Review article

Allotransplantation of donor rectus fascia for abdominal wall closure in transplant patients: A systematic review

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ABSTRACT

Background: Abdominal wall closure after intestinal, multivisceral or liver transplantation can be a major challenge. Different surgical techniques have been described to close complex abdominal wall defects, but results remain variable. Two promising transplant techniques have been developed using either non-vascularized or vascularized donor rectus fascia. This systematic review aimed to evaluate the feasibility, safety, and effectiveness of the two techniques.

Methods: A systematic review was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Human studies published between January 2000 and April 2020 were included. Methodological quality appraisal was done using an adapted 10-item standardized checklist.

Results: The search resulted in 9 articles including 74 patients. Both techniques proved to be feasible and had similar results. After non-vascularized rectus fascia allotransplantation, there was a slightly higher rate of surgical site infections in the earlier reports. Overall, there were few complications, no fascial graft related rejections or deaths. The included articles scored low on quality appraisal, mostly due to the small number of cases and scarcely reported outcome parameters.

Conclusions: This systematic literature review reports two emerging new techniques for complex abdominal wall closure in transplant patients, with promising results. Standardized data collection in a prospective manner could give us more detailed information about short- and long-term outcomes. Preclinical animal studies are necessary for a thorough investigation of the mechanisms of graft integration, the risk of hernia development and the alloimmune response against the graft.

1. Introduction

Primary closure of the abdominal wall after intestinal (ITx), liver (LTx) or multivisceral (MVTx) transplantation can be difficult to achieve due to several factors. Most of these patients have a history of multiple abdominal surgeries, ostomy, fistula(e), wound infections and may have suffered from short bowel syndrome [1–6]. This leads to the presence of a hostile and contracted abdominal wall at the time of their transplantation with subsequent loss of abdominal domain. During

transplantation it is not always feasible to match donor and recipient size which further compromises the abdominal domain. In addition, transplantation itself causes edema of donor organ(s) and recipient's abdominal wall which only aggravates the size mismatch. The non-ability to close the abdomen is mainly a problem in ITx and MVTx, and occurs in 20 to 85% of patients [1,3,4,6–12]. However, closing the abdominal wall is important since the presence of an open abdomen is associated with an estimated morbidity up to 50% and mortality of 10% [3]. Multiple techniques have been developed to facilitate abdominal

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wall closure in transplant patients such as the reduction of donor-organ size and/or enlargement of the recipient's abdominal domain. The latter can be achieved with the use of tissue expanders, reconstruction with mesh materials, component separation techniques, autologous tissue transfer or full thickness abdominal wall transplantation [1,3,4,7,13–15]. Since these surgical techniques are often complex, cause high morbidity, do not always create enough additional space and/or have variable results, transplant surgeons have sought for other options [10]. Gondolesi et al. first introduced the use of non-vascularized donor rectus fascia that was sutured as an inlay patch into the abdominal wall defect [4]. Later, Agarwal et al. presented the en-bloc transplantation of a liver with the vascularized posterior rectus fascia, attached by the falciform ligament [17]. Several additional reports by other transplant groups have been published since then. With this systematic review we want to focus on abdominal wall closure in transplant patients and critically evaluate the vascularized and non-vascularized rectus fascia allotransplantation (ATx) techniques.

2. Materials and methods

2.1. Study selection

This systematic review was performed using standard methodology and was registered in the PROSPERO database (CRD42018093923) (<http://www.crd.york.ac.uk/PROSPERO/>). Results were reported using the PRISMA guidelines.

Study inclusion criteria were: literature written in English, published between January 2000 and April 2020, and only human studies.

Exclusion criteria were: animal studies, review papers, editorials, opinions and biographies.

The following databases were used: Pubmed, Embase and Cochrane Library; <https://clinicaltrials.gov> was checked as well.

The first search was carried out on the 22nd of March 2017. Search

terms were: (abdominal OR 'abdominal wall') AND (closure OR reconstruction OR transplant OR transplantation OR allotransplantation OR allograft) AND (rectus AND fascia OR 'rectus sheath') AND ('multivisceral transplantation' OR 'multiorgan transplantation' OR 'intestinal transplantation' OR 'liver transplantation' OR 'bowel transplantation'). As a second-level search, the references of the full-text articles assessed for eligibility and congress proceedings of the European Society for Organ Transplantation and the Congress of the Intestinal Rehabilitation and Transplant Association were screened for relevant articles. A second search on April 10th, 2020, complemented with independent literature searches were also carried out.

2.2. Data extraction

Data extraction included information on the author, year of publication, center, study design, sample size, sample characteristics (type of transplantation, type of abdominal wall closure, etc.) and reported findings such as the presence of surgical site infections (SSI), ventral hernia occurrence, abdominal closure, rejection, death (Tables 1 and 2) and reoperations (Table 3). Taking of biopsies without performing other actions, was not considered as a reoperation. The extracted data were reviewed by 3 researchers (Y.J., N.V. and L.J.C.).

2.3. Methodological study quality assessment

Eligibility assessment was carried out independently by 2 reviewers (Y.J., N.V.). disagreements were resolved by consensus. Quality assessment of the individual articles was conducted using an adapted 10-item standardized checklist (Table 4), a checklist originally published by our group for a systematic literature review [18]. The scoring and corresponding color scheme applied to each item was: no or not reported: 0 (red); partially reported: 1 (orange) and yes: 2 (green).

Table 1
Patient demographics.

Center	First author	Publication year	Study type	Transplant type	Number of patients	Child or adult	Gender	SOT	Third party graft
DO	Justo [10]	2020	Case report	NVRF ATx	2	1 child, 1 adult	1 F, 1 M	2 LTx	1
CU	Amin [14]	2019	Case series		21	NM	NM	17 ITx 3 LTx 1 KTx	3
KHP	Cassar [2]	2019	Case report		2	2 children	1 F, 1 M	2 cLITx	2
FF	Farinelli [3]	2017	Case series		19	9 children, 10 adults	NM	12 ITx 3 MvTx 2 cLITx 2 LTx	1 0 0 0
CUB	Gerlach [1]	2012	Case series		3	3 adults	NM	3 MvTx	NM
UM, MSSM, FF	Gondolesi [4]	2009	Case series		16	5 children, 11 adults	11 F, 5 M	5 MvTx 4 ITx 1 cLITx 4 LTx 2 mMvTx	2 1 1 4 1
DU	Reddy J [5]	2016	Case series	VRF ATx	6	6 children	NM	2 MvTx 4 LTx	0
UCMC	Lee [15]	2013	Case series		4	4 children	2 F, 2 M	1 mMvTx 3 LTx 1 Re-LTx	0
DU	Ravindra [24]	2011	Case report		1	1 child	1 M	1 cLITx	0

DO = Doce de Octubre University Hospital, Madrid, Spain. KHP = King's Healthcare Partners Denmark Hill Site, London, UK. FF = Hospital Universitario Fundación Favaloro, Buenos Aires, Argentina. CUB = Charité – Universitätsmedizin, Berlin, Germany. UM = University of Miami, Miami, USA. MSSM = Mount Sinai School of Medicine, New York City, USA. CU = Cambridge University Addenbrooke's Hospital, Cambridge, UK. UCMC = University of Chicago Medical Center, Chicago, USA. DU = Duke University, Durham, USA. NVRF ATx = non-vascularized rectus fascia allotransplantation, VRF ATx = vascularized rectus fascia allotransplantation, NM = not mentioned, F = female, M = male, SOT = solid organ transplant, cLITx = combined liver intestinal transplantation, ITx = intestinal transplantation, MvTx = multivisceral transplantation, mMvTx = modified multivisceral transplantation, LTx = liver transplantation, KTx = kidney transplantation, Child = 0–17 years, Adult ≥ 18 years.

Table 2
Study outcomes.

First author	Transplant type	SOT	Short term outcomes									Long term outcomes		Follow-up (months)	
			SSI	Sepsis	SOT Rejection	Graft loss	Fascial closure	Skin closure				Hernia formation	SOT rejection	Mortality	
								I	II	I	II				
Justo I (10)	NVRF ATx	2 LTx	0	0	0	0	1	1	1	1	Bogota bag NM	0	0	0	4.0
Amin I (14)		17 ITx	NM	0	NM	NM	NM	NM	0	NM		NM			
		3 LTx		0					0						
		1 KTx		0					0						
Cassar N (2)	Farinelli PA (3)	2 cLTx	NM	NM	NM	0	0	2	0	2	VAC NM	NM	NM	0	Mean 18,5
		12 ITx	2	NM	0	2	NM	NM	0	3		52.2 +/- 43.6			
		3 MvTx	0			0				0					
		2 cLTx	0			0				0					
		2 LTx	1			1				0					
		3 MvTx	0	NM	NM	0	3	0	0	3		Polygalactin mesh, VAC, STSG	NM	NM	
Gerlach UA (1)	Gondolesi G (4)	5 MvTx	3	1	NM	2*	NM	3	2	Wet to dry dressings	0	NM	3	Mean 17.3	
		4 ITx	0	1				4	0				1		
		1 cLTx	0	0				1	0				0		
		4 LTx	3	2				3	1				2		
		2	1	0				2	0				1		
		mMvTx													
Reddy J (5)	VRF ATx	2 MvTx	0	0	0	NM	1	1	1	1	Polytetrafluoroethylene patch, SG	0	0	1	Median 12.0
		4 LTx					1	3	0	4		0			
Lee JC (15)		1 mMvTx	0	1	0	0	1	0	1	0	VAC, Acellular dermis	0	0	1	Mean 3.7
		3 LTx	1	0	0	1	1	2**	0	2	0	0	0		
		1 Re-LTx	0	0	0	0	1**	0	1	0	0	0	0		
		1 cLTx	NM	NM	0	0	1	0	NM		0	0	0		
Ravindra KV (24)															6.0

NVRF ATx = non-vascularized rectus fascia allotransplantation, VRF ATx = vascularized rectus fascia allotransplantation, I = Primary, II = Secondary, SSI = surgical site infection, NM = non mentioned, VAC = vacuum negative-pressure wound therapy, STSG = Split-thickness skin graft, SG = skin graft, * one partial and one complete removal of the NVRF, ** one patient underwent VRF ATx twice, with secondary and primary fascial closure respectively.

Table 3
Reoperations.

Transplant type	First Author	SOT	Total number of reoperations	Number of patients	Timing of reoperation	Reason for reoperation
NVRF ATx	Justo [10]	LTx	1	1	4 months	1 Biliary anastomotic stricture
	Amin [14]	NM	10	21	NM	NM
	Cassar [2]	cLITx	1	1	1 year	1 Gastrostomy insertion and ileostomy reversal
	Farinelli [3]	ITx	5	4	< 1 month	1 Evisceration
		MvTx	10	3		6 Abdominal collections
		LTx	1	1		5 Abdominal hematomas
						1 Acute intestinal obstruction
		ITx	6	4	> 1 month	1 Intra-abdominal bleeding
		cLITx	1	1		3 Enterectomies for rejection*
						3 Abdominal collections
VRF ATx	Gerlach [1]	MvTx	18	3	NM	1 Acute intestinal obstruction
	Gondolesi [4]	NM	NM	NM	NM	NM
	Reddy J [5]	LTx	Range 2–4	4	NM	Continuity surgery, removal of the temporary mesh and definitive closure
		MvTx		1		
	Lee [15]	mMvTx	4	1	< 1 month**	4 Liver synthetic dysfunction
		LTx	5	2		2 Second look
						1 Definitive closure
						1 Retransplantation ***
						1 Hepatic artery thrombosis
						2 Definitive closure
	Ravindra [24]	LTx	3	3	>1 month**	1 Suprahepatic IVC stenosis
		cLITx	NM	NM		NM

NM = not mentioned, IVC = inferior vena cava, * 1 acute rejection, 2 chronic rejections, ** approximate timing, *** SOT and VRF.

Table 4
Quality assessment.

Num ber	Appraisal question	Justo I (10)	Amin I(14)	Cassar N(2)	Farinelli PA(3)	Gerlach UA(1)	Gondolesi G(4)	Reddy J(5)	Lee JC(15)	Ravindra KV(24)
1	Definition of surgical technique	0	2	2	2	1	2	2	2	1
2	Prospective design	0	0	0	0	0	0	0	0	0
3	Description of time period	1	0	1	2	2	2	1	2	1
4	Description of sampling design	0	0	0	2	2	0	2	1	0
5	Defined criteria for inclusion/exclusion	0	0	0	0	0	0	0	0	0
6	Drop out of final analysis < 20%	2	2	2	2	2	2	2	2	2
7	Specification of population characteristics	1	0	1	1	1	0	1	1	0
8	Data collection by standardized procedures	0	0	0	0	0	1	1	2	0
9	Methods for data analysis	0	0	0	0	1	0	0	0	0
10	Reproducibility study on description of methods	0	0	0	0	0	0	0	0	0

No/Not reported (red) = 0, Partially reported (orange) = 1, Yes (green) = 2, see legend in appendix B

2.4. Results

2.4.1. Study selection

The search resulted in a total of 59 abstracts, including 2 additional abstracts found in the second search [2,10]. Another 4 abstracts were identified through other sources [8,14,19,20], namely congress proceedings and reference scanning. In the PRISMA flow diagram, the numbers of records identified, included and excluded are displayed (Fig. 1 and Appendix B). The search on <https://clinicaltrials.gov> did not reveal any relevant studies. The identification and screening process resulted in a total of 25 full-text articles. These full-text articles were assessed for eligibility. Another 16 papers were excluded for several reasons summarized in Fig. 1. When identical cases were used, the paper with the shortest follow-up or earliest publication date was excluded [17,19,21–23]. Studies conducted in the same center but in different time windows with partially overlapping study populations were not considered redundant. Finally, 9 articles were included in this systematic review.

2.4.2. Descriptive analysis

2.4.2.1. Study type and design. All included articles were published between 2009 and 2020.

The final 9 full-text articles included 6 case series [1,3–5,14,15] and 3 case reports [2,10,24]. All of them were based on a retrospective study design, although 1 mentioned the use of prospectively collected data [3]. Gerlach et al. described ATx of fascia in 5 patients, but in 2 cases neither the type of graft nor the outcome was specified; therefore these 2 cases were not included in the review [1].

2.4.2.2. Patient demographics and centers. From 9 articles, a total of 74 patients were included (Table 1). Three articles concerning non-vascularized rectus fascia (NVRF) ATx [3,4,14] and 3 articles about vascularized rectus fascia (VRF) ATx [5,15,24] overlapped with previous reports which were therefore not included [17,19,21–23]. In 63 patients NVRF ATx and in 11 patients VRF ATx was performed. Apart from the study by Amin et al. which did not mention the patient's age, children accounted for 40,5% of all patients ($n = 53$) with a NVRF ATx and 100% in case of a VRF ATx [14].

In the NVRF group, 51 were performed in association with an ITx (33 isolated ITx, 11 MvTx, 5 cLITx and 2 modified multivisceral transplantation (mMvTx)), 11 with a LTx and 1 with a kidney transplantation. In case of a VRF, 7 were performed with a LTx and 4 with a MvTx. Third party (from a different donor) NVRF was used in 16 cases [2–4,10,14]. For NVRF, apart from the first study where 7 cases of solely anterior fascia were reported [4], most cases were performed with a bilayer sheath for the NVRF including the peritoneal layer [2–4,14]. In case of VRF, only the posterior rectus fascia was used, although this was not clearly described in the poster by Reddy et al. [5,15].

2.4.3. Surgical technique

The included papers reported in detail the following surgical steps at the various centers: procurement, preservation, back-table preparation and transplantation.

2.4.3.1. Non-vascularized Rectus Fascia Allotransplantation

2.4.3.1.1. Donor procurement (2–4,14,19). Acceptance criteria for donor organs at CUB were donor BMI ≤ 25 , donor height < 30 cm and donor weight < 30 kg greater than the recipient.

Several techniques for procurement of the rectus sheath have been

Fig. 1. PRISMA flow diagram.

described. At the Hospital Universitario Fundación Favaloro and the Mount Sinai School of Medicine the technique for whole abdominal wall procurement was mimicked by performing a bilateral subcostal incision which extended to the lateral edge of the rectus muscle up to the pubis [7]. The complete abdominal wall is then reflected caudally. At the University of Miami and the King's Healthcare Partners Denmark Hill Site a cruciate abdominal incision or a thoracoabdominal incision, respectively, is performed down to the fascia. In both centers the skin and subcutaneous tissues are then mobilized as laterally as possible and the whole anterior fascia of the abdominal wall is exposed. At Cambridge University the skin and subcutaneous tissues are left attached to the fascia and rectus muscle.

Subsequently, the anterior and posterior rectus sheaths are incised at the semilunar line and down following the lateral edges up to the pectineal line. If only the anterior rectus sheath is used, it is dissected towards the linea alba and transected there [4]. If both anterior and posterior rectus sheaths are used, the rectus abdominis muscle with both layers of the rectus sheath is excised laterally following the superoinferior axis up to the pubis.

2.4.3.1.2. Preservation and back-table preparation (2–4,14,19). At FF, MSSM, UM and CU, the graft is preserved in University of Wisconsin (UW) or Histidine-Tryptophan-Ketoglutarate solution [3] at 4 °C or on ice. At KHP the rectus muscle graft (with rectus sheath) is rolled in saline-soaked gauzes and kept in sterile cold preservation solution on ice.

If only the anterior rectus sheath is used, the orifices from perforating arteries are closed with 6–0 polypropylene sutures, according to the technique described Farinelli et al. and Gondolesi et al. [3,4].

If the graft consists of the rectus muscle with the fascia attached, first a sharp longitudinal and bilateral opening of the lateral junction of the anterior and posterior fascia is performed, removing the lateral edges (fascia and the transverse, internal and external oblique muscles). Afterwards the rectus muscle is carefully removed towards the linea alba, as well as the remaining fat on the anterior fascia. After closing the small holes (perforating arteries) with polypropylene, the anterior and posterior sheath are loosely approximated by interrupted sutures. After the back-table preparation, the NVRF is preserved in a standard preservation solution at 4 °C.

2.4.3.1.3. Timing of transplantation (4,10). Gondolesi et al. describe a preservation time up to 26 h of the NVRF [4]. Justo et al report a mean cold ischemia time of 295 min (range 200 min – 390 min) and a mean warm ischemia time of 37.5 min (range 30 min – 45 min) for the solid organ transplant (SOT) and 44 h of cold ischemia time for the NVRF [10].

2.4.3.1.4. Recipient procedure (1–4,14). After finishing the SOT, the fascial defect is assessed. Most articles recommended that the recipient abdominal wall has to be prepared with an extended dissection of the skin and subcutaneous tissue to ensure adequate skin flaps and obtain a “tension-free” closure. In some cases, lateral relaxing incisions are proposed to reduce the size of the abdominal defect. The donor rectus sheath is implanted and sutured inlay to the recipient's abdominal fascial edges with interrupted or continuous running 2–0 polypropylene (Prolene®) sutures [3,4]. The use of 2 hemisheaths (anterior and posterior), split at the linea alba, instead of one large rectus sheath is also described in one case [3]. At FF, MSSM and UM a flat drain is placed between the rectus sheath and the skin when possible.

From the 63 patients who underwent NVRF ATx, skin closure was described in 23 patients, of which 14 were closed primarily [4,10]. Methods to manage secondary skin closure were wet to dry dressings ($n = 3$), vacuum negative-pressure wound therapy ($n = 5$), once in combination with a split thickness graft ($n = 1$) [1,2,4]. Temporary coverage of the wound with paraffin gauzes was also described ($n = 2$) [2]. In the series by Gerlach et al. the 3 NVRFs were supported by a polyglactin mesh (Vicryl®) as an underlay [1]. Despite graft edema in 2 of those patients, secondary fascial closure was achieved within 2 days [1]. Gondolesi et al. did not disclose any information about fascial closure

rates [4]. In the series by Farinelli et al. and Amin et al. no details about skin nor fascial closure were given [3,14]. In the other articles primary fascial closure was described in 4 of the 7 NVRF patients [1,10]. Secondary fascial closure was achieved within 2 days to 2 months, with a median of 6 days [2,10].

2.4.3.2. Vascularized rectus fascia allotransplantation. The technique of VRF ATx involves the use of posterior rectus sheath above the umbilicus, which always stays attached to the liver graft by the falciform ligament. This ligament contains the hepatic falciform artery, providing blood flow to the posterior rectus sheath [17].

2.4.3.2.1. Donor procurement (15,21). At DU, Ravindra et al first perform a dye perfusion study to confirm the presence of blood flow through the hepatic falciform artery.

Both groups from the UCMC and DU describe a midline incision through the skin and the subcutaneous fat up to the linea alba, followed by a lateral lift of the obtained tissue flaps (including the anterior fascia and rectus muscle). An edge of 2–4 cm of anterior rectus sheath flanking the linea alba is left attached. Finally, a bilateral incision at the semilunar line, subcostal incisions and an inferior incision at the arcuate line is made. The posterior rectus sheath stays attached to the donor liver via the falciform ligament. The other transplant organs are procured in a standard way.

2.4.3.2.2. Preservation and back-table preparation. Since the VRF graft is in continuity with the liver or multivisceral graft, the preservation is performed in a standard way, no additional dissection is needed and the peritoneal layer is preserved.

2.4.3.2.3. Timing of transplantation (15). Lee et al. report a mean cold ischemia time of 6.7 h (range: 4.8 h – 7.9 h) and a mean warm ischemia time (implantation time) of 35.8 min (range: 29 min – 49 min) [15].

2.4.3.2.4. Recipient procedure (5,15,21). The liver or multivisceral graft is transplanted as per standard protocol with the posterior rectus sheath attached. Next, at UCMC the sheath is implanted as an inlay between the full thickness muscles of the recipient. At DU, the VRF is used as an underlay reinforcement in one case (with primary fascial closure) and as an inlay in the other cases, using polypropylene 4–0 [21].

Skin closure is described in 10 out of 11 VRF ATx, of whom 3 cases were closed primarily [5,15]. In 1 case secondary closure is achieved with the help of a skin graft [5]. In another case acellular dermis is used and in 3 cases an expanded polytetrafluoroethylene (Gore-tex®) patch is used for temporary abdominal closure [5,15]. Primary fascial closure was possible in 50% of the VRF patients. Secondary fascial closure was achieved within 2 to 35 days [5,15,24].

2.4.4. Immunology

Little was described about the adaptation of the immunosuppressive medication in case of fascia transplantation. Since the intestinal graft is characterized by a stronger immunogenicity than for an isolated liver transplant, the immunosuppressive regimen in case of ITx is more profound. Justo et al. and Lee et al. described tacrolimus and steroids as the standard regimen, together with mycophenolate and daclizumab respectively [10,15]. Lee et al. was the only one who clearly states that the immunosuppression regimens were identical to the ones used in LTx without fascial ATx [15]. He also stated that at relaparotomy for second look surgery, biopsies taken from VRF in 4 patients showed no signs of rejection (range postoperative day 1–38) but gave few details. Farinelli et al., Gondolesi et al. and Justo et al. stated that there was no additional immunological risk associated to the use of third party fascial grafts [4,10].

2.4.5. Study outcomes

Table 2 summarizes the study outcomes of the included patients.

2.4.6. Early wound morbidity

The postoperative period was complicated by evisceration within 30 days in 1 ITx patient [3].

SSI's were described in 10 out of 61 (16.4%) NVRF and 1 out of 11 (9.1%) VRF patients. In the NVRF cases, 4 were superficial infections (of which 3 cases where the skin was not closed). SSI was not related to the type of SOT with a rate of 17% ($n = 6/35$ of the reported cases- for intestine-inclusive grafts and 31% ($n = 5/16$ of the reported cases) for an isolated liver transplant. In 6 cases a deep abdominal wall infection occurred, resulting in 1 partial and 4 complete graft removals [3,4]. Two of the NVRF's were replaced by a synthetic mesh and 1 by a third party NVRF. In the VRF cohort, 1 LTx case was complicated by multiple intra-abdominal fluid collections, a biliary leak and a wound infection [15]. In this patient, primary skin closure had not yet been obtained at that time [15].

2.4.7. NVRF and VRF unrelated complications and reoperations (Table 3)

In 10 NVRF cases (5 ITx, 3 MvTx and 2 LTx), intra-abdominal collections or hematomas were reported, including 1 intra-abdominal bleeding [3,10]. For the VRF ATx, 1 intra-abdominal collection was described after LTx [15].

The number of reoperations per patient was mentioned in most papers. They were unrelated to the fascia transplant, apart from NVRF graft removals discussed in the SSI section. In 5 cases, the NVRF was removed at reoperation, kept in preservation fluid and re-implanted at the end of the re-operation [3]. For the VRF, Lee et al. performed 1 re-transplantation of the liver and VRF at day 14 post-transplantation, due to hepatic artery thrombosis [15].

2.4.8. Graft integration, rejection and herniation

Later reoperations allowed some observations on the integration and evolution of the graft after transplantation. For the NVRF, Gondolesi et al. mentioned that, macroscopically, the graft was integrated in the abdominal wall (as part of scar tissue) with a maximum follow-up time of 42 months and Justo et al. confirmed this at 4 months post-transplant [4,10]. Gerlach et al. described the graft as part of the scar tissue without causing herniation (no timing described) [1]. Although adhesions were present intra-abdominally, none or only smooth adhesions were attached to the transplanted peritoneum. This was observed by Farinelli et al. at 2 to 42.5 months post-transplantation, by Cassar et al. after 1 year and by Amin et al. (no timing described) [2,3,14]. At those time points, manipulation, transection and suturing of the transplanted rectus sheath did not cause any complications [2,3,14]. No morphological change compatible with rejection of the NVRF ATx was seen in any patient.

For the VRF, biopsies of the fascia were taken in 3 patients between day 1 and day 38 post-transplant by Lee et al. [15]. They described a viable graft with excellent vascularity, bleeding at the fascial edges and arterial tones on Doppler ultrasound [15]. Furthermore these biopsies revealed no signs of rejection in any case [15].

In the included series of NVRF and VRF, the development of incisional or ventral hernias during the follow-up period was not mentioned or not clearly described for any of the patients (Table 2) other than the one patient who required removal of the NVRF [4].

Graft loss occurred in 5 NVRF patients and in 1 VRF patient, caused by deep abdominal wall infections in 4 cases and retransplantation of the SOT and VRF allotransplant (AT) due to hepatic artery thrombosis in 1 case.

2.4.9. Survival and cause of death

The first NVRF study reported 7 deaths in the postoperative period [4]. The causes of death were all fascial graft unrelated: sepsis (wound-unrelated) ($n = 4$), autoimmune hemolysis ($n = 1$) and post-transplant lymphoproliferative disease ($n = 2$). In later articles the mortality rate dropped to zero [1,2,10].

In the VRF group, 2 patients died, both unrelated to the fascial graft.

One was due to aspergillosis sepsis, the other cause of death was not mentioned, but was not graft-related [5,15].

2.4.10. Quality appraisal

None of the reviewed articles fulfill more than 4 of the 10 selected methodological quality criteria. In a descending order of prevalence, the following elements are satisfactorily addressed (as indicated in Table 4 by a score of 2 and green cell coloring): drop out <20% (all 9 articles), definition of surgical technique (6 articles) [2–5,10,14,15], description of time period (4 articles) [1,3,4,15], description of sampling design (3 articles) [1,3,5], data collection by standardized procedures (1 article) [15]. All other criteria are either partially addressed (score 1, orange) or not reported (score 0, red).

3. Discussion

In 2003, Levi et al. were the first to introduce the abdominal wall transplantation, a vascular composite tissue allograft with the potential advantage of early rejection detection via a skin allograft [6,7,25].

The less complex or less time-consuming NVRF and VRF ATx have successfully been used in transplant surgery since their first description by Gondolesi et al. in 2009 and Agarwal et al. in 2010 respectively. The main purpose of these techniques is (primary) closure of extensive abdominal wall defects, mainly after ITx, MvTx or LTx [4,17] and thereby avoiding an "open abdomen", which severely impacts the morbidity and mortality in this vulnerable transplant population. This review summarizes the experience of 63 NVRF ATx and 12 VRF ATx in 74 transplant patients [1–5,10,14,15,24].

3.1. Technique

The main anatomical difference between the two rectus fascia ATx techniques is the presence of vascularization through the falciform ligament in the VRF ATx. This means that for VRF ATx, inclusion of the liver in the graft is mandatory whereas the NVRF ATx can be used in all types of solid organ transplantation. Furthermore, the NVRF ATx can be procured from a different, third party donor [2–4,10,14] and can be used for larger defects [2]. The NVRF AT consists of the anterior fascia with or without the posterior fascia (sometimes with a rim of anterior fascia at the linea alba). In case of VRF Tx, only the use of the posterior rectus sheath has been reported.

The addition of the RF ATx to the SOT procedure prolongs the procurement and operative time but is less complex and time-consuming in comparison to abdominal wall transplantation or autologous tissue transfer. Since the VRF relies on the arterial vascularization within the falciform ligament, this type of graft is more vulnerable than a NVRF and patency should be assessed prior to procurement.

Although preservation is currently on ice in classic preservation solution, and has been shown safe up to 26 h, prolonging the preservation time or mode (e.g. deepfreezing) of a NVRF graft, might open up the window towards other indications in a non-SOT setting. Further research on this topic is awaited.

3.2. Outcome

Mortality was unrelated to the transplantation of the rectus fascia in both types, 7 (30.4%) in case of NVRF and 2 (18.2%) in case of VRF ATx. Since the VRF is attached to the liver and vascularized through the hepatic artery, thrombosis is the most feared complication. In case of thrombosis (e.g. of the hepatic artery), the liver graft and thus the attached fascia are lost and need to be replaced by a new liver-VRF transplantation [2,15].

Abdominal closure by RF ATx was achieved in all cases. In the studies that described fascial closure, primary closure accounted for 47% and secondary closure for 53% [1,2,5,10,15,24]. Primary skin closure was achieved in 51.5% of all cases that reported details about skin closure,

counting for 60.9% of the NVRF AT and 30.0% of the VRF AT patients (Table 2).

Four out of 13 patients (30.8%) in whom the skin could not be closed primarily developed an SSI. However, secondary skin closure could be achieved in all cases without any graft related complications.

In 2009, Gondolesi et al. were the first to perform a NVRF ATx [4]. In the subsequent study, 7 out of the 16 patients developed SSI's (43.8%). Since this publication it was thought that the NVRF ATx had a higher infection risk than its vascularized variant. It was hypothesized that the blood flow through the vascularized fascia improves the viability and the immune response against infections. In addition, the administration of systemic antibiotic treatment and the wound healing could be more efficient through the native vascularization of the VRF AT [4,15,21]. The occurrence rate of SSI's remained higher after NVRF ATx than after VRF ATx (9.1%). Nevertheless, this risk has decreased from 43.8% to a range from 0 to 15.8% in later NVRF ATx publications [1–3,10].

It should be noted that transplant patients (particularly ITx and MvTx recipients) are already more prone to infections, due to their immunosuppressive status, prolonged hospitalization and malnutrition [4]. The presence of chronic contamination (wound infections, enterocutaneous fistulae and/or ostomies) increases the risk of SSI's even more. Although intestine-related grafts depend on higher levels of immunosuppression than LTx, SSI did not relate to the type of graft in this review. More data on the incidence of SSI's is warranted.

We recommend that in future studies results should be analyzed in the context of LTx versus ITx separately. With ITx one should take into account the higher risk of contamination, the potential need for a stoma and the higher immunosuppressive requirements. These are important factors when analyzing post-operative complications, in particular SSI's and hernia formation. The included articles don't allow us to differentiate for most outcomes between the two types of SOT. Although outcome in general was very satisfying.

The NVRF AT has proven to integrate well into the hosts abdominal wall and allows post-transplant manipulation (re-elevation and re-inset) for reoperations [1–4,10], also when only the anterior NVRF AT was used [4]. However, data on the latter are limited. We assume that for the NVRF AT the presence of the peritoneum to the posterior fascia might be the reason why it has no tendency to form adhesions. At re-exploration it has been described in 2 patients that the VRF graft was well revascularized in the immediate (post-operative day 0, 2 and 3) and late postoperative periods (post-operative day 31 and 38) [15]. It is still unknown whether or not revascularization occurs and if this could also be the case for NVRF grafts. We hypothesize that the surrounding tissues provoke neovascularization. The role of the different surrounding tissues in this (peritoneum, subcutaneous tissues, and others...) has to be studied. Nevertheless, it has been noticed that the integration of the posterior layer of the NVRF graft resulted in less development of intra-abdominal adhesions to the RF.

The rate of RF ATx graft loss was 12.8%, either caused by severe infections or by non-related causes. For the future we suggest to collect more information on timing of the NVRF and VRF integration into the recipient tissue, and if possible, to combine it with standard imaging of duplex ultrasound or computed tomography.

3.3. Immunology

Fascia is considered poorly immunogenic due to its constitution and, in case of the NVRF AT, its avascularity [2,4]. Therefore, it has been hypothesized that ABO- and human leukocyte antigen-matching is not mandatory. Third party (e.g. from a different donor) NVRF were successfully used in 16 cases [2–4,10,14]. Cassar et al. were the only ones using an ABO-matched third party NVRF out of precaution [2].

An issue to be taken into account is the peritoneal layer attached to the posterior RF [2]. In contrast to fascia, the peritoneum is cell-rich and assumed to be an important immunogenic trigger for rejection although this does not seem to be a clinically relevant problem in this population

under immunosuppression [1–4,10,14].

Life-long immunosuppression after organ transplantation is mandatory. Even in case of a third party NVRF, Farinelli et al., Gondolesi et al. and Justo et al. state that there is no immunological disadvantage associated ($n = 16$) [3,4,10].

Within the included articles no rejection of the RF ATx was documented while SOT rejection occurred in 3 patients (4.1%) [3]. This seems to confirm that in this population of already immunosuppressed patients, there does not seem to be an additional immunogenicity related to the fascial component of the graft; and probably no need for additional or modified immunosuppression.

The seemingly low additional immunogenicity of the RF ATx could lead to the application of this technique in low or even non-immunosuppressed patients with complex abdominal defects who are not treatable by more conventional techniques.

To investigate these immunological and rejection issues in more detail and to evaluate the alloimmune response elicited by the peritoneum and/or the rectus fascia, a high-quality allogeneic animal model is needed.

3.4. Hernia occurrence

Adequate abdominal wall closure and strong tissue integration is crucial to prevent incisional hernia occurrence. Hernia formation is an important prognostic factor, especially for long-term outcomes such as quality of life, patient satisfaction, rehospitalizations and reoperations [26]. Although not clearly explained, Gondolesi et al. described that one patient developed a hernia after the NVRF was removed [4]. Additionally the early post-operative period of 1 patient was complicated by evisceration [3]. This required a re-operation, but no re-transplantation of the NVRF.

The incidence of long-term herniation or bulging is scarcely reported in the included articles. It is intriguing that a technique of inlay graft placement (without overlap with the native tissue) which has been largely abandoned in abdominal wall mesh reconstructions by general surgeons, seems to function properly in this challenging group of complex and immunocompromised patients.

Further investigations on neovascularization and formation of mature collagen in an allogeneic animal model are therefore needed. In addition, high quality clinical and radiological data through prospective transplant registries with a follow-up of at least one year post-transplant could provide better data on this important patient outcome parameter.

3.5. Study quality

Due to lack of standardized data reporting, the information within this systematic review remains incomplete. In the quality appraisal the overall score on reproducibility was very low. None of the included articles had a prospective design. Lee et al. were the only ones who had a relatively standardized data collection [15]. The included articles contain 3 posters of which the data are only briefly described [5,14,24]. The incidence of SSI's is not reported by default [2,3,24], nor the detailed postoperative course [14,24] or the immunological implications. There were only two articles, that discuss warm ischemia and operative time [10,15]. Furthermore, it should be mentioned that VRF ATx has only been performed in children.

Another issue is the publication of patients who have already been published in a previous article. The exact amount of 'overlapping' patients was not explicitly mentioned, but we suspect overlap with previous reports in at least 4 of the included publications [3–5,23].

4. Conclusion

Vascularized and non-vascularized rectus fascia allotransplantation are promising techniques for complex abdominal wall reconstruction after solid organ transplantation. Both have proven to achieve

abdominal wall closure after transplantation. Although these two techniques seem to be feasible, safe and effective, more detailed and more long-term results are lacking, specifically on the occurrence of SSI's, rejection and herniation.

Hence, we want to emphasize the importance of prospective data collection, such as the outcome parameters discussed in this systematic review.

Furthermore, preclinical research with a high-quality allogeneic animal model could help to answer questions on immunological aspects and graft integration on the short -and long-term by clinical, biomechanical, histopathological and immunohistochemical analysis. This will provide the necessary information before applying this technique to a population of patients with complex abdominal wall defects (outside the setting of solid organ transplantation) who would not be amenable to more conventional techniques.

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Appendix A. Abbreviations

1	PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
2	ITx	intestinal transplantation
3	cLITx	combined liver intestinal transplantation
4	LTx	liver transplantation
5	MvTx	multivisceral transplantation
6	NVRF	non-vascularized rectus fascia
7	ATX	allotransplantation
8	VRF	vascularized rectus fascia
9	mMvTx	modified multivisceral transplantation
10	KTx	kidney transplantation
11	SOT	solid organ transplant###
12	DO	Docede Octubre University Hospital
13	KHP	King's Healthcare Partners Denmark Hill Site London
14	FF	Hospital Universitario Fundación Favaloro
15	CUB	Charité - Universitätsmedizin Berlin
16	UM	University of Miami
17	MSSM	Mount Sinai School of Medicine
18	CU	Cambridge University Addenbrooke's Hospital
19	UCMC	University of Chicago Medical Center
20	DU	Duke University
21	NM	not mentioned
22	F	female
23	M	male
24	UW	University of Wisconsin
25	SSI	Surgical site infections
26	AT	allotransplant
27	VAC	vacuum negative-pressure wound therapy
28	STSG	Split-thickness skin graft
29	SG	skin graft
30	RF	rectus fascia

Appendix B. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.trre.2021.100634>.

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