	0	0	0	0	0	0	0	0
Iversen E	2010	Hernia. 2010 Dec	152	0	0	0	0	0	1	0	0	3	3	0

Adherences/Adhesions

None of the considered studies reported evidence of adherences or adhesions due to the mesh [7-20].

Enterocutaneous Fistula

None of the considered studies reported evidence of enterocutaneous fistula due to the mesh [7-20].

Seroma

For seroma, the two versions of the meta-analysis reported different incidence values. In particular, in version#1 none of the considered studies reported evidence of seroma due to the mesh. In version#2 only one case of seroma (without indication of the time of occurrence) was reported, and meta- analysis results are presented in the forest plot in **Figure 7**. As it emerges from the I2 statistic and the p-value of the Q statistic, studies included in this meta-analysis are homogeneous (I2=0%, p- val-

ue=0.79). The pooled incidence of seroma that emerged from version#2 is 0.00% (95% CI: 0.00%- 0.00%).

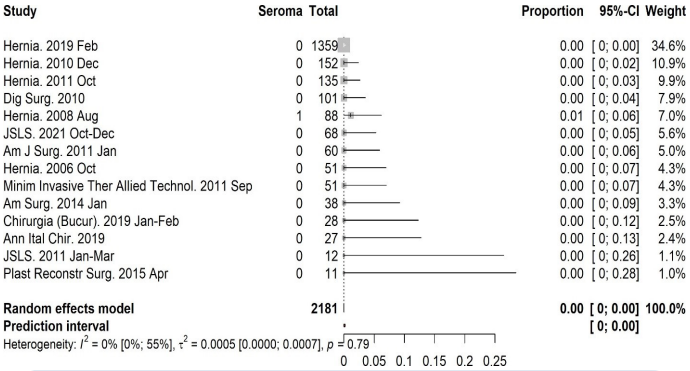

Figure 7: Forest plot of the proportional meta-analysis of seroma incidence (version#2) for ventralex meshes.

Foreign Body Sensation

A total of 15 cases of foreign body sensation out of 2181 patients were reported in the analyzed studies [7-20]. The meta-analysis results are presented in the forest plot in **Figure 8a**. As it emerges from the I2 statistic and the p-value of the Q statistic, studies are heterogeneous (I2=73%, p-value<0.01). One outlier study was detected using the above-mentioned metrics [14] that was removed from the meta-analysis. After outlier removal, the studies still resulted to be moderately heterogeneous (I2=56%, p-value<0.01), and the forest plot is shown in **Figure 8b**. No other outliers were detected, and one borderline study was identified [11]. None of the moderator variables were able to explain the heterogeneity. The pooled incidence of foreign body sensation is 0.00% (95% CI: 0.00% - 0.43%).

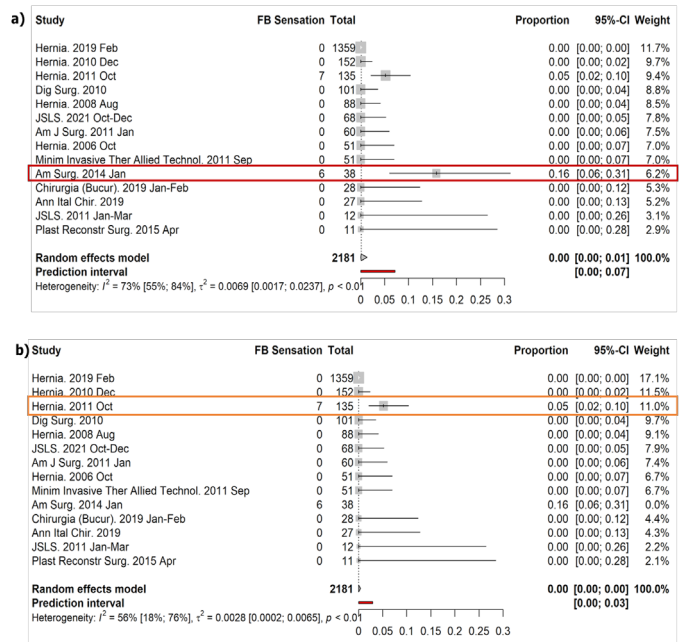

Figure 8: (a and b): Forest plot of the proportional meta-analysis of foreign body sensation incidence for ventralex meshes before (panel a) and after (panel b) outlier removal. Outlier study is highlighted with the red rectangle, borderline study is highlighted with the orange rectangle.

Bowel Obstruction/Occlusion

None of the considered studies reported evidence of bowel obstruction/occlusion due to the mesh, for both meta-analysis versions [7-20].

Recurrence

For recurrence, the two versions of the meta-analysis reported different incidence values. Regarding version#1, 12 cases of recurrence were identified, and results are presented in the forest plot in **Figure 9a**. As it emerges from the I2 statistic and the p-value of the Q statistic, studies included in this meta-analysis are heterogeneous (I2=71%, p-value<0.01). Two outlier studies were detected [14,20], that were removed from the meta-analysis. After outlier removal, the studies resulted in homogeneous (I2=19%, p-value=0.26) and the forest plot is shown in **Figure 9b**. The pooled incidence of recurrence for version#1 is 0.00% (95% CI: 0.00% - 0.10%). Regarding version#2, 64 cases of recurrence were identified and results are presented in the forest plot in **Figure 10**. Studies included in this meta-analysis are heterogeneous (I2=69%, p-value<0.01). No outlier studies were detected and three borderline studies were identified [15,10,20]. None of the moderator variables were able to explain the heterogeneity. The pooled incidence of recurrence for version#2 is 0.58% (95% CI: 0.00% - 2.06%).

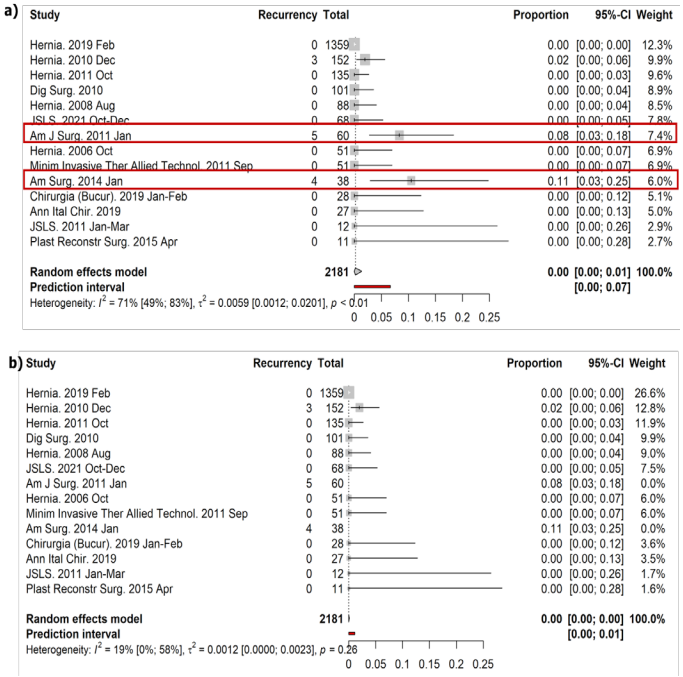

Figure 9: Forest plot of the proportional meta-analysis of recurrence incidence (version#1) for ventralex meshes before (panel a) and after (panel b) outlier removal. Outlier studies are highlighted with the red rectangles.

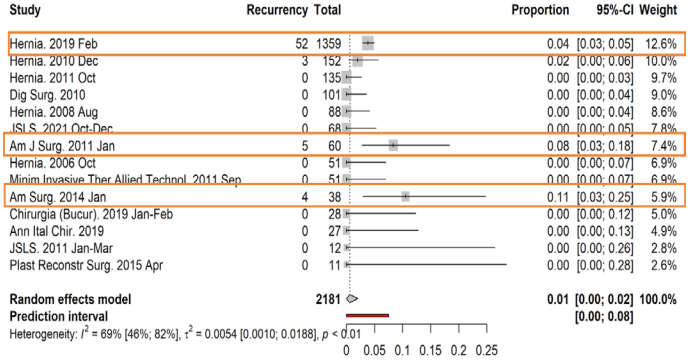

Figure 10: Forest plot of the proportional meta-analysis of recurrence incidence (version#2) for ventralex meshes. Borderline studies are highlighted with the orange rectangles.

Mortality

None of the considered studies reported evidence of mortality due to the mesh [7-20].

Risk of bias evaluation

Figure 11 were reported the ROBINS-I conducted for observational and RCT studies analyzed [7-20].

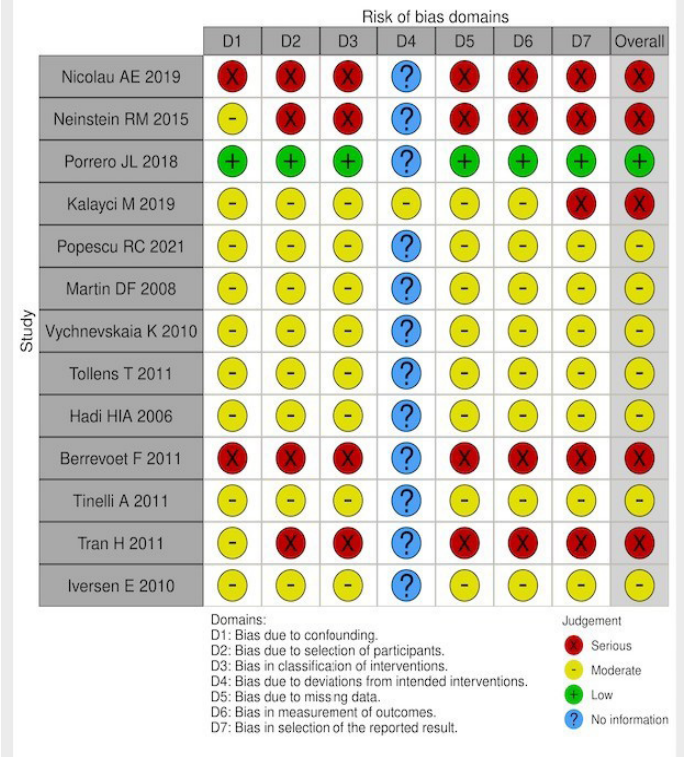

Figure 11: ROBINS-I for observational studies analyzed in case of Ventralex meshes.

Discussion

Abdominal wall hernia, as umbilical and epigastric hernia, is a frequent clinical condition and surgical repair, especially prosthetic repair, is required [1].

The need for a parietal reinforcement to close abdominal wall hernia is almost established from several studies and guidelines and decreases a recurrence risk of a half percent [36]. Intraperitoneal mesh positioning is considered shorter in operative time but may be associated with increased complications, especially between viscera and meshes [1]. Many devices were studied and proposed for defect repair, and marketing is very stimulated to produce more and more effective, safe, and economical prostheses. A central role seems to be linked to the device's capability to expand correctly intraperitoneally, avoiding fixation at the muscular edge, maintaining the correct deployment, and reducing recurrence and mesh shrinkage [14]. Despite that, in the literature remain no clear consensus about the definition of different complications and no clear cause that can occur: the type of device, the surgical techniques, or other conditions. This problem makes it difficult to speak a common language in different clinical articles and, thus,

compare studies and perform international registries. There are the principal difficulties found in this analysis.

Three main types of prosthetic mesh are available on the market. Synthetic mesh (PP or polyester) is characterized by high tensile strength and vigorous tissue ingrowth and is unsuitable for intra-abdominal placement because of the high risk of bowel adhesions. Composite mesh is a dual-sided prosthetic having a synthetic parietal side to promote a strong repair and a visceral surface that repels tissue ingrowth and decreases adhesion formation. Biologic mesh is a collagen-based human, porcine, or bovine scaffold that can be positioned in the extra- or intra-peritoneal position, and is very useful in the infected or contaminated field [37]. The choice to analyze the composite mesh was aimed at evaluating what were the most used prostheses, in abdominal wall surgery, for both open and laparoscopic IPOM approaches [37]. In the literature, we found these 4 meshes: Composix, FLaPp mesh, CMC mesh, and Ventralex. As reported in the results, we performed an accurate analysis of complications that can occur and that can be related to these types of meshes, to try to better define the role of these devices. Moreover, we try to compare new devices evaluating the risk profile and safety of the intraperitoneal bicomponent meshes produced by Dipromed SRL compared to similar characteristic prostheses produced by the leading company (Bard®), in current clinical practice. According to that, the analysis of single studies included in the meta-analysis was performed with expert hernia surgeons that were asked to evaluate complications related to mesh or technique, to minimize the risk of bias. From that analysis, we identify some borderline and outlier studies that we explain below.

In the case of Composix mesh (as also CMC and FLaPp meshes), only in version#2 (without indication of the time of occurrence) the pooled incidence of seroma is 1.50% (95% CI: 0.01% -4.40%). The difference between the two versions is probably due to the lack of standardization to seroma definition, as explained before. In this version, no outliers were detected but a borderline study was identified. This study [8] has been kept on the analysis because is not an outlier, however, from the text of the article, there is no clear explanation of why there was this difference in seromas rate because it is a very resumed study. Regarding recurrence rates, no differences were found in the two versions (13 cases, the pooled incidence is 0.11% (95% CI: 0.00% - 1.45%)). However, we found an outlier study [22] that was removed. Probably, the difference in terms of recurrence reported in this study is statistically given by the high rate of recurrence in the two devices compared (Composix Kugel compared to Ventrio (9/48 vs 1/72 patients)). No cases of chronic pain, mortality, adherences/adhesions, or bowel Obstruction/Occlusion were found.

In the case of Ventralex mesh, results reported only in version#2 (without indication of the time of occurrence) 1 case of seroma (pooled incidence is 0.00% (95% CI: 0.00% - 0.00%)). Fifty cases of foreign body sensation (pooled incidence is 0.00% (95% CI: 0.00% - 0.43%)): one study was excluded because outlier [14] and another was included but is borderline for analysis [11]. Regarding recurrence rates we found differences in rates in two versions: in version#1, 12 cases of recurrence were found, and with the exclusion of two outlier studies, the pooled incidence was 0.00% (95% CI: 0.00% - 0.10%) [14,20]; in version#2, 64 cases of recurrence were identified, with a pooled incidence of 0.58% (95% CI: 0.00% - 2.06%) including 3 borderline studies without outliers [14,9,20]. No differences between studies were found in terms of surgical technique, publication years of the studies, or journal quartile; no clear explanation for the heterogeneity of these studies can be argued. However, Bensaadi et al. [14] performed an RCT with a long-term follow-up (3 years) that can explain the difference between the other retrospective studies. Moreover, the heterogeneity given by the

study of Porrero et al. [9] can be explained by the sample size (more than 1300 patients) and the very long follow-up (more than 4 years) also if it is a retrospective study. Similarly, the study by Berrevoet et al. [20] differs from the homogeneity because is a prospective study with a follow-up longer than 2 years. The different study designs of the two outliers studies can be considered a bias of this meta-analysis and cause of that we considered more real and near to surgical reality the results given by version#2.

In the literature was reported a recurrence rate of Ventralex patch between 0 to 14.8%, especially after long follow-up (> 20 months) [14]. Some authors found during reoperation a stiffened-up or shrunken in size of the device, increasing the recurrence rate [11,38]. Cause of that, Bensaadi et al. [14] in the RCT compared Ventralex patch with Cabs' Airâ (a round dual layer with the same component but delivered with a balloon to better deploy the mesh intraperitoneally and with 2-4 stitches to fix him) focused on recurrence rate. A possible explanation of the high recurrence rate in long follow-ups seen during the reoperations seems to be related to a missed control after mesh positioning of the good deployment, or that the two heavyweight layers may cause an important foreign reaction with significant tissue fibrosis and shrinkage. Due to the study characteristics and the specific outcome, the recurrence rate is higher in the three borderline studies than in other studies. No cases of mortality, adherences/adhesions, bowel Obstruction/Occlusion, or enterocutaneous fistula.

In conclusion, this metanalysis shows a globally low complications rate for Ventralex and Composix meshes in abdominal wall hernia in both open and laparoscopic use. Despite the type of analysis included in metanalytic design should be the most correct and real in terms of results, we can see as this approach plays an important role in highlighting heterogeneous studies because not similar in sample and design. However, we have to take into mind this phenomenon and stressed the importance to speak the same language to achieve truer, comparable, and effective results to guide clinical practice.

Conclusions

In conclusion, data reported in this meta-analysis won't compare different types of meshes commonly used in surgical practice to evaluate the safety profile and the risk of complications mesh-related. However, due to the different language in complications classification, version#2 appeared more

comprehensive and nearer to reality. Including studies with stronger study designs and longer follow up (more than 2 years), it is possible to find complications like recurrence and foreign body sensation which probably take longer to appear.

Conflict of interest disclosure

Giulia Montori, Giorgio Mazzarolo, Samanta Rosati, Licitra Edelweiss, Monica Ortenzi, Mauro Podda, Andrea Dal Borgo, Alberto Sartori, Emanuele Botteri, Giuseppa Procida, Michelangelo Salemi, Gabriella Balestra, and Ferdinando Agresta have nothing to disclose.

Acknowledgement

The idea was to performe a comparison about mehes with similar characteristics and use, to compare with meshes that we use frequently in our clinical practice, to evaluate the complications. The systematic review was then conducted independently by the authors as well as the discussion and conclusions.

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