Long-Term, Prospective, Multicenter Study of Poly-4-Hydroxybutyrate Mesh (Phasix Mesh) for Hernia Repair in Cohort at Risk for Complication: 60-Month Follow-Up

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BACKGROUND: Long-term resorbable mesh represents a promising technology for ventral and incisional hernia repair (VIHR). This study evaluates poly-4-hydroxybutyrate mesh (P4HB; Phasix Mesh) among comorbid patients with CDC class I wounds.

STUDY DESIGN: This prospective, multi-institutional study evaluated P4HB VIHR in comorbid patients with CDC class I wounds. Primary outcomes included hernia recurrence and surgical site infection. Secondary outcomes included pain, device-related adverse events, quality of life, reoperation, procedure time, and length of stay. Evaluations were scheduled at 1, 3, 6, 12, 18, 24, 30, 36, and 60 months. A time-to-event analysis (Kaplan-Meier) was performed for primary outcomes; secondary outcomes were reported as descriptive statistics.

RESULTS: A total of 121 patients (46 male, 75 female) 54.7 ± 12.0 years old with a BMI of 32.2 ± 4.5 kg/m^2 underwent VIHR with P4HB Mesh (mean ± SD). Fifty-four patients (44.6%) completed the 60-month follow-up. Primary outcomes (Kaplan-Meier estimates at 60 months) included recurrence (22.0 ± 4.5%; 95% CI 11.7% to 29.4%) and surgical site infection (10.1 ± 2.8%; 95% CI 3.3 to 14.0). Secondary outcomes included seroma requiring intervention (n = 9), procedure time (167.9 ± 82.5 minutes), length of stay (5.3 ± 5.3 days), reoperation (18 of 121, 14.9%), visual analogue scale–pain (change from baseline –3.16 ± 3.35 cm at 60 months; n = 52), and Carolinas Comfort Total Score (change from baseline –24.3 ± 21.4 at 60 months; n = 52).

CONCLUSIONS: Five-year outcomes after VIHR with P4HB mesh were associated with infrequent complications and durable hernia repair outcomes. This study provides a framework for anticipated long-term hernia repair outcomes when using P4HB mesh. (J Am Coll Surg 2022;235:894–904. © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American College of Surgeons. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 [CCBY-NC-ND], where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.)

Abbreviations and Acronyms		
MCID	=	minimal clinically important change
MR	=	myofascial release
P4HB	=	poly-4-hydroxybutyrate
SF-12v2	=	12-Item Short Form Health Survey, version 2
SSI	=	surgical site infection
VAS	=	Visual Analogue Scale

Resorbable biomaterials have been used for abdominal wall reconstruction for decades, beginning with rapidly resorbing materials such as polyglactin 910 (a copolymer of glycolide and lactide) and polyglycolic acid.[1,2] These materials resorb rapidly and lose mechanical strength and have been used primarily for temporary abdominal closure or other staged repairs rather than long-term hernia repair.[1,2] More recently, hernia meshes comprised of resorbable polymers such as polyglycolide, polylactide, trimethylene carbonate, ultra-pure fibroin derived from silk, and poly-4-hydroxybutyrate (P4HB) have been used in abdominal wall reconstruction.[1] These materials have longer resorption periods ranging from 4 to 36 months. Phasix Mesh (comprised of P4HB) offers one of the longest resorption periods

and is essentially resorbed in 12 to 18 months.[1,3,4] In hernia repair, a long-term resorption profile represents a unique advantage, allowing the mesh to provide mechanical support to the repair site during the critical period of healing and tissue remodeling, preventing early recurrence, and gradually transferring the load back to the abdominal wall.

Several clinical studies have reported outcomes associated with P4HB mesh with a variety of hernia repair techniques and patient populations.[5-14] The majority of these studies have reported medium-term outcomes in the range of 18 to 36 months.[5-13] The current study is uniquely designed to evaluate clinical outcomes of P4HB mesh along a continuum of early, intermediate, and long-term timeframes. Early and intermediate data have been published previously.[5,6] The current study provides critical insight into long-term clinical outcomes such as hernia recurrence at 60 months after implementation. The strength of the repair at 60 months after implementation is solely dependent on the strength of the patient's native abdominal wall tissue, as well as any tissue regenerated at the repair site over time. The objective of the current study is to evaluate long-term clinical outcomes of ventral and incisional hernia repair with P4HB mesh among patients at risk for postoperative complications.

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METHODS

The methods for this trial have been described in previous publications and are repeated here for clarity.[5,6]

Study design

This study represents a prospective, multicenter, open-label study to assess the safety, performance, and outcomes of poly-4-hydroxybutyrate mesh (Phasix Mesh, CR Bard, Inc) for primary ventral or incisional or multiply recurrent hernia repair in a cohort at risk for complications. This study has been registered with ClinicalTrials.gov (ClinicalTrials.gov/NCT01961687).

Patients were considered at risk for complications with 1 or more of the following comorbidities: BMI between 30 and 40 kg/m^2 (inclusive), active smokers, COPD, diabetes mellitus, immunosuppression, coronary artery disease, chronic corticosteroid use (more than 6 months of systemic use), hypo-albuminemia (preoperative serum albumin less than 3.4 g/dL), advanced age (75 years or more), or renal insufficiency (serum creatinine concentration 2.5 mg/dL or more). Patients, investigators, and surgeons were not blinded to study treatment. The study was designed to treat 120 patients at 16 US sites. The protocol was approved by the IRB at each institution, and all patients provided informed consent before enrollment. Recruitment occurred through the surgical offices of the investigators during the period from October 2013 to January 2015. Investigators were selected based on experience with hernia repair techniques. No specific training was required for participation due to the similarity in technique required for P4HB mesh relative to other meshes.

Inclusion/exclusion criteria

Patients 18 years or older, with primary ventral, primary incisional, or recurrent incisional hernia (not to exceed 3 recurrences), were evaluated for eligibility, including 1 or more comorbidities listed here, class I surgical wound (defined by the CDC),[15] and 10 to 350 cm^2 hernia defect suitable for repair via retrorectus or onlay mesh (with or without myofascial release [MR]). Exclusion criteria included 4 or more previous hernia repairs (of the index repair), peritonitis, on or anticipated to be placed on chemotherapy during study period, BMI greater than 40 kg/m^2, cirrhosis of the liver and/or ascites, American Society of Anesthesiology class IV or V, diagnosed HIV infection, life expectancy of less than 2 years at time of enrollment, planned intra-abdominal mesh placement or bridged repair, surgical wound designated class II (clean-contaminated), class III (contaminated), or class IV (dirty-contaminated) defined by the CDC[15] (no device

is currently indicated for use in contaminated or infected fields), active or latent systemic infection, pregnant or plans to become pregnant during study period, currently breast-feeding, enrolled in another clinical study within the last 30 days, part of site personnel directly involved with study, known allergy to the test device or component materials, or any condition that, in the opinion of the investigator, would preclude the use of the study device, or preclude the patient from completing the follow-up requirements.

Surgical technique

All patients were administered antibiotics according to hospital protocol and underwent open ventral hernia repair. Intraoperative inclusion and exclusion criteria were assessed and documented. Patients meeting intraoperative eligibility criteria received P4HB mesh, overlapping the defect by at least 5 cm with 6 to 12 resorbable sutures placed at approximately 5- to 6-cm intervals around the periphery. It is important to note that "5-cm overlap" encompasses overlap both cranial and caudal to the defect for a total of 5 cm longitudinally, rather than 5 cm cranially and 5 cm caudally, which would lead to 10 cm overlap overall. The same definition of overlap applies to the width dimension. The hernia defect was closed by approximating the fascial edges, including myofascial release, if required. The fascial and subcutaneous layers were closed with sutures, and the skin was closed with staples and/or sutures. Operative details including hernia defect size, mesh size, mesh position, repair technique, use of myofascial release, suture type, number of sutures to secure mesh, and procedural time were collected. Postoperative care was performed consistent with surgeon practice at each site.

Data collection

Postoperative patient visits were scheduled at 1, 3, 6, 12, 18, 24, 36, and 60 months, and a telephone interview was conducted at 30 months. Medical history, demographic information, and all current prescription and over-the-counter pain medications were recorded. The Pain Visual Analogue Scale (VAS) and quality-of-life assessments—Carolinas Comfort Scale and 12-Item Short Form Health Survey, version 2 (SF-12v2)—were completed preoperatively and at scheduled intervals.

Study endpoints

Primary endpoints included hernia recurrence and surgical site infections (SSI). Hernia recurrence was assessed by physical examination at each study visit. A recurrent hernia was defined as any hernia identified

or confirmed by the investigator, during any study follow-up visit, within 7 cm of the repair. Hernia recurrence identified via incidental MRI or CT scan were evaluated by the operating surgeon for clinical significance and confirmation.

SSI was assessed by physical examination with confirmation by gram stain and culture. Superficial and deep SSI were classified according to CDC guidelines.[16] Device-related complications and reoperations were also recorded.

Analysis population

Data are presented for all patients implanted with P4HB mesh. GraphPad Prism 6.01 statistical software was used to generate frequency counts and percentages (categorical variables) and mean ± SD (continuous variables). A time-to-event analysis (Kaplan-Meier) was performed for primary outcomes. Patients who did not complete the study were censored at the last available follow-up time. Fisher's exact 2-tailed test was used to evaluate differences between various subgroups in analyses (p < 0.05 was considered statistically significant; no adjustment was made for multiple comparisons). All subgroup analyses were intended to be exploratory in nature and hypothesis-generating to inform the design of future trials. A paired, nonparametric Wilcoxon signed-rank test was performed to compare quality-of-life data at 60 months with baseline values (p < 0.05 was considered statistically significant). This work complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria.[17]

RESULTS

Patient demographics

As shown in Figure 1 and Table 1, a total of 139 patients met the initial screening criteria for the study. Eighteen patients were ultimately excluded, and 121 patients were implanted with P4HB mesh.

The majority of patients were non-Hispanic/Latino, White, females with a mean ± SD age of 54.7 ± 12.0 years and BMI of 32.2 ± 4.5 kg/m^2. Nearly all of the patients (n = 117, 96.7%) had a history of abdominal incisions(s). Previous incisions were located at the current hernia site in approximately half of the patients (n = 62, 51.2%). Patient-reported comorbidities included obesity, diabetes, COPD, active smoker, coronary artery disease, immunosuppression, advanced age, chronic corticosteroid use, hypoalbuminemia, and renal insufficiency, which are reported in Table 1. Approximately two-thirds of the patients reported 2 or more comorbidities (n = 79, 65.3%).

Preoperative data

Hernias were divided between primary hernias (n = 71, 58.7%; Table 1) and recurrent hernias (n = 50, 41.3%). The majority of the hernias were located in the midline (n = 102, 84.3%), with a small number of suprapubic, subxiphoid, or "other" locations (ie superior to umbilicus, midline to suprapubic, lower abdomen, subcostal, flank, paramedian, and midline to subxiphoid).

Operative characteristics

Detailed operative data are shown in Table 2. The majority of patients underwent ventral hernia repair with P4HB mesh via retrorectus repair (n = 88, 72.7%), with a mean defect length of 14.7 ± 5.6 cm, width of 8.6 ± 3.4 cm, and area of 108.2 ± 68.2 cm^2. Approximately one-third of the defects were classified as "Swiss cheese" defects (n = 39, 32.2%). In patients undergoing retrorectus repair, 45 used MR, with the majority undergoing posterior (n = 26) or Ramirez/open repair (n = 15) and only a few open/endoscopic (n = 2) or endoscopic/minimally invasive (n = 2) repairs. In those patients undergoing retrorectus repair without MR, the majority underwent Rives-Stoppa repair (n = 41 of 43). In patients undergoing onlay repairs, the majority did not require MR (n = 24), and a few (n = 8) used MR in a Ramirez/open fashion. Additionally, a single patient (n = 1, 0.8%) underwent open Rives-Stoppa repair of a right flank hernia and was not classified as retrorectus or onlay, but rather as "other."

The fascia was reapproximated in 113 (93.4%) patients, and P4HB mesh with a mean length (26.4 ± 5.1 cm), width (21.3 ± 4.9 cm), and area (461.7 ± 173.5 cm^2) was used to reinforce the repair in all treated patients (n = 121, 100%). P4HB mesh was fixated to the abdominal wall using a mean of 12.5 ± 13.5 fixation points. Nearly all fixation was accomplished with sutures (n = 116, 95.9%), but a small number of patients received mechanical or other types of fixation. Almost all of the patients (n = 107, 88.4%) required at least 1 drain, and the longest overall drain duration was 11.9 ± 8.9 days. The average surgical procedure time was 167.9 ± 82.5 min (mean ± SD, Table 3). Only a small percentage of patients required negative pressure wound therapy (n = 13, 10.7%), and the majority of those wounds were open (n = 10 of 13). A single patient (n = 1) had both an open and a closed wound that required negative pressure wound therapy. The average length of stay was 5.3 ± 5.3 days (mean ± SD, Table 3).

Postoperative outcomes

A total of 54 (44.6%) patients completed the study at the 60-month follow-up visit (Fig. 1 and Table 1).

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│          Patients Screened          │
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┌─────────────────────────────────────┐
│     Met initial screening criteria   │
│               N = 139                │
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┌─────────────────────────────────────┐
│       Treated with P4HB Mesh         │
│               N = 121                │
└─────────────────────────────────────┘
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Did Not Complete Study
n=67
Lost to follow-up after 3 attempts to contact
(n=19)
Subject no longer wishes to participate (n=6)
Subject withdrew due to adverse event (n=6)
Site did not extend study beyond 3 years (n=5)
Subject moved to area without study site
(n=2)
Site did not extend study beyond 2 years (n=1)
Subject unable to meet follow-up
requirements (n=1)
Sponsor's decision (n=2)
Investigator's decision (n=1)
Death (n=7)
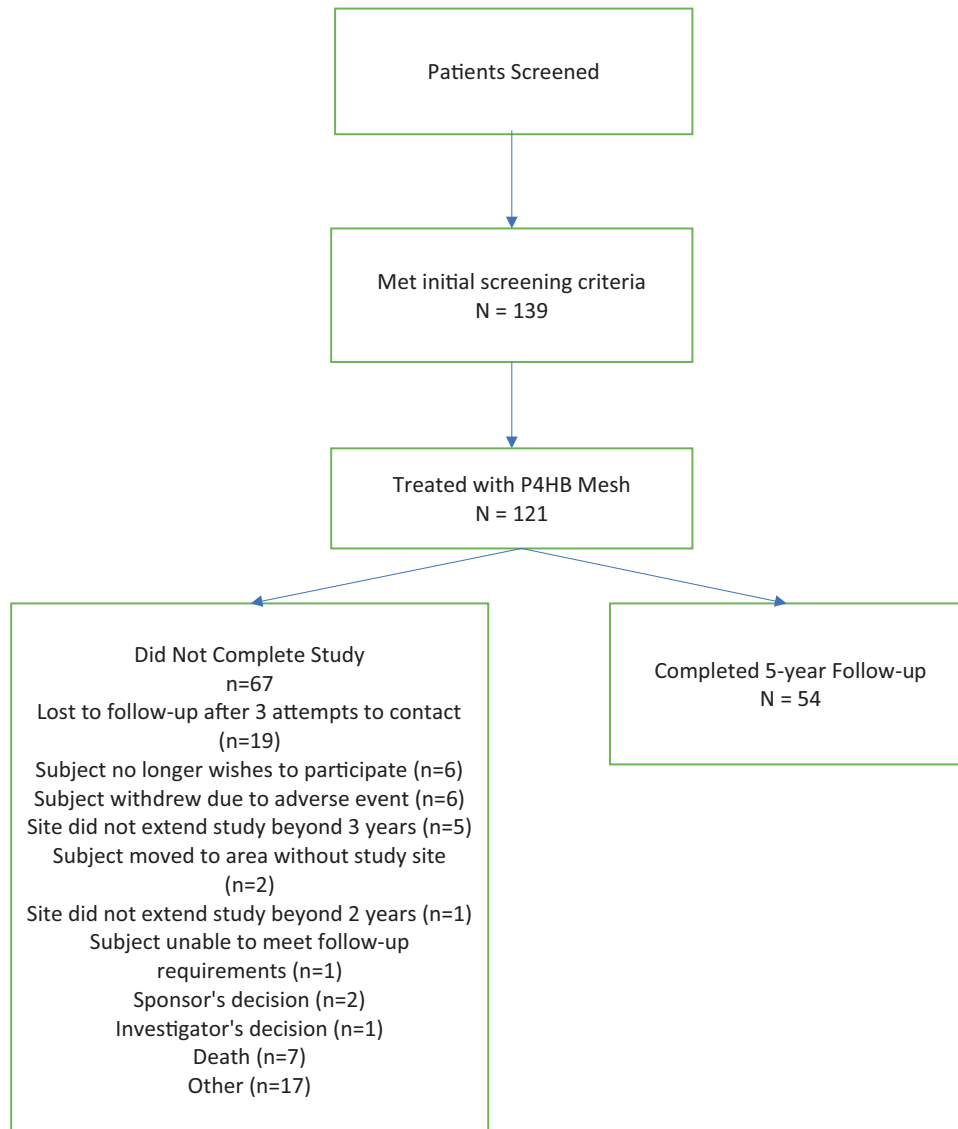Other (n=17)

Completed 5-year Follow-up
N = 54

Figure 1. Flow of patients throughout the study period. P4HB, poly-4-hydroxybutyrate.

The majority of the patients who did not complete the study were lost to follow-up after 3 attempts to contact them (n = 19). Another group of patients withdrew consent or chose to end their participation when the study period was extended (n = 12). Similarly, several study sites elected not to extend the study beyond the originally planned 24-month final time point, which removed an additional 6 patients from later follow-up.

The primary outcomes of recurrence and SSI are summarized in Figure 2 and Table 3. Using Kaplan-Meier methods to account for censoring, the 60-month recurrence rates were estimated to be 22.0% ± 4.5% (mean ± SD; 95% CI 11.7% to 29.4%) for all patients treated with P4HB mesh. The number of patients remaining in the trial at each time interval is noted below the x-axis. On average, the time to recurrence was 771.6 ± 397.1 days (mean ± SD). A small number of patients experienced SSI. Again, using Kaplan-Meier methods to account for censoring, the 60-month SSI rates were estimated to be 10.1% ± 2.8% (mean ± SD; 95% CI 3.3% to 14.0%) for all patients treated with P4HB mesh. The average time to SSI was 15.2 ± 9.3 days (mean ± SD), and no SSIs were reported 37 days after implementation.

Secondary endpoints included surgical procedure time, length of stay, reoperation rate, seroma requiring intervention, device-related adverse events, and quality-of-life assessments and are depicted in Figure 2 and Tables 3 and 4. Out of a total of 20 hernia recurrences, slightly more

Table 1. Preoperative Data: Patient Demographics and Hernia Data

Demographic and hernia characteristic	Data
Patient treated with P4HB mesh, n	121
Patients with 5-year follow-up, n (%)	54 (44.6)
Sex, n (%)	
Male	46 (38)
Female	75 (62)
Ethnicity, n (%)	
Not Hispanic or Latino	113 (93.4)
Hispanic or Latino	8 (6.6)
Race, n (%)	
Black	5 (4.1)
White	116 (95.9)
Age, y, mean ± SD	54.7 ± 12.0
BMI, kg/m^2, mean ± SD	32.2 ± 4.5
Patient with previous abdominal incision, n (%)	117 (96.7)
No. of previous incisions, mean ± SD	3.0 ± 2.2
Previous incision at current hernia site	62 (51.2)
No. of comorbidities, n (%)	
1	42 (34.7)
2	45 (37.2)
3	25 (20.7)
≥4	9 (7.4)
Comorbidity, n (%)	
Obesity	95 (78.5)
COPD	34 (28.1)
Coronary artery disease	26 (21.5)
Diabetes	40 (33.1)
Active smoker	28 (23.1)
Immunosuppressed	10 (8.3)
Chronic corticosteroid use	6 (5.0)
Hypoalbuminemia	3 (2.5)
Advanced age	6 (5.0)
Renal insufficiency	1 (0.8)
Hernia diagnosis, n (%)	
Primary ventral	17 (14.0)
Primary incisional	54 (44.6)
Recurrent ventral	15 (12.4)
Recurrent incisional	35 (28.9)
Hernia location, n (%)	
Midline	102 (84.3)
Suprapubic	5 (4.1)
Subxiphoid	3 (2.5)
Other	11 (9.1)

P4HB, poly-4-hydroxybutyrate.

Table 2. Perioperative Data: Mesh/Defect Size and Operative Technique

Mesh/defect size and operative technique	Data
Defect, cm, mean ± SD	
Length	14.7 ± 5.6
Width	8.6 ± 3.4
Mesh, cm, mean ± SD	
Length	26.4 ± 5.1
Width	21.3 ± 4.9
Fixation, n (%)	
Suture	116 (95.9)
Mechanical	4 (3.3)
Unknown	1 (0.8)
Fascia reapproximated, n (%)	113 (93.4)
Operative technique, n (%)	
Retrorectus	43 (35.5)
Retrorectus with MR	45 (37.2)
Onlay	24 (19.8)
Onlay with MR	8 (6.6)
Other	1 (0.8)
Negative pressure wound therapy, n (%)	13 (10.7)
No. of drains, n (%)	107 (88.4)
0	14 (11.6)
1	30 (24.8)
2	60 (49.6)
≥3	17 (14.0)

MR, myofascial release.

than half required reoperation (n = 12), and 8 required no further action. An additional 6 patients required reoperation due to SSI, intestinal perforation, hematoma, nontherapeutic laparotomy, or fat necrosis. P4HB mesh was explanted at the time of reoperation in 4 patients. A single patient (1) underwent 2 reoperation procedures. The first was debridement of skin and subcutaneous tissue necrosis at 28 days after implementation, and the second reoperation occurred at 1,023 days after implementation for a hernia recurrence. A total of 9 patients experienced a seroma that required intervention, occurring an average of 175.5 ± 382.3 days after implementation (mean ± SD). Device-related adverse events were ascribed by the individual investigators according to their judgment. Some investigators qualified recurrence as device-related, and others did not. Because recurrence is an expected possible outcome of hernia repair, recurrences were excluded from device-related adverse events in Table 3. There were a total of 8 device-related adverse events, with a small number of patients affected by seroma, deep incisional wound infection, diastasis, pyrexia, small bowel obstruction, or abdominal pain. Seroma and SSI that were apparent at the level of the mesh were ascribed by the investigator as "device-related" in contrast with those observed

Table 3. Study Endpoints: Primary and Secondary

Study endpoint	Data
Primary, Kaplan-Meier at 60 mo, %, mean ± SD (95% CI)	
Recurrence, n = 20	22.0 ± 4.5 (11.7–29.4)
Surgical site infection, n = 12	10.1 ± 2.8 (3.3–14.0)
Secondary	
Surgical procedure time, min, mean ± SD	167.9 ± 82.5
Length of stay, d, mean ± SD	5.3 ± 5.3
Recurrence by hernia type, n (%)	
Primary ventral	1 (5.9)
Primary incisional	10 (18.5)
Recurrent ventral	3 (20.0)
Recurrent incisional	6 (17.1)
Reoperation rate, n (%)	18 (14.9)
Time to reoperation, d, mean ± SD	700.4 ± 553.2

in a different tissue plane. The earliest reported adverse events averaged 634.2 ± 491.8 days after implementation (mean ± SD).

VAS for pain decreased significantly from 3.5 ± 3.2 before surgery (baseline) to 0.6 ± 1.7 at 60 months (p < 0.0001). Carolinas Comfort Scale–Total Score trended down, but did not reach statistical significance with a score of 40.1 ± 28.6 before surgery (baseline) and a score of 4.9 ± 14.2 at 60 months (p = 0.50). For the SF-12v2 scores, the Physical Component Score increased significantly from 38.9 ± 9.8 before surgery (baseline) to 47.0 ± 9.6 at 60 months (p < 0.0001). Similarly, the SF-12v2 Mental Component Score increased significantly from baseline (46.7 ± 10.8) to 60 months (51.4 ± 9.7, p = 0.03). Quality-of-life assessment values for all intermediate time points are depicted graphically in Figure 2.

In addition to the overall rates of recurrence and SSI, several subgroups were investigated using Fisher's exact 2-tailed test (Table 5). Surgical technique and mesh-to-tissue overlap were the most remarkable results. Patients who underwent onlay repair experienced significantly greater risk of recurrence compared with those who underwent a retrorectus repair (p = 0.02). Additionally, patients with less than 5 cm or less than 10 cm mesh-to-tissue overlap in both length and width dimensions experienced greater risk of recurrence compared with patients who received larger pieces of P4HB mesh. Hernia-related complications were graded according to the Clavien-Dindo classification system (**Supplemental Digital Content 1**, http://links.lww.com/JACS/A134).[18] There were no grade IVa, IVb, or V complications and very few grade II, IIIa, or IIIb

complications. There were several grade I complications, with the majority attributed to pain/tenderness, abdominal wound dehiscence, hematoma, and seroma.

DISCUSSION

The long-term evaluation of hernia repair outcomes in the US creates many challenges due to the healthcare delivery system and migratory population. This study represents unique long-term insight into the outcomes of ventral hernia repair 5 years after repair. Very few studies report on outcomes with a 5-year duration of follow-up, yet even fewer studies are prospective. This study highlights the challenges with hernia follow-up in that approximately 50% of the patients were evaluated at 5 years. Nevertheless, this study provides important insight into outcomes among those undergoing repair with an absorbable P4HB mesh at a timeframe when the mesh is no longer providing any contribution to the strength of the repair. Approximately 4 of 5 patients were free of hernia at the conclusion of the study. Among the 20 known recurrences, 12 patients underwent reoperation for hernia recurrence. These results are consistent with long-term recurrence[19] and reoperation[20] rates reported with synthetic mesh. This study compares well with another study reporting on long-term outcomes with P4HB mesh.[21] In a retrospective series of 31 patients with a median follow-up of 98 months, recurrences after P4HB repairs occurred in 12.9% with a 10% reoperation rate. Additionally, the current study provides insight into long-term complications associated with mesh. No mesh-related complications were identified beyond the early postoperative period, and none of the patients developed mesh infection or mesh-related complications throughout the entirety of the study period. Due to the relatively low number of patients completing the 60-month follow-up, the ability to draw definitive conclusions about long-term mesh-related complications is limited. However, the observations of the lack of long-term mesh-related complications are an important finding in an era in which the drawbacks of mesh have called into question the benefits of mesh use.

The current study provides insight into the risk for both mesh complications and recurrence through the use of fascial approximation with reinforcement with a P4HB absorbable mesh. Further work is required to delineate the best populations for each type of repair and mesh, but an absorbable mesh provides a high likelihood of long-term success in selected patients. Future hernia research should focus on patient factors beyond comorbidities that may help delineate the need for permanent mesh as opposed to absorbable mesh during ventral hernia repair.
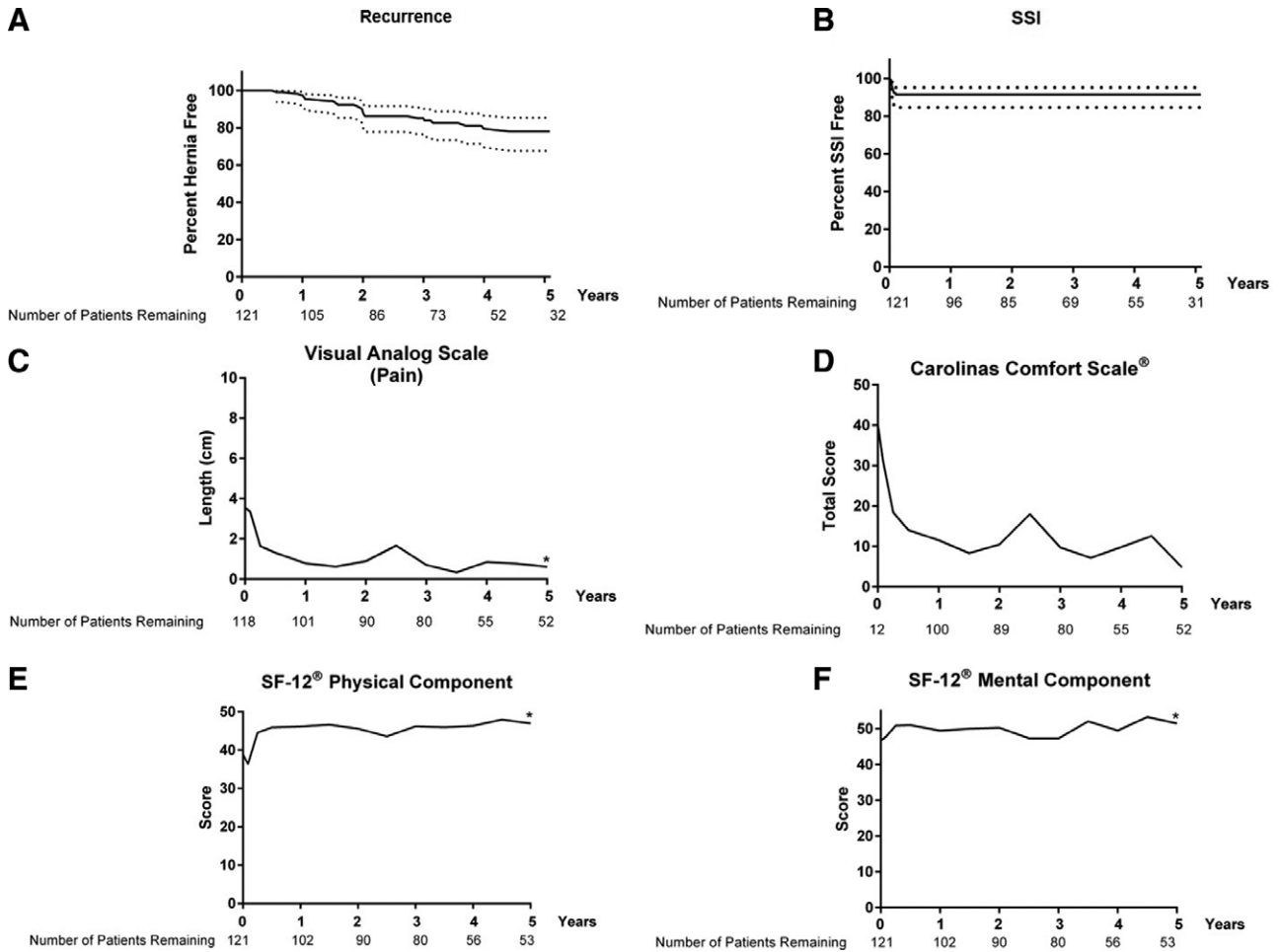
Figure 2. Primary and secondary study endpoints: (A and B) Kaplan-Meier curves for hernia recurrence and surgical site infection (SSI) in all patients treated with poly-4-hydroxybutyrate mesh (dotted lines = 95% CI; there were no additional SSI after 37 days). (C) Visual Analogue Scale for Pain (mean). (D) Carolinas Comfort Scale–Total Score (mean). (E) SF-12 Physical Component Score (mean). (F) SF-12 Mental Component Score (mean). *p < 0.05 (baseline vs 60 months).

Table 4. Quality-of-Life Metrics

	Baseline			Change from baseline		
Quality-of-life metric	n	Score	60-mo score	n	Score	p Value
Visual Analogue Scale: Pain, cm, mean ± SD	118	3.5 ± 3.2	0.6 ± 1.7	52	−3.16 ± 3.35	<0.0001
Carolinas Comfort Scale: Total Score, mean ± SD	12	40.1 ± 28.6	4.9 ± 14.2	52	−24.3 ± 21.4	0.50
SF-12 Physical Component Score, mean ± SD	121	38.9 ± 9.8	47.0 ± 9.6	53	7.4 ± 10.0	<0.0001
SF-12 Mental Component Score, mean ± SD	121	46.7 ± 10.8	51.4 ± 9.7	53	3.2 ± 10.8	0.03

The concept of an absorbable mesh is not without precedent. In fact, a study involving another absorbable mesh product composed of polyglycolide-trimethylene carbonate demonstrated 17% recurrence and 18% SSI 24 months after retrorectus or intraperitoneal implantation in clean-contaminated or contaminated hernias.[22] However, the current study provides even greater insight into

long-term outcomes with 60-month follow-up. Future prospective randomized trials will be necessary to delineate the risks and benefits of absorbable vs synthetic mesh.

Independent of mesh type, this study highlights variability in outcomes related to technique. Similar to other studies,[23] patients undergoing preperitoneal or retrorectus repairs experienced fewer recurrences than those

Table 5. Raw Percentages and Fisher's Exact Test p Values for Subanalyses of Primary Outcomes

	Recurrence rate			SSI		
Characteristic	n/N	Calculated raw percentage	Fisher's exact test 2-tailed p Value	n/N	Calculated raw percentage	Fisher's exact test 2-tailed p Value
All patients	20/121	16.5	n/a	12/121	9.9	n/a
Sex			0.61			0.03*
Male	9/46	19.6		1/46	2.2	
Female	11/75	14.7		11/75	14.7	
No. of comorbidities			>0.99			0.06
1	7/42	16.7		1/42	2.4	
≥2	13/79	16.5		11/79	13.9	
Operative technique			>0.99			0.36
With MR†	9/53	17.0		7/53	13.2	
Without MR†	11/67	16.4		5/67	7.5	
Retrorectus vs onlay			0.02*			>0.99
Retrorectus†	10/88	11.4		9/88	10.2	
Onlay†	10/32	31.3		3/32	9.4	
Total overlap in length and width			0.04*			0.13
<10 cm	13/53	24.5		8/53	15.1	
≥10 cm	7/68	10.3		4/68	5.9	
Total overlap in length and width			0.005*			0.69
<5 cm	8/20	40.0		1/20	5.0	
≥5 cm	12/101	11.9		11/101	10.9	
SSI			>0.99			n/a
Patients with SSI	2/12	16.7		12/12	100.0	
Patients without SSI	18/109	16.5		0/109	0.0	

*p < 0.05.
†n = 120.
MR, myofascial release; n/a, not applicable; SSI, surgical site infection.

undergoing an onlay repair. Although this should not imply that onlay repairs should be abandoned, use of a retrorectus technique is likely to reduce the risk for hernia recurrence in absorbable mesh hernia repairs.

Additional factors beyond mesh placement such as degree of overlap and mesh-to-defect ratio similarly impact hernia outcomes. The placement of large meshes with significant overlap beyond the defects of a hernia is accepted as surgical dogma. This study has demonstrated the impact of limited overlap on hernia recurrence rates. Patients with less than 10 cm of total mesh overlap relative to defect in the longitudinal access (5 cm on either side) had a 3-fold increase in hernia recurrence rates, which was even greater for patients with less than 5 cm of total longitudinal mesh overlap (2.5 cm on either side). Interestingly, lateral mesh overlap less than 10 cm overall did not impact hernia recurrence rates, likely related to the offloading of midline tension associated with the hernia dissection. This suggests that the placement of mesh that extends both

superior and inferior to the incision is an important aspect of hernia repair and may be a significant driver for hernia recurrences. Interestingly, among the onlay repairs in the study, many patients did not have mesh overlap extending above and below the defect. This might explain the increased recurrence rate reported in the onlay group.

Although the study was not powered to evaluate the impact of SSI on recurrence, those with postoperative SSI did not experience increased long-term hernia recurrence rates, contrary to published outcomes with synthetic mesh.[24] An unexpected finding was the reduced incidence of SSI rates in male patients compared with female patients. In the subanalyses, we were unable to delineate a rationale for this difference based on technique or patient characteristics. Despite this finding, sex did not impact hernia recurrence rates. Female sex has been previously reported to be associated with increased risk for poor outcomes in ventral hernia repair independent of comorbid conditions.[25] Whether this difference is a result of chance,

an unstudied variable, or sex alone will require future investigation.

Limitations of this study include the fact that this is not a randomized trial. However, it is a prospective trial with 5-year follow-up. Long-term follow-up is always a challenge with studies like this, especially in the US with multiple insurers and a lack of standardized health records. We also acknowledge the limitations of our statistical analyses, namely that the current study was not powered to detect differences between subgroups of interest. Nevertheless, we found these initial subgroup analyses interesting and provocative, and future investigation is warranted. Additionally, this study did not use the minimal clinically important difference (MCID) score to contextualize the results and differentiate between "statistically significant" and "clinically relevant" outcomes, particularly as they relate to patient-centered outcomes such as quality-of-life metrics. Although the published literature reports MCID for VAS and SF-12 v.2 in spinal procedures, caution should be exercised in using MCID generated for a different disease state. Several published studies also report MCID for hernia-related quality-of-life metrics (Hernia-related Quality-of-Life survey and modified Activities Assesment Scale), but none report on VAS, Carolinas Comfort Scale, and SF-12 in a hernia population. Future studies are certainly warranted to generate MCID for more outcomes associated specifically with abdominal wall reconstruction.

CONCLUSIONS

Five-year outcomes after ventral and incisional hernia repair with P4HB mesh are associated with infrequent complications and durable hernia repair outcomes. Although limited by the extended study duration and associated loss to follow-up, this study provides a framework for anticipated long-term hernia repair outcomes when using P4HB mesh.

Author Contributions

Study conception and design: All authors
Acquisition of data: All authors
Analysis and interpretation of data: Deeken, Badhwar, Roth
Drafting of manuscript: Deeken, Roth
Critical revision: Badhwar, Deeken, Roth

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Invited Commentary

Hernias and Novel Devices/Implants: Raising the Bar for Patient Safety

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In their recent study, Roth and colleagues[1] completed a single-arm trial assessing a novel implant, poly-4- hydroxybutyrate (PH4B). They should be commended for completing a 5-year prospective study. The trial was well conducted and provided prospective data of mid-term clinical (eg recurrence) and patient-centered outcomes. They evaluated 121 patients with a mean follow-up of 5 years and noted recurrence of 22% ± 4.5%, surgical site infection of 10.1% ± 2.8%, and improvement in Carolinas Comfort Scale total score (change from baseline of −24.3 ± 21.4 at 60 months).

It is important to consider completeness of follow-up when interpreting a clinical trial. This study had only 44.6% follow-up at 5 years. Patients who drop out of studies are more likely to have had adverse outcomes. It is estimated that, among patients who do not follow up, complication rates are likely 2 to 5 times greater.[2] It is widely accepted that at least 80% follow-up is needed to achieve valid conclusions.[3,4] There are several statistical methods to adjust for dropouts, including imputation and weighing, but none were employed.[2] In this study, the

authors report a 22% recurrence rate; however, a sensitivity analysis with an imputed 2 to 5 times increased recurrence rate among those who did not follow up would provide a more precise estimated recurrence rate of 34% to 65%.

Although this is a well-conducted prospective cohort study, a randomized controlled trial (RCT) would have provided data at low risk for bias and with greater applicability. RCTs are the gold standard in clinical research. Although time and cost are often cited as barriers to performing RCTs, it is unlikely that the cost and time of a multicenter prospective observation study would be much different from a RCT.

We have seen this approach play out previously with multiple devices in hernia operations. Two critical examples stand out: biologic mesh and Physiomesh (Ethicon). Initial studies of biologic mesh and Physiomesh, including similar single-arm cohort studies, showed "acceptable" rates of infection, recurrence, or complications.[5,6] In non-randomized comparative studies, many authors have demonstrated favorable outcomes using biologic mesh (vs synthetic mesh) and Physiomesh.[7] Despite only limited data at high risk for bias and no RCTs assessing the safety or efficacy of biologic mesh and Physiomesh, both were widely adopted. Recently, both meshes have been proven to be fatally flawed. Several RCTs comparing biologic and synthetic mesh were completed, and all showed a higher recurrence rate and wound complications using biologic mesh.[8-11] A small pilot RCT completed in less than a year demonstrated unreasonably high recurrence rates with Physiomesh.[12] European databases collecting nearly a decade's worth of hernia repair outcomes data finally provided the data to end the sale/use of Physiomesh through voluntary withdrawal of the defective product.[13,14]

Although industry will fund prospective single-arm trials, they often will not fund a RCT comparing their product with another product. Data from prospective single-arm studies can be spun to be interpreted in any manner, and RCTs are less subject to "spin." Society grants and NIH funding are rarely awarded for device trials because review committees argue that this research should be funded by industry. Thus, many medical devices are in use for years before there is even an attempt to obtain data at low risk for bias.

Currently, companies are not required to provide level 1 data for a device to be marketed and used in clinical practice. Via the 510K pathway, devices can be cleared when there is a predicate device with the same purpose and "similar" technology already on the market (eg biologic mesh was similar enough to polypropylene mesh, and Physiomesh was similar enough to other intraperitoneal onlay mesh meshes). Clinical studies may or may