

Outcomes of Poly-4-hydroxybutyrate Mesh in Ventral Hernia Repair: A Systematic Review and Pooled Analysis

Joseph A. Mellia, BA*
 Sammy Othman, BA*
 Hani I. Naga, BA*
 Charles A. Messa IV, BS*
 Omar Elfanagely, MD*
 Yasmeen M. Byrnes BA*
 Marten N. Basta, MD†
 John P. Fischer, MD, MPH*

Background: Within the past decade, poly-4-hydroxybutyrate (P4HB) biosynthetic mesh has been introduced as a potential alternative to traditional biologic and synthetic mesh in ventral hernia repair (VHR). The aim of this study was to systematically assess clinical outcomes with the P4HB in VHR.

Methods: A literature search identified all articles published in 2000 involving the use of P4HB in VHR. Descriptive statistics were used to synthesize collective data points, including postoperative outcomes. A pooled analysis of postoperative outcomes was performed using chi-square test and Fisher exact test.

Results: Across 7 studies, the P4HB was used in 453 patients. The mean rate of surgical site infection (SSI) was 6.8% (31/453), reoperation 10.7% (30/281), and recurrence 9.1% (41/453). At an average follow-up of 26.8 months, the incidence of recurrence was 10.4% (28/270). Onlay was significantly associated with increased recurrence (14.2% versus 4.4%, $P = 0.001$). Among sublay placements, there was no difference in recurrence in clean (Center for Disease Control [CDC] 1) or contaminated (CDC >1) wounds (2.7% versus 6.1%, $P = 0.585$), but contaminated wounds were associated with increased SSI (2.7% versus 15.2%, $P = 0.028$). Ventral Hernia Working Group grade 2 and 3 did not have different incidences of recurrence (8.0% versus 5.1%, $P = 0.526$) nor SSI (5.1% versus 14.6%, $P = 0.265$).

Conclusions: Overall, clinical outcomes of the P4HB mesh in VHR are acceptable. The P4HB mesh serves as a reliable alternative to traditional synthetic and biologic mesh across a range of defect characteristics and patient health conditions. Further research is needed to better understand the conditions in which it may provide a clinical benefit over traditional mesh types. (*Plast Reconstr Surg Glob Open* 2020;8:e3158; doi: 10.1097/GOX.0000000000003158; Published online 16 December 2020.)

INTRODUCTION

Ventral hernia is the protrusion of intestinal contents through fascial defects in the abdominal wall, usually at the location of a previous incision, as is the case with incisional ventral hernia.^{1,2} The use of mesh reinforcement is an advancement in surgical technique that has reliably reduced hernia recurrence following a ventral hernia repair (VHR).^{3,4} However, complications associated with the use of synthetic nonabsorbable mesh, such

as infection, chronic pain, and mesh extrusion, remain a significant challenge.⁵

A synthetic nonabsorbable mesh is traditionally made of polypropylene, polytetrafluoroethylene, polyester, or a combination of these materials.⁶ Despite its demonstrated ability to dramatically reduce recurrence,^{3,4} the synthetic mesh raises concern for chronic infection in contaminated, high-risk settings and complex surgical scenarios.⁷ To improve outcomes and decrease complications in these circumstances, a biologic mesh was developed and introduced.⁸ The biologic mesh minimizes the foreign body response, thereby preventing bacterial invasion and decreasing the risk of infection, while simultaneously revascularizing host tissue.^{9,10} However, despite these advantages, the biologic mesh is not readily utilized owing to its significant cost and lack of long-term data.¹¹ Within the past decade, long-acting resorbable biomaterials have

From the *Division of Plastic Surgery, Department of Surgery, University of Pennsylvania, Philadelphia, Pa.; and †Department of Plastic and Reconstructive Surgery, Brown University, Providence, R.I. Received for publication July 20, 2020; accepted August 7, 2020.

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been introduced as a potential alternative to both biologic and synthetic counterparts,¹² with the goal of leveraging the benefits of both meshes. Like the biologic mesh, the biosynthetic mesh is theorized to decrease the risk of infection.¹³ However, it also handles like the synthetic mesh, providing immediate structural support¹⁴ and possibly reducing recurrence rates.

Resorbable biosynthetic meshes maintain their mechanical strength during the early stages of healing and gradually resorb to rebuild connective tissue.¹⁵ Poly-4-hydroxybutyrate (P4HB) is a naturally-derived, fully-resorbable monofilament construct, which slowly degrades into native collagen in 12–18 months.^{15,16} While various studies have identified the advantages of the P4HB in both clinical and preclinical settings, a consensus of VHR outcomes using the P4HB is lacking. In the present study, the authors aimed to analyze clinical outcomes following VHR with P4HB mesh reinforcement. Herein, we systematically reviewed the published literature on the P4HB in VHR.

METHODS

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,¹² a full literature review of PubMed, Web of Science, and Embase databases was conducted. A search string strategy was devised to capture the use of P4HB for VHR using Boolean operators AND/OR to combine the following terms: “hernia,” “ventral hernia,” “incisional hernia,” “phasix,” “P4HB,” “biosynthetic mesh,” and “poly-4-hydroxybutyrate.”

Inclusion criteria encompassed reports detailing the use of P4HB mesh for VHR in any plane for patients aged 18 years or older. Relevant articles were extracted from citations when applicable. Both prospective and retrospective studies, including case-series and cohort studies, were included. Articles were considered if they were published in the year 2000 or after, and if they were available in English or had an English translation. Exclusion criteria included the use of P4HB for purposes other than VHR. Review articles, abstracts, and editorials were also excluded. Using Rayyan QCRI software,¹⁷ 2 authors (J.A.M. and S.O.) independently reviewed the title and abstract of all search results for inclusion and exclusion criteria. Discrepancies between author article review were resolved through discussion with the senior author (J.P.F.).

Outcomes of interest included incidence of hernia recurrence, reoperation, surgical site infection (SSI), and any other surgical site complications reported. Patient demographics, comorbidities, and surgical history were also collected. Wound characteristics were recorded, including Center for Disease Control (CDC) surgical wound classifications and the Ventral Hernia Working Group (VHWG) classification, in addition to location of mesh placement and length of follow-up. Descriptive statistics were used to synthesize collective data points, and chi-square test and Fisher exact test were used for a pooled analysis of postoperative outcomes.

RESULTS

A total of 963 articles were identified on the initial database review (Fig. 1). Of the total articles, only 417

remained after removal of duplicates. Screening the title and abstract resulted in 11 articles remaining for a full text review. Following the full text review, 8 articles were deemed appropriate for inclusion and qualitative analysis. A total of 7 studies were included in the quantitative analysis, since 1 article did not separate outcomes of P4HB from those of other biosynthetic meshes, namely Gore Bio-A (WL Gore) and TIGR-Matrix (Novus Scientific).

Summary of Study Design

Table 1 summarizes the study designs of the included articles. All articles reported on clinical outcomes associated with P4HB use for VHR. Three articles^{21,22,25} also described quality of life variables associated with P4HB use, and 1 article²² described the cost of P4HB. Four articles were retrospective studies providing level III evidence,^{18,20,22,23} and 4 were prospective studies offering level II evidence.^{19,21,24,25} All studies investigated patients undergoing VHR, with one focusing specifically on patients with a high risk for postoperative complications.¹⁹ Two studies targeted patients specifically undergoing complex abdominal wall reconstruction,^{18,24} which was defined as bilateral component separation²⁴ in one and not clearly defined in the other.¹⁸

The method of postoperative follow-up was outlined in 7 of 8 studies. Five studies assessed long-term clinical outcomes beyond 12 months using telephone interviews.^{19,21–23,25} In 2 articles,^{22,25} patients with positive findings on telephone interview were prompted to return to the clinic for follow-up.

Description of Sample Sizes and Placement of Mesh

P4HB was used in a total of 453 patients. The included studies used only P4HB in their biosynthetic mesh group except for the study by Sahoo et al,²⁰ which also included Gore Bio-A (WL Gore) and TIGR-Matrix (Novus Scientific) (Table 2). Two studies included a side-by-side comparison of the P4HB mesh with either the porcine cadaveric biologic mesh¹⁸ or the polypropylene synthetic mesh.²⁰

P4HB was placed in an onlay position in 40.8% (185/453) of cases and a sublay position in 55.2% (250/453) (Table 2). Although nearly all cases used either onlay or sublay, the location of P4HB was not consistent across studies. While 4 studies included patients with a mesh in the same location, 4 included patients with a mesh in various locations. Of the studies where a mesh was placed in the same location, 2 studies^{18,24} used onlay and 2 studies^{21,23} used sublay. One study included inlay placement,²⁰ but it was used only in 2 cases. One study placed the P4HB in the underlay position.²⁵

Characteristics of Patient Cohorts

P4HB was used in various types of VHRs, classified by the CDC wound classification, American Society of Anesthesiologist (ASA) physical status classifications, and VHWG classification (Table 3). Most cases were CDC wound class 1 (79.5%, 276/347), followed by class 2 (11.5%, 40/347), class 3 (6.1%, 21/347), and class 4 (2.9%, 10/347). The majority of cases were ASA class 3 (65.7%, 115/175), followed by followed by ASA class 2 (38.9%, 68/175), class 4 (4.6%, 8/175), and class 1 (2.3%,

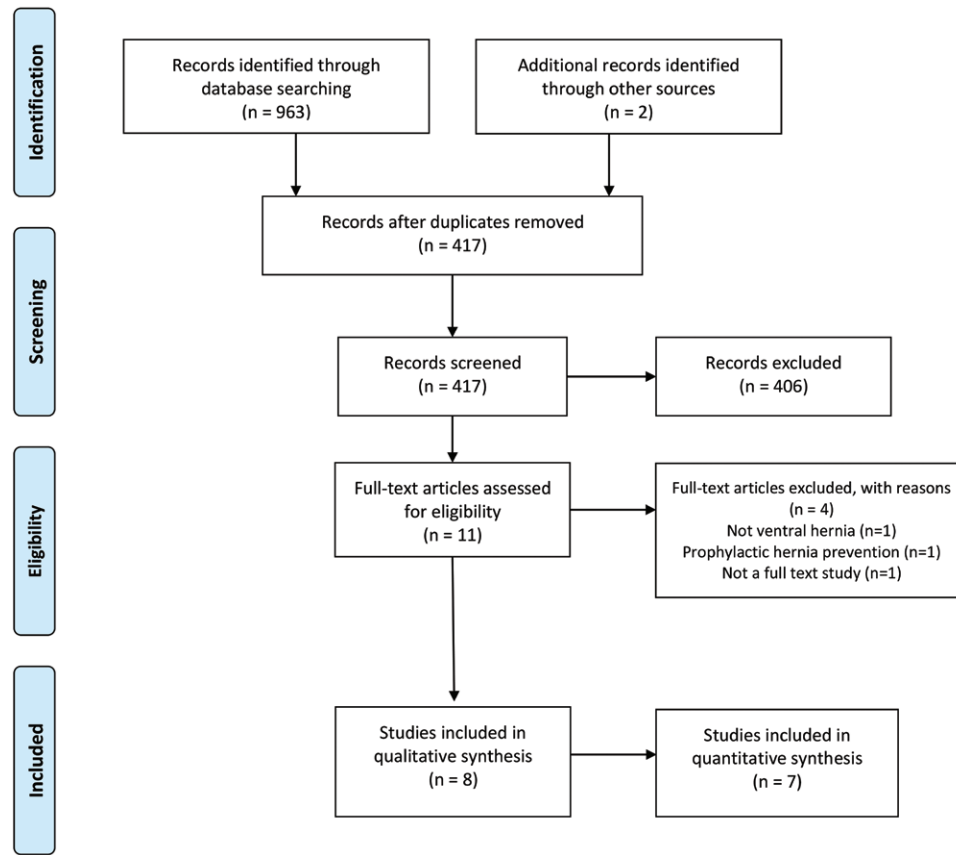


Fig. 1. PRISMA diagram.

4/175). Lastly, most cases were either VHWG grade 2 (47.9%, 79/165) or grade 3 (46.1%, 76/165), followed by grade 1 (11.1%, 10/90). Two studies did not report CDC wound class,^{18,25} 3 studies did not report ASA classification,^{18–20,25} and 4 studies did not report VHWG.^{18,19,21,24}

Patient comorbidities are outlined in Table 4. The average age for patients receiving P4HB was 55.3 years, and the average body mass index (BMI) was 31.6 km/m². Other comorbidities included 56% (194/347) hypertension, 22.7% (103/453) diabetes, 27.4% (110/402) current or former tobacco user, 82.4% (187/227) previous abdominal operation, 63.9% (209/327) obese, and 28% (72/257) cardiovascular/ coronary artery disease. Age, diabetes mellitus, and BMI were the only patient characteristics reported consistently across all studies.

Summary of Postoperative Outcomes

For P4HB groups, the mean incidence of SSI was 6.8% (31/453), reoperation 10.7% (30/281), and recurrence 9.1% (41/453) (Table 5). At an average follow-up of 26.8 months for patients in 4 studies^{22–25} that reported mean follow-up, the recurrence incidence was 10.4% (28/270). Recurrence demonstrated a positive correlation with average follow-up time ($r^2 = 0.9654$) (Fig. 2). Outcomes were not consistently reported across studies. However, the most commonly reported outcome was SSI, which was reported in all included studies, followed by hernia recurrence^{18,19,21–25} and reoperation.^{18,19,22,24,25}

Other surgical site complications were either grouped into poorly defined categories or variably reported. One study¹⁸ reported a “complication rate” of 22.6%, without characterizing the specific complications. Another reported complication rate was broken down into “minor” and “major complications,” which were 19% and 20%, respectively. Minor was defined as not requiring surgical intervention, while major was defined as recurrence, readmission, and need for reoperation.

Studies that reported specific surgical site complications for P4HB did so inconsistently. These complications included seroma (6.6%, 21/316),^{19,20,22–24} cellulitis (3%, 2/101),^{20–22} dehiscence (3.0%, 3/101),^{21,22} nonhealing wound (16%, 11/70),^{20,22} exposed graft (2/31, 6.5%),¹⁸ mesh exposure (8%, 8/105),²⁴ skin/soft tissue ischemia/necrosis (3.2%, 1/31),^{20,21} suture abscess (5%, 5/105),²⁴ superficial wound breakdown (17%, 18/105),²⁴ and deep/organ infection (0%, 0/75).²⁵ Procedural or surgical interventions after initial operation, if specified, included interventional radiology drainage (4.2%, 3/70),²² debridement (2.9%, 2/70),²² redo hernia repair (50%, 15/31),¹⁸ superficial infection requiring procedural intervention (4.0%, 3/75),²⁵ seroma requiring percutaneous drainage (6.7%, 5/75),²⁵ and mesh explantation (2.2%, 4/180) at an average 26.8 months follow-up.^{22–25} If studies not reporting this outcome are assumed to have 0 events, then the incidence of mesh explanation is 0.88%

Table 1. Summary of Study Design

Study	Aims	Study Design	Target Patient Population	Selection Criteria		Exclusion	Method of Follow-up
				Inclusion	Exclusion		
Buell et al, ¹⁸ 2017	To evaluate the use of P4HB in CAWR	Retrospective (level III)	Patients undergoing CAWR	None stated	None stated	1 visit per wk in an outpatient clinic	
Roth et al, ¹⁹ 2018	To evaluate rates of recurrence, SSI, and seroma 18 mo following VHR with P4HB in subjects at a high risk for postoperative complications	Prospective (level II)	Patients undergoing VHR with a high risk for postoperative complications	Primary VH, primary IH, or recurrent IH (not to exceed 3 recurrences), ≥1 comorbidity, 10–350 cm ² hernia defect	≥4 previous VHR (of the index repair); BMI > 40 kg/m ² , ASA class 4 or 5; planned intra-abdominal mesh placement or bridged repair; CDC class 2, class 3, or class 4*	Outpatient clinic visits at 1, 3, 6, 12, 18, 24, and 36 mo after operation; telephone interview at 30 mo	
Sahoo et al, ²⁰ 2017	To evaluate the use of biosynthetic and polypropylene mesh in elective VHR and investigate differences in early wound morbidity after VHR within CDC class 2 and 3 cases	Retrospective (level III)	Patients undergoing elective open VHR	Midline IH, prophylactic IV antibiotics within 1 h of operation, 30-d follow-up data	None stated	Outpatient clinic visit within 30 d of operation	
Plymale et al, ²¹ 2018	To evaluate clinical and QoL outcomes of patients with CDC class 1 and 2 VH and IH undergoing repair with P4HB	Prospective (level II)	Patients undergoing VHR	VH, IH, or first-recurrent IH, 10–250 cm ² , CDC wound class 1 or 2, ASA class B 3	Tetracycline and/or kanamycin allergy, bridged repair required, nonsurgical candidates	Outpatient clinic visits at 2–4 wk, 3, 6, 12, and 24 mo after operation; QoL assessed at baseline, 12 and 24 mo	
Messa et al, ²² 2019	To evaluate the clinical outcomes, QoL, and cost associated with P4HB in VHR	Retrospective (level III)	Patients undergoing VHR	None stated	P4HB for prophylactic laparotomy reinforcement, parastomal hernia repair >1 piece of mesh, <12 mo follow-up	Outpatient clinic visits until 16 mo after operation, then telephone surveys; QoL assessed at 0–3, 3–6, 6–12, 12–18, 18–24, and >24 mo after operation	
Pakula and Skinner, ²³ 2020	To report our preliminary outcomes using P4HB for a variety of complex hernias	Retrospective (level III)	Patients undergoing elective open midline repair of VH or IH with P4HB	None stated	Minimally invasive approaches and hernias not involving the midline, such as isolated lumbar, isolated flank, and isolated parastomal	Outpatient clinic visits at 2 wk, 3 mo, 6 mo, and 1 y, then telephone surveys	
Levy et al, ²⁴ 2020	To describe our initial experience performing CAWR utilizing CS and P4HB mesh as onlay reinforcement	Prospective (level II)	Patients undergoing CAWR	Bilateral CS	Laparoscopic or combined laparoscopic/open repair, primary fascial repair could not be achieved (requiring a bridging mesh)	Not specified	
Rognoni et al, ²⁵ 2020	To analyze the clinical outcomes and QoL consequences of hernia repairs using P4HB mesh prostheses performed in Italy to add evidence to support the choice of new generation biosynthetic prostheses	Prospective (level II)	Patients undergoing abdominal hernia repair	VHWG grade 2 or 3, at least 18 mo follow-up	None stated	Outpatient clinic visits at 8 d, 30 d; telephone follow-up at 6–12–18–24–36–48–60 mo; in cases of suspected relapse or complications, telephone follow-up is associated with an outpatient visit	

BMI, body mass index; CAWR, complex abdominal wall reconstruction; CS, component separation; IH, incisional hernia; QoL, quality of life; VH, ventral hernia, VHR, ventral hernia repair. *See publication for full exclusion criteria.

Table 2. Description of Sample Size and Mesh Placement

Study	Sample Size (n)	Mesh (n)		P4HB Placement (n)			
		P4HB	Comparison Group	Onlay/Overlay	Inlay	Sublay/RR/RM	Underlay/Intraperitoneal
Buell et al, ¹⁸ 2017	73	31	Porcine cadaveric: 42	31*	0*	0*	0*
Roth et al, ¹⁹ 2018	121	121	—	Without MR: 24 With MR: 8	0	Without MR: 43 With MR: 45	0
Sahoo et al, ²⁰ 2017*	232	Biosynthetic = 58	Polypropylene: 174	Biosynthetic: 5 Polypropylene: 16	Biosynthetic: 2 Polypropylene: 2	Biosynthetic: 51 Polypropylene: 156	0
Plymale et al, ²¹ 2018	31	31	—	0	0	31	0
Messa et al, ²² 2019	70	70	—	14	0	56	0
Pakula and Skinner, ²³ 2020	20	20	—	0	0	20	0
Levy et al, ²⁴ 2020	105	105	—	105	0	0	0
Rognoni et al, ²⁵ 2020	75	75	—	3	0	55	14
		P4HB total = 453		P4HB total = 185	P4HB total = 0	P4HB total = 250	P4HB total = 14

Biosynthetic group in Sahoo et al²⁰ includes P4HB, Gore Bio-A, and TIGR Matrix; therefore, not included in P4HB total.

*Not directly stated but inferred from methods of manuscript.

MR indicates myofascial release; RM, retromuscular; RR, retrorectus.

Table 3. Selected Preoperative Patient Characteristics for Patients Receiving P4HB

Study	CDC Wound Class (n)				ASA Class (n)				VHWG Grade (n)		
	Class 1	Class 2	Class 3	Class 4	Class 1	Class 2	Class 3	Class 4	Grade 1	Grade 2	Grade 3
Buell et al, ¹⁸ 2017	—	—	—	—	—	—	—	—	—	—	—
Roth et al, ¹⁹ 2018	121	0	0	0	—	—	—	—	—	—	—
Sahoo et al, ²⁰ 2017*	—	34*	24*	—	—	—	—	—	23*	77*	75*
Plymale et al, ²¹ 2018	30	1	0	0	†	†	†	—	—	—	—
Messa et al, ²² 2019	45	18	4	3	1	31	38	0	10	35	25
Pakula and Skinner, ²³ 2020	7	5	8	0	3	6	11	—	0	4	16
Levy et al, ²⁴ 2020	73	16	9	7	0	31	66	8	—	—	—
Rognoni et al, ²⁵ 2020	—	—	—	—	—	—	—	—	0	40	35
Total = 276 Total = 40 Total = 21 Total = 10 Total = 4 Total = 68 Total = 115 Total = 8 Total = 10 Total = 79 Total = 76											

Biosynthetic group in Sahoo et al²⁰ includes P4HB, Gore Bio-A, and TIGR Matrix; therefore, not included in P4HB total.

*Data reported for propensity-matched analysis.

†Specific numbers not reported.

Table 4. Patient Comorbidities

Study	Mesh	Age (y)	HTN (%)	Diabetes (%)	BMI (km/m ²)	Tobacco (%)	Previous Abdominal Operation (%)	Obesity (%)	CVD/CAD (%)
		Buell et al, ¹⁸ 2017*	P4HB	56.9	77.4	25.8	29.9	—	93.5
Roth et al, ¹⁹ 2018	Porcine cadaveric	52.5	73.8	40.5	31.7	—	95.2	28.6	—
Sahoo et al, ²⁰ 2017	P4HB	54.7	59.5	33.1	32.2	23.1	—	78.5	34.7
Plymale et al, ²¹ 2018	Biosynthetic	61	—	24	31	7	—	—	—
Messa et al, ²² 2019	Polypropylene	64	—	26	31	7	—	—	—
Pakula and Skinner, ²³ 2020	P4HB	52	—	25.8	33	22.6	96.8	—	16.1
Levy et al, ²⁴ 2020	P4HB	58.6	59	23	33	50	94	59	—
Rognoni et al, ²⁵ 2020	P4HB	47	40	35*	35	—	45	—	35*
		59.2	46.7	13.3	29.1	14.3	—	59.1	23.8
		59	—	23	30	35	71	35	—
		P4HB mean = 55.3	P4HB total = 56 (194/347)	P4HB total = 22.7 (103/453)	P4HB mean = 31.6	P4HB total = 27.4 (110/402)	P4HB total = 82.4 (187/227)	P4HB total = 63.9 (209/327)	P4HB total = 28 (72/257)

Comorbidities reported in fewer than 4 studies were not included. Biosynthetic group in Sahoo et al²⁰ includes P4HB, Gore Bio-A, and TIGR Matrix; therefore, not included in P4HB totals and means.

BMI indicates body mass index; CAD, coronary artery disease; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension.

*Combined DM and CAD.

Table 5. Summary of Selected Postoperative Outcomes for P4HB

Study	Duration of Follow-up	SSI (%)	Reoperation (%)	Recurrence (%)
Buell et al, ¹⁸ 2017	—	P4HB = 12.9, Porcine cadaveric = 31	P4HB = 6.5, Porcine cadaveric = 14.3	P4HB = 6.5, Porcine cadaveric = 23.8
Roth et al, ¹⁹ 2018	79% complete	9	—	9
Sahoo et al, ²⁰ 2017*	18 mo follow-up 30 d	Biosynthetic = 22.4, Porcine cadaveric = 11	—	—
Plymale et al, ²¹ 2018	2 wk (n=31) 3 mo (n=28) 6 mo (n=29) 12 mo (n=26) 24 mo (n=13)	0	—	0
Messa et al, ²² 2019	Mean = 24 mo	8	11	5.7
Pakula and Skinner, ²³ 2020	Mean = 21.1 mo	10	—	0
Levy et al, ²⁴ 2020	Mean = 36 mo	5	15	17
Rognoni et al, ²⁵ 2020	Mean = 26 mo	4	5.3	8
		P4HB total = 6.8 (31/453)	P4HB total = 10.7 (30/281)	P4HB total = 9.1 (41/453)

Biosynthetic group in Sahoo et al²⁰ includes P4HB, Gore Bio-A, and TIGR Matrix; therefore, not included in P4HB totals.

(4/453). Overall, studies concluded that the clinical outcomes of P4HB mesh were acceptable (Table 6).

Pooled Analysis of Hernia Recurrence, SSI, and Reoperation

A pooled analysis and comparison of outcomes based on the onlay or sublay position showed no difference for SSI (6.6% versus 6.5%, $P = 0.986$) and reoperation (12% versus 8.9%, $P = 0.626$). However, the onlay position was significantly associated with an increased incidence of hernia recurrence (14.2% versus 4.4%, $P = 0.001$) (Table 7). Among sublay placements, there was no difference in hernia recurrence in clean (CDC 1) or contaminated (CDC>1) wounds (2.7% versus 6.1%, $P = 0.585$), but contaminated wounds were associated with increased SSI (2.7% versus 15.2%, $P = 0.028$) (Table 7). VHWG grade 2 and 3 did not have different incidences of recurrence (8.0% versus 5.1%, $P = 0.526$) nor SSI (5.1% versus 14.6%,

$P = 0.265$). In addition, SSI incidence did not correlate with recurrence incidence ($r^2 = 0.001$) (Fig. 3).

Comparative Outcomes of P4HB

Two of the 7 studies compared P4HB outcomes with outcomes of another type of mesh, either synthetic or biologic. In comparison with porcine cadaveric mesh in patients with primarily onlay mesh placement, P4HB demonstrated a superior clinical performance with a shorter drain time, fewer complications, and decreased recurrence.¹⁸ Furthermore, in cases with ischemic wound flaps, flap necrosis, and exposed mesh, P4HB experienced significantly greater ingrowth of granulation and decreased time to wound contraction and closure compared with the porcine cadaveric group. Although not statistically significant, a higher percentage of skin grafts were required to manage wound breakdown in the porcine cadaveric group compared with the P4HB group.

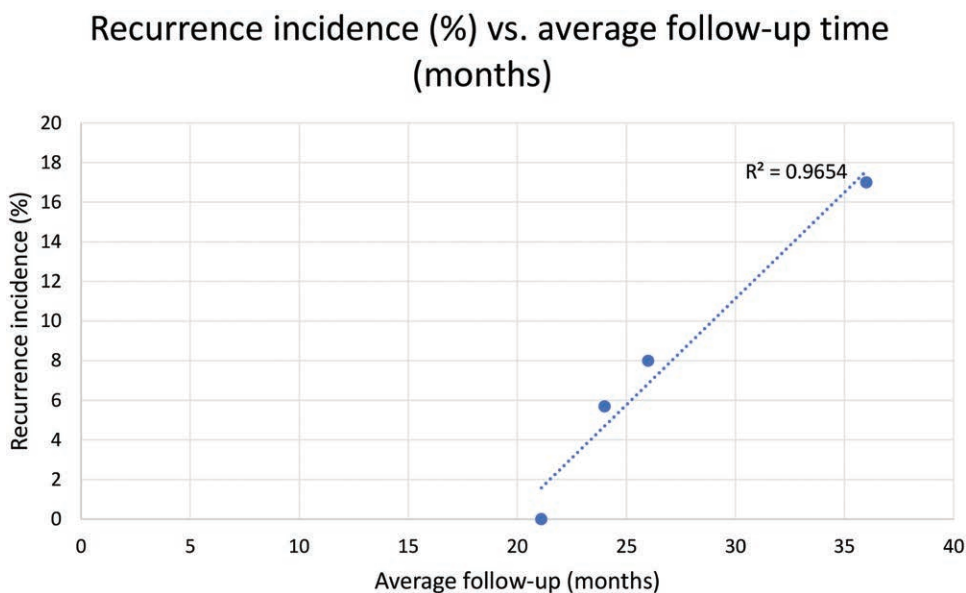


Fig. 2. Recurrence incidence (%) vs. average follow-up time (months).

Table 6. Conclusions of Studies

Study	Conclusion (Verbatim)
Buell et al, ¹⁸ 2017	In our early clinical experience with the absorbable polymer matrix scaffold P4HB, it seemed to provide a superior clinical performance and a value-based benefit compared with the porcine cadaveric biologic mesh.
Roth et al, ¹⁹ 2018	High-risk VIHR with P4HB mesh demonstrated positive outcomes and a low incidence of hernia recurrence at 18 mo.
Sahoo et al, ²⁰ 2017	The biosynthetic mesh appears to have higher rates of 30-d wound morbidity compared with that of the polypropylene mesh in elective OVHR with clean-contaminated or contaminated wounds.
Plymale et al, ²¹ 2018	Ventral hernia repair with P4HB bioresorbable mesh results in favorable outcomes. Early hernia recurrence was not identified among the patient cohort. Quality of life improvements were noted at 24 mo versus baseline for this cohort of patients with the bioresorbable mesh. Use of P4HB mesh for ventral hernia repair was found to be feasible in this patient population.
Messa et al, ²² 2019	P4HB mesh for complex VHR is associated with favorable 2-y clinical outcomes, acceptable hernia recurrence rate, and a significant improvement in QoL. This study supports the use of biosynthetic mesh as an effective biomaterial for complex VHR.
Pakula and Skinner, ²³ 2020	Complex hernia repairs using the bioabsorbable mesh were done in a small cohort of high-risk patients. These data demonstrate good outcomes with limited morbidity and mortality. There were no recurrences.
Levy et al, ²⁴ 2020	These data demonstrate a relatively low rate of hernia recurrence, seroma, and other common complications of CAWR in a highly morbid patient population.
Rognini et al, ²⁵ 2020	P4HB meshes have proved to be suitable prostheses in preventing recurrence, with promising outcomes in terms of early and late complications and in improving patient quality of life.

OVHR, open ventral hernia repair; QoL, quality of life; VHR, ventral hernia repair.

Although P4HB may have a clinical benefit over the biologic mesh, one study suggested that biosynthetic mesh, including P4HB, may lead to worse outcomes in comparison with the polypropylene synthetic mesh in contaminated (CDC > 1) wounds.²⁰ In this included article, a propensity-score matched comparison showed no significant difference between biosynthetic mesh and polypropylene mesh for 30-day surgical site occurrence or readmission, but SSI, surgical site occurrence requiring procedural intervention, and reoperation rates were significantly higher in the biosynthetic group.²⁰

Quality Assessment

Since half of the studies had a retrospective design, we were not able to evaluate the quality of the studies by any validated scoring system. Instead, a qualitative assessment was performed (Table 8), which was adapted from Darehzereshki et al.⁸ Only one study²⁰ addressed the incompleteness of outcome data, which was exhibited by all studies.

DISCUSSION

P4HB is a new and increasingly utilized surgical scaffold in VHR. It is a slow-resorbing, biosynthetic graft

developed as a potential alternative to traditional biologic and synthetic counterparts. To our knowledge, this is the first systematic review on clinical outcomes associated with P4HB. In summary, we demonstrated that P4HB is commonly used in obese patients or those with previous abdominal operations. ASA class 3 was most common, indicating a moderately impaired physical status. P4HB was used in multiple hernia types, primarily CDC wound class 1 and VHWG grade 2 and 3. Overall, complication rates were 6.8% for SSI, 10.7% for reoperation, and 9.1% for recurrence, which correlated positively with follow-up time and underscores the importance of a long-term follow-up.²⁶ At an average follow-up of 26.8 months, the recurrence rate was 10.4%. Onlay was significantly associated with an increased incidence of recurrence. Wound contamination (CDC >1 and VHWG grade 3) was not associated with increased recurrence. Overall, the present study demonstrates that P4HB has acceptable outcomes across a range of hernia characteristics and patient health conditions.

The 6.8% SSI incidence reported in these studies is compelling, especially considering the contaminated (CDC > 1) wound status of 20.5% patients undergoing repair with P4HB. This incidence is similar to that of the biologic mesh, 10.9%, and lower than that using nonbiologic, 36.5%, in a meta-analysis of outcomes in various wound settings.⁸ A possible explanation for P4HB's favorable incidence of SSI may be its chemical composition. P4HB is composed of monomers of butyrate, a short-chain fatty acid that has been demonstrated to have antimicrobial characteristics.²⁷ Although it has not been proved in humans, animal models have shown that butyrate may protect against sepsis.²⁸ P4HB's anti-inflammatory and antimicrobial properties may decrease SSIs following repair of contaminated wounds, in which the synthetic mesh is typically avoided. Comparing P4HB use in VHWG grade 3 (contaminated) with that in grade 2, there was no difference in the incidence of SSI, which supports this notion because contaminated wounds are typically associated

Table 7. Pooled Analysis of Postoperative Outcomes

	VHWG Grade 2	VHWG Grade 3	P Value
HR	6/75 (8.0%)	4/79 (5.1%)	0.526
SSI	2/39 (5.1%)	6/41 (14.6%)	0.265
	Onlay	Sublay	
HR	26/182 (14.2%)	11/250 (4.4%)	0.001
SSI	10/150 (6.6%)	7/107 (6.5%)	0.986
Reoperation	18/150 (12%)	5/56 (8.9%)	0.626
	Sublay		
	Clean (CDC 1)	Contaminated (CDC >1)	
HR	2/74 (2.7%)	2/33 (6.1%)	0.585
SSI	2/74 (2.7%)	5/33 (15.2%)	0.028

HR indicates hernia recurrence.

Bolded values' significance was defined as $p < 0.05$.

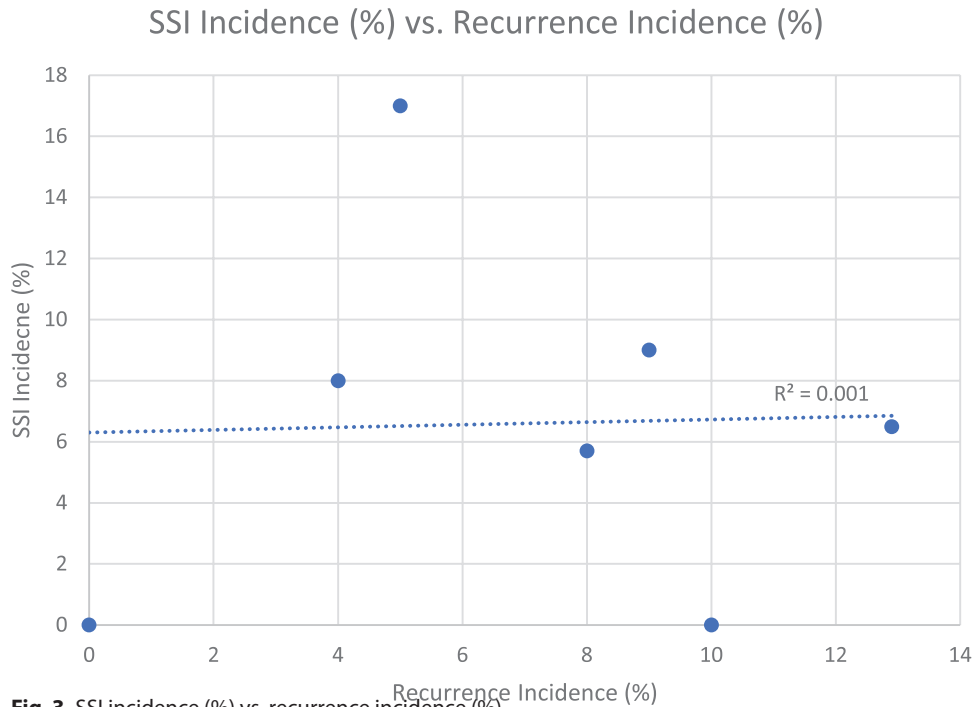


Fig. 3. SSI incidence (%) vs. recurrence incidence (%).

with an increased incidence of SSI.²⁹ This potential benefit of P4HB may decrease the cost of care, as SSI is often managed with mesh explanation, a procedure that increases the cumulative cost of care from \$6,983 to \$21,889 per patient.³⁰ Supporting this notion, mesh explanation in the included studies that reported it was rare, 2.2% at 26.8 months follow-up, and as low as 0.88% if studies not reporting this outcome are assumed to have 0 events. A low incidence of mesh explantation may have also contributed to a lower overall reoperation rate of 11.4% in comparison with the 17% rate reported for VHR with mesh.³¹ Although it appears that the PH4B mesh is associated with lower rates of SSI, further comparative studies are needed to draw a definitive conclusion.

Interestingly, SSI did not correlate with recurrence. SSI is an established predictor of recurrence.³² It is thought that inflammation in the setting of infection accelerates enzymatic degradation of the biologic mesh,³¹ weakening the scaffold and predisposing to recurrence. Unlike the biologic mesh, the P4HB degrades by a hydrolytic process into CO₂ and H₂O, which may reduce the inflammatory response.¹⁴ This is a potential mechanism by which the P4HB protects against recurrence in the setting of SSI, but further research is needed to confirm this.

Another favorable outcome of the P4HB was its 9.1% overall recurrence incidence, which is comparable to commonly reported rates ranging from 10% to 50%.³³ Notably, recurrence increased with the average follow-up time. This finding is expected in VHR. In the case of VHR using a P4HB mesh, specifically, this finding is not surprising because the P4HB naturally degrades at 12–18 months, which limits the structural support that it provides thereafter.^{15,34} However, even the longest average follow-up, 30.1 months, had a recurrence of 11.3%,

which may be considered acceptable. Although surgeons generally agree that mesh reduces recurrence, the optimal anatomical placement remains a debate. Our study shows that the onlay position was significantly associated with increased recurrence, an association that has been supported using other mesh types even with the component separation technique.^{35,36} One possible explanation for this finding is that patients undergoing P4HB placement as onlay are a morbid, at-risk subgroup of patients who lack an intact posterior rectus sheath necessary for sublay placement. Another possible explanation is that onlay position naturally gets exposed to more contaminants, which may infect the mesh and lead to more rapid P4HB dissolution, thereby decreasing the tensile strength and support it provides the abdominal wall. In general, recurrence rates in VHR using P4HB mesh are acceptable, although onlay placement may increase the rate.

The aforementioned outcomes highlight the versatility of P4HB biosynthetic mesh. Synthetic mesh is often avoided in contaminated fields, as it may serve as a nidus for infection. Instead, many surgeons opt to utilize the biologic mesh in these settings, as it is associated with decreased SSI.^{37,38} This study showed that P4HB mesh, in harnessing the “biologic” component of biologic mesh, may be placed in contaminated fields with generally acceptable results. Among sublay placements, we found no difference in recurrence in contaminated (CDC > 1) wounds. Unsurprisingly, contaminated (CDC > 1) wounds were associated with an increased SSI, 15.2%, but even this SSI incidence is lower than that reported for biologic (STRATTICE) mesh, 30%, in the same wound type.³⁹ This finding aligns with the demonstrated clinical benefit of the P4HB over the biologic mesh in an included study that compared both in primarily onlay location.¹⁸ Similarly, the

Table 8. Quality Assessment of the Included Studies

Study	Design/ Recruitment	Methods of Follow-up	Location of Mesh Reported	Type of Fascial Repair Reported		Fixation Technique Reported		Incomplete Outcome Data Addressed	Free of Selective Reporting	Description of Methods Weakness and Other Bias
				M	R	M	R			
Buell et al, ¹⁸ 2017	Retrospective/ chart review	Clinic follow-up once/ wk, then unclear	Yes	Yes	No	No	No	No	No	Small sample size; single surgeon experience; variable use of component separation; incomplete data for variables collected; does not mention how costs were ascertained; no mention of follow-up
Levy et al, ²⁴ 2020	Retrospective/ chart review	Unclear	Yes	Yes	No	Yes	No	No	No	Intermediate follow-up; no direct comparison of PH4B to other synthetics
Messa et al, ²² 2019	Retrospective/ chart review	Unclear; by telephone if over 16 mo from VHR and unable to f/u in clinic for 6 mo Clinic notes	Yes	Yes	No	Yes	No	No	No	Single surgeon; variable mesh location; variable fixation technique; lack of comparison to other mesh types; costs representative of 1 institution
Pakula and Skinner, ²³ 2020	Retrospective/ chart review	Clinic notes	Yes	Yes	No	Yes	No	No	No	Small sample size; a lack of comparison with other mesh types; variable follow-up duration
Plymale et al, ²¹ 2018	Prospective pilot study	Follow-up occurred at 2–4 wk, 3, 6, 12, and 24 mo	Yes	Yes	No	Yes	No	No	No	Small sample size; only 1 patient w/ wound > class 1; variable follow-up duration
Roth et al, ¹⁹ 2018	Prospective/ open-label, nonblinded	Postoperative patient visits at 1, 3, 6, 12, 18, 24, and 36 mo then telephone interview at 30 mo	Yes	Yes	No	Yes	No	No	No	Variable mesh location; no direct comparison of PH4B with other synthetics; only class 1 wounds included; variable follow-up duration
Sahoo et al, ²⁰ 2017	Retrospective/ AHSQC database	Unclear	Yes	Yes	No	No	No	Yes	No	Retrospective registry based; multiple mesh products consolidated to 2 groups; exclude coated polypropylene mesh;
Rognoni et al, ²⁵ 2020	Prospective	Outpatient clinical visits at 8 d, 30 d; telephone follow-up at 6–12–18–24–36– 48–60 mo; in cases of suspected relapse or complications, telephone follow-up is associated with an outpatient visit	Yes	No	Yes	No	No	No	No	30-d outcomes only Possible registry data input errors; no detailed analysis of patient subgroups

AHSQC, Abdominal Hernia Society Quality Collaborative; F/u, follow up; M, methods; R, results.

John P. Fischer, MD, MPH

Division of Plastic Surgery, Department of Surgery
University of Pennsylvania Health System
51 North 39th Street
Wright Saunders Building
Philadelphia, PA 19104
E-mail: john.fischer2@pennteam.upenn.edu

present study demonstrated that the P4HB mesh was successfully employed in various VHWG grade classifications. VHWG grade 2 and 3 did not have different outcomes, which provides more support for its potential versatility.

This systematic review has several limitations. First, although the quality across studies was satisfactory, selective reporting of outcomes was exhibited by all 7 included articles, with only 1 article addressing this limitation. Incomplete description of outcomes limited the ability to provide complete collective data for outcomes other than SSI, reoperation, and recurrence. In addition, outcomes for specific CDC wound class or VHWG grades were not reported, limiting our ability to conduct a more comprehensive meta-analysis of outcomes. This meta-analysis would have better illuminated the specific conditions in which P4HB has a clinical benefit, which would have improved our understanding of P4HB utility. Second, not many studies are yet available, and only 2 compared P4HB with either the biologic or synthetic mesh. This small number of head-to-head comparisons further limited our ability to determine whether or not P4HB is clinically superior to traditional meshes. Lastly, the reviewed articles were heterogeneous in nature, with slightly different target populations, sample characteristics, methods, and duration of follow-up, limiting our ability to directly compare variables between studies. Despite these limitations, several prospective studies have been completed according to *ClinicalTrials.gov* (NCT02712398, NCT02053168, NCT01961687, NCT02720042). These will add to the growing body of data on P4HB and potentially enable a rigorous quantitative analysis of outcomes.

Our findings warrant further investigations into the specific role that the P4HB mesh plays in the hernia repair algorithm. Future prospective studies with a longer term follow-up, especially those that compare the P4HB not only with the synthetic and biologic mesh, but also with other types of biosynthetic mesh are necessary. Although P4HB has a \$9570.07 per case advantage over the porcine cadaveric mesh,¹⁸ it will be critical to better understand the economic impact of P4HB in VHR, moving forward. It has been reported that the P4HB mesh is associated with improved quality of life,^{21,22} but whether or not it provides a quality of life benefit over traditional meshes in VHR is not yet known. Ultimately, further research elucidating the association between P4HB mesh and interrelated outcomes, such as clinical complications, healthcare expenditure, and patient quality of life, will be needed to elucidate the role of P4HB in VHR.

CONCLUSIONS

Herein, we present the first systematic review of the literature on outcomes following P4HB mesh use in VHR. Overall, clinical outcomes of the P4HB mesh are acceptable. While there are not many studies, the existing evidence suggests that the P4HB mesh may serve as a reliable alternative to the traditional synthetic and biologic mesh in VHR. Further research is needed to better understand whether the P4HB provides a clinical benefit over traditional mesh types and, if so, in which situations it is most advantageous.

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