THE EVALUATION OF INCISIONAL NEGATIVE PRESSURE WOUND THERAPY FOR THE PREVENTION OF SURGICAL SITE INFECTION AFTER COMPLEX INCISIONAL HERNIA REPAIR

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ABSTRACT

Introduction: Patients undergoing complex incisional hernia repair (IHR) are at high risk of developing wound complications including wound infection. These wound complications, termed surgical site occurrences (SSO), comprise surgical site infection (SSI), hematoma, seroma, wound dehiscence, and enterocutaneous fistula. SSOs can have devastating consequences, especially when they involve prosthetic surgical mesh implanted during a complex IHR. Incisional negative pressure wound therapy (iNPWT) is a prophylactic therapy proposed as a means to prevent SSO in closed surgical incisions. However, few comparative studies have evaluated the effectiveness of this wound management strategy after IHR. Inconsistent reporting of wound outcomes across such studies may also have implications in the interpretation of their results. Thirty-day outcomes, which have been frequently used in comparative-effectiveness research, may miss a substantial number of SSO after IHR. The objective of this thesis was to (1) evaluate the effectiveness of iNPWT after IHR following its adoption at an academic hospital, and (2) to determine the optimal length of follow-up to detect wound complications after IHR.

Methods: All adult patients undergoing open incisional hernia repair at a single center from 2016-2019 were reviewed. A commercial iNPWT dressing was used at the discretion of the surgeon. In the first study, patients were grouped by type of dressing; iNPWT or standard sterile dressings (SSD). Coarsened exact matching was used to create balanced cohorts for comparison based on established risk factors for surgical site infection. The primary outcome of the first study was the composite incidence of superficial and deep incisional SSI within 30 days. The second study's primary outcome was the proportion of SSIs occurring within 180 days that were detected at 30, 60, and 90 days of follow-up. Time-to-event analysis and Cox-proportional hazards regression was performed to identify independent risk factors for SSI.

Results: 235 patients underwent open IHR. Among these, 114 were complex IHR and a total of 85 cases were included after matching (34 iNPWT, 51 SSD). The composite incidence of superficial and deep SSI

was 19.3% (11.8% vs. 27.5%, p=0.107), with significantly lower rates of deep SSI in patients receiving iNPWT (2.9% vs. 17.6%, p=0.045). After accounting for residual differences between groups, iNPWT was associated with decreased incidence of composite SSI (RR 0.36, 95%CI [0.16, 0.87]). Median length of stay was longer in patients with iNPWT (7 vs. 5 days, p=0.001). There were no differences in SSO, overall complications, readmission, or emergency department visits at 30 days. Among all 235 open IHR included in the second study, median follow-up time was 102 days. Overall incidence of SSI was 15.8% with median time to occurrence of 23 days. Incidence of non-infectious SSO was 35.5%, and wound-related readmission was 12.8%. Among 37 SSI at 180 days, 81.6% (n=30) were diagnosed at 30 days, 89.5% (n=33) at 60 days, and 92.3% (n=35) at 90days.

Conclusion: In patients undergoing complex IHR, the use of iNPWT was associated with a lower incidence of SSI at 30 days. A considerable proportion of wound complications occurred beyond 30 days, however. A 30-day endpoint detected only 81% of SSIs occurring within 180 days of surgery, while 90-day endpoint detected 92%. These results support the evaluation of this intervention in randomized controlled trials and surgical quality surveillance programs using 90-day wound outcomes. Future studies should focus on the cost effectiveness of iNPWT, its impact on long term hernia recurrences, and the identification of the patients most likely to benefit from this intervention.

RESUME

Introduction: Les patients qui subissent une cure d'hernie incisionnelle (CHI) présentent un risque élevé de développer des complications au niveau de leur plaie. Parmi ces complications, on compte l'infection du site opératoire (ISO), l'hématome, le sérome, la déhiscence de la plaie et la fistule entéro-cutanée. Ces complications peuvent avoir des conséquences dévastatrices, en particulier lorsqu'elles impliquent un treillis chirurgical implanté pendant la CHI. La thérapie par pression négative incisionnelle (TPNi) en usage unique est une thérapie pour prévenir l'ISO dans les incisions chirurgicales fermées. Cependant, peu d'études comparatives ont évalué l'efficacité de cette thérapie dans le contexte de la CHI. De plus, l'état des plaies et les complications y étant reliées ne sont pas systématiquement détaillés dans ces études, ce qui pourrait influencer leurs conclusions. Enfin, un délai de 30 jours post-op est souvent employé, ce qui pourrait laisser échapper un grand nombre d'ISO. Le but de cette thèse est d'évaluer l'efficacité de TPNi à réduire le taux d'ISO après la CHI, suite à son adoption dans un hôpital universitaire. Ensuite, nous voulions déterminer la durée de suivi optimal pour détecter les complications des plaies après la CHI.

Méthodes: Les dossiers de tous les patients adultes ayant subi une CIH dans un centre hospitalier universitaire de 2016 à 2019 ont été révisés. Un pansement TPNi commercial a été utilisé à la discrétion du chirurgien. Dans la dernière étude, les patients ont été regroupés par type de pansement; TPNi ou pansements stériles standard (PSS). L'appariement a été utilisé pour créer des cohortes équilibrées en fonction des facteurs de risque bien établis d'ISO. Le principal résultat à l'étude était le taux d'ISO de la plaie superficielle et profonde à 30 jours. L'issue secondaire était le taux de détection d'ISO de la plaie durant une période de 180 jours, tel que mesuré à 30, 60, et 90 jours post-opératoires. Une analyse de survie et une régression aléatoire proportionnelle de Cox ont été effectuées pour identifier les facteurs de risque associés à l'ISO dans cette cohorte.

Résultats: 235 patients ont subi une CHI ouverte. De ces 114 CHI étaient complexes, et parmi ces cas, 85 patients ont été appariés à une cohorte historique (34 TPNi, 51 PSS). L'incidence d'ISO de la plaie était de 19,3% (11,8% vs 27,5%, p = 0,107), avec des taux significativement plus faibles d'ISO profond chez les patients recevant la TPNi (2,9% vs 17,6%, p = 0,045). Après avoir ajusté pour les différences résiduelles entre les cohortes appariées, la TPNi était associé à une diminution de ISO (RR 0,36, IC à 95% [0,16, 0,87]). La durée de séjour médiane était plus longue chez la cohorte de TPNi (7 vs 5 jours, p = 0,001). Il n'y avait aucune différence dans le taux de complications de plaies non-infectieuses, de complications globales, de réadmissions ou de visites à l'urgence à 30 jours. Parmi les 235 CHI ouverts inclus dans la deuxième étude, le temps de suivi médian était de 102 jours. L'incidence globale d'ISO était de 15,8% avec un délai médian d'apparition de 23 jours. L'incidence des complications de plaie non-infectieuses était de 35,5% et de 12,8 pour la réadmission. Parmi 37 ISO à 180 jours, 81,6% (n = 30) ont été diagnostiqués à 30 jours, 89,5% (n = 33) à 60 jours et 92,3% (n = 35) à 90 jours.

Conclusion: Chez les patients subissant un CHI complexe, la TPNi a été associée à une incidence d'ISO plus faible à 30 jours. Cependant, une proportion considérable de complications de la plaie est survenue après ce délai. La mesure de ISO à 30 jours n'a détecté que 81% des SSI survenant dans les 180 jours suivant la chirurgie, tandis que la mesure à 90 jours en a détecté 92%. Donc, ces résultats soutiennent la conduite d'essais cliniques randomisés contrôlés afin de mieux évaluer l'efficacité de cette intervention, ainsi que des programmes de surveillance de la qualité chirurgicale allant jusqu'à 90 jours post-op. Dans l'avenir, les études devraient se pencher sur la rentabilité de la TPNi, sur son impact sur les récidives d'hernie à long terme et l'identification des patients qui pourraient en bénéficier le plus.

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CONTRIBUTION OF AUTHORS

This thesis was written by Brent Hopkins (BH), who is the primary author of both manuscripts presented in this thesis. BH was involved in the study design, data collection, analysis, interpretation of results, and drafting of both manuscripts. Liane S Feldman (LSF) was the principal investigator of the manuscripts. Lawrence Lee (LL) and Eric Latimer (EL) were the primary supervisor and co-supervisor to this thesis.

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GLOSSARY

Abbreviation	Term
NPWT	Negative pressure wound therapy
iNPWT	Incisional negative pressure wound therapy
RCT	Randomized Controlled Trial
SSOPI	Surgical site occurrence requiring procedural intervention
SSO	Surgical site occurrence
SSI	Surgical site infection
VHR	Ventral hernia repair
AWR	Abdominal wall reconstruction
IHR	Incisional hernia repair
VHWG	Ventral Hernia Working Group
MHGS	Modified Hernia Grading Scale
VHRS	Ventral Hernia Risk Score
HW-RAT	Hernia Wound Risk Assessment Tool
ACS-NSQIP	American College of Surgeons National Surgical Quality Improvement Program
CDC	Centers for Disease Control
CDC NHSN	Centers for Disease Control National Healthcare Safety Network
AHSQC	America's Hernia Society Quality Collaborative
EuraHS	European Hernia Society

CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION TO ABDOMINAL HERNIA

Abdominal hernias are a common affliction that account for more than 800,000 surgical procedures in the United States (1), and more than 50,000 in Canada annually. A hernia is defined as "the protrusion of an organ or tissue out of the body cavity in which it normally lies" (2). While hernias occur in a variety of locations throughout the body, they are a common problem in the abdomen.

1.1.1 ANATOMY AND PATHOPHYSIOLOGY

The abdomen is a large body cavity that contains a variety of digestive, excretory, endocrine, and reproductive organs with an accompanying network of ducts, lymphatics, blood vessels, and fatty tissue. From a simple biomechanical perspective, the abdomen is a cylinder packed with these contents and braced by a wall of bone, muscles, and tendons. The pressure within the abdomen is distributed across the surface of this muscular wall, which contains and protects the viscera, bends and rotates the trunk, and generates the pressures needed to defecate, cough and sneeze. A hernia occurs when an anatomic weak-point, or *defect,* develops in the abdominal wall. As pressure within the abdomen increases, the contents of the abdomen will begin to protrude at this site. Most commonly, the herniating material is intraabdominal fat or a segment of the small intestine, which are the most loosely attached and superficial structures under the anterior abdominal wall.

The anterior abdominal wall consists of nine layers, but among these, the muscular and fascial layers are critical to its strength and integrity. Fascia is a type of connective tissue, similar to tendons and ligaments, that exists as taut sheets that envelop muscles and other structural components of the body. In the abdominal wall, defects in fascia are often responsible for the development of hernias. When a

fascial defect is exposed to chronic pressures, it may balloon to become a sac filled with tissue from inside the abdominal cavity.

When evaluating a hernia, a physician may see or palpate a prominent bulge that can often be pushed back into the abdomen. At the level of the abdominal muscles, a rim of normal and taut fascia can often be felt outlining the circumference of the defect. If a hernia is not readily obvious, a physician may ask a patient to cough or bear-down, which increases intraabdominal pressure to produce a palpable impulse or cause intra-abdominal contents to re-hernia through the defect. Often, a clinical exam alone is sufficient to diagnose a hernia. However, other adjuncts such as ultrasound imaging (US) or computed tomography (CT) may be useful to diagnose or further characterize a hernia defect.

1.1.2CLINICAL PRESENTATION AND DIAGNOSIS

Many hernias are asymptomatic and may present as a scarcely noticeable or transient bulge. Even small hernias can be painful, however and pain is the indication for surgery in as many as 78% of hernia repairs (3). Lower back pain and discomfort are also common, especially in large hernias. Large and pendulous hernias can exert pressure on the surface of the skin, causing thinning and eventually ulceration at their apex.

Hernias are often relatively benign and do not require an urgent surgical repair. However, hernias can become complicated and develop into a life-threatening problem that requires immediate surgical intervention. In 2013, the Word Society of Emergency Surgery (WSES) published guidelines for the emergency repair of abdominal hernias, which reviewed a simple and classic clinical categorization of abdominal hernias that is useful for surgical decision making. A hernia can exist in one of three states; it can be reducible, incarcerated, or strangulated (4). A ***reducible*** hernia is one whose contents spontaneously or easily fall back into the abdomen. In general, asymptomatic and reducible hernias can either be observed or repaired on an elective basis to prevent complications in the future. ***Incarcerated***

hernias are those whose contents have become stuck outside the abdominal wall in a hernia sac. Incarcerated hernia cannot be reduced again, even with non-surgical therapeutic manoeuvres. When an incarcerated hernia contains a loop of small intestine, it will often cause a bowel obstruction by kinking or constricting the intestine at the aperture of the facial defect. Acutely incarcerated hernias should be repaired urgently. ***Strangulated*** hernias occur when the blood supply to a hernia's contents has been compromised. A hernia containing a loop of small intestine that becomes strangulated requires an immediate surgical intervention, as this loop of bowel will quickly become ischemic and perforate, leading to sepsis and possibly death.

1.1.3 CLASSIFICATION

Abdominal hernias are classified by their etiology and then anatomic location. First, hernias are classified as either ***primary*** or ***incisional*** hernias. Those resulting from aberrant development or anatomic points of weakness are considered ***primary*** hernias. Hernias that occur at the site of a prior surgical incision, are called ***incisional*** hernias. Secondly, hernias are referred to by their anatomic location. ***Lumbar*** hernias occur posteriorly, most often at one of two points of weakness between the large muscles of the back and where the anterior abdominal wall muscles attach to the ribs and spine. ***Groin*** hernias occur at the intersection of the abdomen and pelvis, most commonly at the site of a defect remaining from the descent of the testes into the scrotum during early development. ***Ventral*** hernias occur in the anterior surface of the abdominal wall, most often at the navel where, after the umbilical cord has shriveled and fallen off after birth, a small defect can persist.

1.2 INCISIONAL VENTRAL HERNIA

The research questions addressed in this thesis involve ***incisional ventral hernias***, which we will refer to simply as *incisional hernias (IH)*. Many studies group primary and incisional ventral hernias together when evaluating their surgical repair and use the term *ventral hernia repair* (VHR). Others maintain a distinction, referring specifically to *incisional hernia repair* (IHR) to the exclusion of primary ventral

hernias. While VHR and IHR overlap and are often used somewhat interchangeably, the distinction is important to bear in mind.

Most IHs occur in a ventral location for the simple reason that most laparotomies—the technique of accessing the abdominal cavity via a surgical incision—are performed using an incision through the anterior abdominal wall. A vertical midline laparotomy is a common choice among abdominal surgeons, as it is easily closed and can be extended readily in a cranial or caudal direction to provide excellent visual exposure and access to the entire contents of the abdomen. Some evidence suggests that transverse incisions may be associated with lower rates of incisional hernia (5). However, incisional hernia is a frequent long-term complication after any laparotomy.

IH has an incidence of 5-20% (6–8) and may be as high as 25% at 3 years after a midline laparotomy (9). A national population-based study estimated that 365,000 VHRs were performed in the United States in 2006, at a total procedural cost of $3.2 billion (10). Among these VHRs, at least 100,000 were incisional hernia repairs (IHR) (1). Still, these represent only a fraction of patients with IH, as many patients are observed without ever undergoing surgery.

The formation of IH likely involves altered collagen metabolism in the extracellular matrix during wound healing (11,12). Patients with connective tissue diseases, abdominal aortic aneurysms, or a history of primary ventral hernias are at higher risk of IH after laparotomy (13,14). Similarly, malnutrition, old age, smoking, obesity, immunosuppression, and malignancy can all affect wound healing and increase the risk of IH (7,15,16). Aberrant events during wound healing, especially post-operative wound infection, are associated with increased risk of IH and the recurrence of a hernia after surgical repair (17,18).

Many clinical trials and meta-analyses have addressed the optimal surgical techniques for abdominal closure in order to minimize the risk of IH. In general, a ‘mass closure’ technique–closing the fascia in a single layer–using a slowly absorbable suture in a continuous running technique appears to be most

effective and efficient (6,19). Further, a suture-to-wound length ratio of at least 4:1 is preferred (20,21), and some RCTs have supported “small stitches” placed 5mm from the wound edge and 5 mm apart (22). In particularly high-risk patients, the prevention of IH using prophylactic permanent synthetic surgical mesh has even been proposed. The prophylactic use of mesh was supported by an RCT of patients undergoing elective abdominal aortic aneurysm repair, however concerns regarding long-term risks of mesh will likely need to be addressed before this strategy is widely accepted (14,23).

1.2.1 CLASSIFICATION AND COMPLEXITY

In 2009, the European Hernia Society (EuraHS) introduced an anatomic classification system for IH, with the purpose of improving the comparability of research studies. This classification system specifies the hernia’s location on the abdominal wall, its dimensions, a taxonomy based on width, and if the hernia represents a recurrence (24). This system is important to assure homogeneity across research studies, especially considering the variety of surgical approaches, techniques, and materials available to surgeons when planning a repair. For certain questions, however, the high degree of detail in this system may be a hindrance.

Abdominal hernias have been more broadly categorized by an assessment of how challenging they are to repair. Descriptors like ‘complex’ have often been used to make such distinctions. Though commonly used in surgical vernacular and the hernia literature, ‘*Complex* abdominal hernia’ was only formally defined in 2014 during a series of consensus meetings by an international committee of hernia experts (25). The committee agreed on a minor-moderate-major classification of hernia complexity based on factors pertaining to the hernia’s size and location, the degree of contamination of the soft-tissues, the patient’s history and risk factors, and the clinical scenario.

1.2.2 INCISIONAL HERNIA REPAIR

A conservative approach and watchful waiting appears to be safe in select patients with asymptomatic and reducible ventral hernias, as well as chronically incarcerated ventral hernias (26–28). Still, nearly 20% of patients with an IH who chose observation will undergo surgery within 5 years, and 4% develop an acute complication that requires urgent or emergent repair. Multicentre randomized controlled trials (RCTs) are underway to evaluate this conservative approach to ventral hernias compared to more immediate repair (27).

It is generally agreed that patients with symptomatic hernias should be offered a surgical repair. However, severe obesity, active smoking, and poor diabetic control remain relative contraindications, as these carry an unacceptably high risk of postoperative complications and hernia recurrence. Patients, especially with modifiable risk factors such as these, should be medically optimized prior to any attempted repair. Referral to an appropriate medical consultant, a pre-habilitation program, and evaluation for bariatric surgery may be of value in these circumstances (29,30).

To repair an IH, surgeons have a variety of techniques at their disposal. Many national and international societies have published guidelines regarding the IHR that share some common principles (31–33). The choice of surgical technique or approach depends on the complexity of the hernia, the health of the patient, the resources available, and the surgeon's own skillset and experience. Hernias can be repaired laparoscopically or via an open surgical incision, however, in large and complex hernias—those often greater than 10cm in width—an open approach is the most prudent. To reduce the risk of hernia recurrence, the repair of any defect greater than 2cm should be reinforced with a permanent surgical mesh whenever possible. However, in the context of an emergency and contaminated surgery, the use of mesh may be obviated by an unacceptably high risk of infection. An important principle in the repair of any hernia is to reapproximate healthy edges of fascia without tension. In large hernias, component

separation—a group of techniques whereby one of the three muscular layers of the abdominal wall is cut and released—should be performed to achieve a tension-free re-approximation of midline fascia.

While these shared principles exist, the repair of IH remains an active area of research and innovation, often without a clear consensus among experts on many of the details: the optimal technique of component separation remains controversial; advanced minimally invasive techniques continue to be developed and studied; biologic and biosynthetic materials remain to be evaluated for long term outcomes; and novel wound management strategies have yet to be evaluated in prospective RCTs (32,34,35). IH repair is an increasingly complex area of surgical expertise, marked by ongoing innovations and research that aim to improve outcomes for patients.

1.2.3 POST-OPERATIVE COMPLICATIONS

IHR is associated with high rates of hernia recurrence and wound complications. Advances in surgical techniques and technology—including synthetic mesh, optimal mesh positioning, the use of component separation, and minimally invasive techniques—have enabled progress in reducing recurrence rates and wound complications. Still, these complications remain common.

Hernia recurrence

An influential RCT in the New England Journal of Medicine in 2000 demonstrated the superiority of mesh in VHR (36). Among the 154 patients randomized, the incidence of hernia recurrence was 43% after suture repairs, and only 24% after mesh repairs. While this represented a dramatic improvement, one quarter of patients in the treatment group experienced hernia recurrence at 3 years. On longer-term follow-up recurrence rates appear to be substantially higher still. In 2015, a large prospective cohort study of more than 1,300 VHRs reported recurrence rates of 60%-70% at 12 years (17). Further, the risk of recurrence increased with each subsequent repair of a recurrent hernia, leading the authors to describe a “vicious cycle” of hernia repair, wound complication, recurrence, and reoperation. Similar

patterns have also been shown in a state-level population-based database in the United States (37). In 2016, a nation-wide Danish registry study of more than 3,000 IHRs reported more optimistic results, with a recurrence rates among mesh repairs of only 12% at 5 years, and a 5% incidence of mesh-related complications (38). Annual cost saving of US $32 million have been estimated for every 1% reduction in VHR performed in the United States (10). Reducing the incidence of new and recurrent IHs is also a worthy cause for patients, who could be spared from a cycle of adverse events and interventions. RCTs of prophylactic mesh reinforcement in high-risk patients after clean abdominal surgery have demonstrated encouraging results (14,23). However, the long-term sequelae of mesh reinforcement have yet be evaluated and this approach remains controversial.

Surgical Site Occurrences

Compared to a standard midline laparotomy, open IHR involves more extensive disruption to the tissues of the abdominal wall, which predisposes patients to wound complications. These include seroma, hematoma, wound dehiscence, enterocutaneous fistula, and wound infection. Together these complications have been termed ***surgical site occurrences*** (SSO) (39). SSOs are not unique to hernia repairs, but their incidence is greater after IHR than after other abdominal procedures. As an indicator of severity, SSOs can be further distinguished by the need for procedural intervention. Recently the term ***SSO requiring procedural intervention*** (SSOPI) has been introduced for complications that require reoperation, percutaneous drainage, or other therapeutic procedures (40).

A ***seroma*** is a contained accumulation of sterile lymphatic and extracellular fluid within the tissue-layers disrupted during surgery. In complex hernia repairs, surgeons often place a closed-suction drain within dissected spaces to draw-out fluid that would otherwise accumulate after surgery. These drains are followed closely and removed in the first week or two after surgery to avoid infection. Seromas that do form, often resorb slowly over several weeks. However, seromas that are large or uncomfortable may need to be aspirated. A seroma can also become infected, leading to a deep abscess and a chronic

infection of surgical mesh, which may require surgical revision. Similarly, a ***hematoma*** is an accumulation of coagulated blood, with a clinical course and risk profile similar to a seroma.

Wound dehiscence is the separation of the healing wound, often at the level of the skin and subcutaneous tissue. Wound dehiscence causes a significant delay in wound healing and skin closure, often requiring a resource-intensive regimen of daily wound packing over the course of several weeks, or the application of a Vacuum Assisted Closure (VAC) device. A wound dehiscence represents a break in the skin's protective barrier and also predisposes patients to infection.

Enterocutaneous fistula is a rare but devastating complication in which a tract develops between the small intestine and the skin, sometimes due to a small bowel injury, anastomotic leak, or the erosion of mesh into an adjacent segment of bowel. The tracking of enteric contents through the abdominal wall and drainage at the skin is highly morbid, prone to chronic infection, and often requires prolonged therapy and surgical revision.

Surgical Site Infection **(SSI)** is a term used to encompass infections occurring after surgery in any tissues or body cavity involved in the procedure (41). Incisional SSI is a post-operative infection involving a surgical wound and can be both a precursor or consequence of a non-infectious SSO. The overall incidence of SSI is reported at 2-5% after inpatient surgery, although incidence varies significantly based on the type of surgery, patient comorbidities, wound contamination, and other surgical factors (42). SSIs are responsible for significantly longer lengths of stay, increased health care costs, and unplanned hospital readmissions, at an estimated annual cost between US $3.5 billion and $10 billion according to the American College of Surgeons (43). SSIs are associated with 3% mortality, most of these deaths being directly attributable to the SSI (44). Since the 1970's the US Centers for Disease Control (CDC) surveillance programs have monitored rates of SSI in participating acute care hospitals, and SSI has since

become a routinely measured quality indicator for surgical safety and hospital performance globally (43,45,46).

The most widely used criteria to define SSI are published by the CDC and categorize SSIs as those involving the superficial or deep tissues of an incision (*Superficial* and *Deep Incisional SSI*) or those involving the organ or body cavity accessed during surgery (*Organ/Space SSI*). Strict clinical criteria are used to define each category for consistency in clinical research, quality surveillance, and for pay-for-performance metrics in certain settings.

Incisional SSIs are classically characterized by fever, pain, and redness at the site of a surgical incision, often accompanied by the drainage of pus. Superficial incisional SSIs tend to occur within a predictable window between 2 and 7 days after surgery—although certain aggressive infections do occur earlier—and may occur significantly later after certain procedures, including open VHR. Treatment of a superficial SSI involves opening the wound, draining the pus, cleaning and debriding dead or unviable tissue, and administering antimicrobials as needed. The wound is left open and packed with sterile gauze that is changed routinely as the wound heals slowly over the course of several weeks.

In the context of VHR, SSI is associated with as much as a 4-fold increase in the risk of hernia recurrence. Many superficial SSIs can be treated successfully as described above. However, a deep SSI involving synthetic mesh represents the contamination of a foreign body that is difficult to treat with antimicrobials. While some mesh infections can be salvaged with long courses of antibiotics and appropriate wound care, surgical excision is often required. In the context of contamination and active infection, mesh reinforcement cannot safely be performed at the same time as excision. Hernia recurrence is anticipated following the excision of infected mesh, and a subsequent hernia repair is often planned for the future.

1.2.4 RISK SCORES AND CLASSIFICATION

The most widely used classification system for SSI is the CDC's wound classification system. This system can be applied to any type of surgery. It is not specific to VHR, but is an element of all the risk scores created for VHR. Class I wounds are considered clean, often involving uncontaminated and sterile soft tissues. Class II wounds involve "clean-contaminated" procedures, including elective gastrointestinal resections. Class III wounds are "contaminated" and involve active inflammation at the site of incision or gross spillage of gastrointestinal contents. Class IV wounds are "dirty" and involve active infection or extensive contamination.

Many risk score and surgical guidelines have been produced for VHR. In 2010, acknowledging a high incidence of wound complications and a gap in evidence to guide surgical decision-making, a group of experts from across the United States gathered to develop recommendations for VHR based on a review of the literature (39). This group was named the Ventral Hernia Working Group (VHWG). A focus of their work was to create a stratification system for SSO that could be used to guide decision-making around the use of mesh and the selection of mesh materials to avoid poor outcomes. Based on risk factors identified in cohort studies, the group developed the 4-level VHWG Grading Scale to accompany a treatment algorithm for VHR.

A modified 3-level version of this grading system, dubbed the Modified Hernia Grading Scale (MHGS), was proposed in 2012 by Kanters et al following a validation study in 299 VHRs (47). The MHGS has received criticism due to the breadth of its highest-risk category, as it fails to delineate between degrees of contamination (48). Recent evidence suggests that the use of certain synthetic and biosynthetic mesh may be safely used in the context of contaminated surgical fields (49,50).

In 2013, Berger et al developed the Ventral Hernia Risk Score for SSI and SSO (VHRS for SSI, VHRS for SSO) based on risk factors identified from 888 VHRs performed at a single centre (51). These scores are

calculated based on a point system weighted by the estimated odds ratios for the following risk factors: mesh implantation, concomitant repairs, the creation of skin flaps, American Anesthesia Class 3 or greater, body mass index greater than 40, and CDC wound class 4. The VHRS was later externally validated in a cohort of 436 patients, with modestly better performance than the VHWG grade and the CDC's wound classification.

In 2015, using ACS-NSQIP databases, Fischer et al identified more than 49,000 open VHRs all performed from 2005-2011, and developed the Hernia Wound Risk Assessment Tool (HW-RAT). HW-RAT assigns weighted risk scores to 21 risk factors identified through an iterative backwards stepwise bootstrap regression. Total scores were then stratified into five risk levels, in which SSO risk ranged from 3.3% (HW-RAT=1) to 26.5% (HW-RAT=5). HW-RAT had better discrimination and overall performance than prior risk scores on internal validation in ACS-NSQIP data. Interestingly, the patient-related factors identified carried only a low or intermediate risk in the HW-RAT model. The most important risk factors identified were all surgical factors, including operative time, degree of wound contamination, and component separation. These surgical risk factors may be a surrogate of hernia complexity, but HW-RAT also highlights the importance of further optimizing surgical techniques and wound management strategies.

1.3. INCISIONAL NEGATIVE PRESSURE WOUND THERAPY

This thesis evaluates a novel wound management strategy called *incisional negative pressure wound therapy* (iNPWT) in the prevention of SSI after IHR. The following section will discuss its origins and the evidence supporting its use.

1.3.1 HISTORY OF NEGATIVE PRESSURE WOUND THERAPY

Contemporary negative pressure wound therapy (NPWT) was developed in the 1990s in North Carolina to manage chronic open wounds that were difficult to treat. NPWT systems consist of 4 components:

(1) a sealed foam dressing (open-cell foam is cut to size and gently placed to fill the wound cavity, and a thin adhesive sheet of plastic is placed over the wound to form an impermeable barrier);
(2) a computer-controlled pump, used to generate a vacuum, i.e. 'negative pressure';
(3) tubing, which connects the sealed dressing to the vacuum pump and serves as a conduit to draw exudate and liquid material from the wound; and
(4) a reservoir, usually located within the pump unit, that collects this waste material.

When the vacuum is applied to the dressing, the foam shrinks and pulls the wound edges centrally. NPWT is thought to function by removing debris and exudate from the wound bed. As well, the negative pressure relieves the tension across the wound edges to promote healing. Dressings are changed every two to three days, at which point the wound is assessed and the foam is replaced with a progressively smaller foam to accommodate for the decreasing width and depth of the healing wound.

In his book *Pressure Injuries, Diabetes, and Negative Pressure Wound Therapy*, Melvin Shiffman provides a historical account NPWT. A similar published history of NPWT is authored by Christine Miller in the Journal of the American College of Clinical Wound Specialists. NPWT had its origins in fire cupping, which was practiced as early as 1000 BC in ancient China, then Babylon and Greece centuries later (52). Fire cupping is performed by lighting a small amount of alcohol at the bottom of a glass or ceramic cup and quickly placing the cup's mouth over a wound site. As the alcohol and air are quickly consumed by flame, a vacuum-seal is created and will draw exudates from the wound. Later, the Roman Era saw a practice of wound-sucking, in which healers would use their own mouths to suck out pus and blood clots from deep battle wounds (53). Wound-sucking was eventually replaced in the 19th century with the invention of the suction syringe, which was used to remove these materials. Wound-sucking and fire cupping are described as the rudimentary origins of negative pressure wound therapy by Shiffman and Miller.

In 1997, Argenta and Morykwas, a plastic surgeon and a biomedical engineer from Wake Forest University in North Carolina, described a technique to close complex wounds using controlled subatmospheric pressure (125mmHg below atmospheric pressure) applied through an open-cell foam dressing placed within a wound cavity (54). They named the technique “vacuum-assisted closure” (VAC), an acronym that has since become synonymous with NPWT. Initially the authors had devised the VAC technique for patients with chronic and “unsalvageable” wounds, who were too debilitated to benefit from surgery, often after many failed attempts of tissue coverage using myocutaneous tissue flaps or skin grafts. In these patients, VAC would serve as an adjunct to surgery, whereby the wound environment could be optimized to increase the likelihood that a skin graft or tissue flap would successfully ‘take’ to a healthier wound bed. They used the VAC technique on a series of three-hundred difficult-to-treat wounds, beginning with large pressure ulcers and vascular ulcers. After encouraging results in 171 of 175 of these chronic wounds, the authors moved onto more acute wounds, including exposed orthopaedic hardware, infected and dehisced surgical wounds, large soft-tissue avulsions, grossly contaminated or dirty wounds, and abdominal eviscerations. In total, 296 of the 300 wounds were successfully closed with either the VAC technique alone or VAC followed by a split-thickness skin graft or a rotational tissue flap.

The authors attributed the success of VAC to three likely mechanisms: (1) the removal of excess fluid and increased tissue perfusion, (2) decreased bacterial colonization, and (3) upregulation of tissue factors promoting wound healing in response to mechanical forces. These mechanisms were supported by animal studies which they presented in an accompanying publication (55).

Today, there are several commercially available NPWT systems designed specifically for both open wounds and for closed incisions. Overall, these devices have been a commercial success, generating billions in annual revenue among industry leaders (56).

1.3.2 EVIDENCE FOR NPWT IN OPEN WOUNDS

Despite its widespread adoption and commercial success, there is surprisingly little evidence supporting the use of NPWT, including its primary indication in healing open wounds. In a 2015 Cochrane Review, two decades after the commercialization of NPWT in North America, Dumville et al found only two small RCTs meeting their inclusion criteria that evaluated the use of NPWT for open surgical wounds (57) These studies had a combined total of only 69 patients and compared NPWT to silicone dressings in *time to healing* in infected groin wounds after vascular surgery and in wounds following pilonidal sinus excision. The data were considered to be low quality and the results simply too imprecise to draw any meaningful conclusions.

In Quebec, acknowledging the need for clinical guidance in the absence of clear evidence, the *Institut national d'excellence en santé et service sociaux* (INESSS) produced recommendations for the use of NPWT in complex wounds. They based their guidelines on an in-house systematic review of the literature(58). Similarly, INESSS found that data surrounding the efficacy of NPWT were not reliable enough to demonstrate its superiority compared to standard dressings for acute post-surgical wounds, although some low-quality evidence did support its use in chronic diabetic foot ulcers. While no patient-specific factors clearly predicted the effectiveness of NPWT, INESSS did suggest that patients were most likely to benefit from NPWT with the involvement of a "wound-care team", i.e. a group of professionals whose clinical practice is focused on the management of complex wounds. While NPWT did appear to be safe when used appropriately in this context, the routine collection of safety data was a valuable next step identified by the INESSS report.

Some of the safety concerns in the INESS report stemmed from FDA *Safety Communications* regarding multiple reports of deaths and injuries associated with NPWT (59). In November 2009, the FDA published a preliminary public health notification indicating 6 deaths and 77 injuries associated with NPWT. Following this report's dissemination to the medical community, an additional 6 deaths and 174

injuries were reported to the FDA, all occurring within 2 years prior to the report. Most of these events, which had occurred in long-term care facilities or in patients' homes, were related to uncontrolled bleeding or infection. In September 2015, Health Canada issued a similar *Health Product InfoWatch* following a sudden NPWT-related death reported by the coroner. The death was attributed to uncontrolled bleeding after the application of NPWT over an exposed vascular graft in an anticoagulated patient. An accepted contraindication to NPWT is an exposed vascular graft directly in contact with the foam dressings of an NPWT device, and manufacturers warn that anticoagulated patients at risk of bleeding should be monitored in an appropriate care-setting, as determined by a treating physician (60).

Despite a lack of robust evidence and these safety concerns, NPWT remains a popular and widely accepted therapy, largely due to a conviction among health professionals of its effectiveness, and the convenience it provides to both patients and to health care workers. NPWT dressings can be left in place for 2-5 days before requiring a dressing change depending on the clinical indication. This may reduce the burden on nursing and wound care professionals by minimizing dressing changes that are often required for moist wounds that quickly saturate wound packing materials. These advantages are particularly salient after hospital discharge, as the frequency of home visits by community nurses and or clinic visits by patients can also be minimized.

1.3.3 EVIDENCE FOR NPWT IN CLOSED-INCISIONS (iNPWT)

In 2010, the PREVENA™ Wound Management System (KCI, Texas, USA) was licensed in Canada, becoming the first NPWT device intended for use on closed surgical incisions (61). PREVENA is similar in design to traditional NPWT devices, with some improvements and adaptations. It has a small and portable battery-powered vacuum pump, a reservoir, tubing, and a silver-impregnated open-cell foam dressing that are all supplied together as a disposable single-use unit. PREVENA is applied immediately after surgery to a wound that has been closed with sutures or staples, then left in place with the vacuum pump activated for 2-7 days (60). Similar to any NPWT system, the goal is to create an isolated wound

environment to prevent bacterial colonization, to remove exudate via the vacuum system, and to relieve tension across the wound to promote a healthy environment for wound healing. A similar proprietary dressing intended for closed incisions is the PICO™ (Smith&Nephew, ON, Canada). Collectively, these novel NPWT devices have been termed “prophylactic”, “incisional”, “closed-incision” or “single-use” NPWT. In this thesis, we refer to these devices as *incisional negative pressure wound therapy* (iNPWT).

The use of iNPWT was first described in orthopaedic and cardiac surgery in patients at high risk of wound infection (62,63). This practice began with the placement of traditional VAC dressings over closed wounds and was then followed by proprietary single-use dressings.

A 2014 Cochrane Review investigated iNPWT for the healing of skin grafts and surgical wounds (64). Nine trials were included and the pooled results found no differences in surgical site infection (three trials 232 patients, RR 1.02 95%CI 0.41-2.54) or in the formation of seroma or hematoma (0.95 95%CI 0.31 - 2.20). The review received some criticism for excluding one large RCT with favourable results from the orthopaedic literature due to a flaw in its study design. Overall the authors had concerns regarding study quality and highlighted the need for larger and higher quality studies.

In 2016, Hyldig et al published a subsequent meta-analysis in the British Journal of Surgery. The review identified 10 RCTs evaluating iNPWT, with a total of 1,089 patients and 1,311 incisions (65). These studies, which included 6 unpublished clinical trials, involved a diversity of surgical procedures and three different proprietary dressings (PREVENA, PICO, and VAC). Procedures included hip and knee replacement, repair of pelvic and hip fractures, median sternotomy, bilateral breast reduction surgery, lower extremity amputations, and abdominal surgery. The primary outcomes were surgical site infection, wound dehiscence, and seroma formation. Follow-up varied widely from 10 days to 1 year. The pooled analysis found a significant reduction in the incidence of wound infection among patients receiving iNPWT (RR 0.54, 95%CI 0.33 - 0.89, NNT 25). While promising, the authors refrained from

making clinical recommendations based on these results largely due to significant concerns regarding the clinical and methodological heterogeneity of the trials. Duration of follow-up was highly variable, and in some cases inadequate. Also, the reporting of randomization and allocation concealment were often missing or inappropriate. Finally, nine of the ten studies had industry sponsorship or involvement. Overall, the authors concluded that sufficiently powered and methodologically rigorous RCTs were still needed, particularly including high-risk patients in whom iNPWT may be most impactful. Furthermore, the applicability of the review to abdominal surgery was questionable, given that only three of the 1,089 procedures comprising the meta-analysis involved a laparotomy.

The most recent comprehensive review of iNPWT is an updated Cochrane Review from 2019 that reported an additional twenty five studies, totalling 2,533 patients (62). The combined results favoured an effect of iNPWT in reducing SSI (RR 0.67, 95%CI 0.53 - 0.87), however, again, the quality of the evidence was considered “low to very low” after downgrading due to serious risks of bias. The authors had concerns regarding allocation concealment, the blinding of outcome assessors, and the involvement of industry in more than half of the trials. Still, the overall point estimate and confidence intervals were promising. A subgroup analysis of abdominal surgeries (5 trials, 520 patients total) found no significant effect of iNPWT in preventing SSI (RR 0.69, 95% CI 0.35 - 1.37). The largest of these trials randomized 375 patients to iNPWT or standard sterile dressing after open gastrointestinal, pancreatic, or cytoreductive surgery for cancer (66). This study found no difference in the incidence of SSI between the groups. In a prefatory retrospective study of 191 similar cases published four years prior to this RCT, the authors had reported a significant reduction in superficial SSI (OR 0.29, 95% CI 0.11 - 0.81) among patients receiving iNPWT (67). Their 2017 paper called attention to the pitfalls of retrospective case series analyses, commonplace in the surgical literature, whose promising results often cannot be replicated when the RCT is performed.

Overall, iNPWT is supported largely by retrospective studies and small RCTs limited by high risks of bias. The few high-quality RCTs have mostly failed to support the use of NPWT in preventing SSI in closed incisions, with the exception of groin incisions. However, because of its favourable results in high-risk wounds and its good safety profile, iNPWT is an attractive therapy in high-risk patients, especially following procedures where the consequences of a wound infection could be devastating (68). In contrast to traditional NPWT in open wounds, adverse events with the use of iNPWT appear to be limited to skin blistering, mostly following orthopaedic procedures when dressings have been placed on extensor surfaces (62). Still, a recent RCT of iNPWT in 1600 obese women undergoing caesarean section reported the incidence of skin blistering at 7%, which prompted a premature stop to the trial as no effect of iNPWT on SSI incidence was identified at interim analysis (69).

1.3.4 EVIDENCE FOR iNPWT IN VENTRAL HERNIA REPAIR

VHR differs importantly from standard midline laparotomies or Pfannestiel incisions used in other common abdominal procedures. Complex VHR involves an extensive disruption to the tissues of the abdominal wall, which predisposes these procedures to higher rates of wound complications. iNPWT's proposed mechanisms of action could plausibly mitigate the deleterious effects of such extensive dissections on wound healing. Already, the Society of American Gastrointestinal and Endoscopic Surgeons' (SAGES) Manual of Hernia Repair and a World Health Organization (WHO) international consensus group recommend the use of iNPWT in particularly high-risk patients and procedures (45,70). In the absence of high-quality evidence, these recommendations come after weighing the low risk-profile of iNPWT against the potential to avoid the devastating consequences of SSO in these targeted populations. If iNPWT has even a modest effect on long-term outcome of mesh infection or hernia recurrence, it may have important morbidity and cost implications.

Until 2020, no published RCTs have evaluated the use of iNPWT in IHR. Most of the evidence regarding iNPWT in these procedures comes from low-quality and retrospective studies or case-series. A recent

systematic review on this topic identified 11 studies for meta-analysis (34). However, only 6 of these studies involved hernia repair (71–76), and two additional retrospective studies have since been published since this review (77,78).

Four of these studies support an effect of iNPWT in reducing SSI, whereas four do not. The retrospective design of these studies brings considerable inherent risks of bias. As well, differences in patient-related risk factors, varying patient selection criteria, operative techniques, and differing outcomes are all sources of heterogeneity across these studies. Nonetheless, they all report SSI incidence after high-risk VHR among patients receiving iNPWT and compare these cases to historical controls who received standard sterile dressing. A cautious assessment of their pooled results is warranted. In Figure 1, an updated meta-analysis of these retrospective studies is presented.

In four of these studies, iNPWT was used at the discretion of the surgeon. While this represents a real-world implementation of iNPWT in many clinical settings, this approach may introduce selection bias—which will be magnified in a direct before-and-after comparison—and confounding on a variety of patient-related risk factors, hernia characteristics, surgical techniques, and surgeon practice patterns. Together, these could all influence the use of iNPWT and differentially affect outcomes between the comparison groups. It is difficult to disentangle the direction of this bias given the variation in how patients at high risk of wound complications are managed.

The other studies reported consecutive series of cases performed by a single surgeon, which helps to control for many confounders, provided that the surgeon's patient population, operative techniques, and outcomes have not otherwise changed over time. However, there may still be significant heterogeneity given the rapid changes in surgical VHR techniques over time.

Another source of heterogeneity in these studies exists in the measurement and reporting of wound outcomes across these studies. Comparative effectiveness studies regarding SSI and SSO often report

30-day outcomes as a widely accepted standard based on quality surveillance guidelines and classic surgical teaching. However, late outcomes beyond 30 days are common after hernia repair and in procedures involving prosthetic materials. Due to the routine use of synthetic mesh in hernia repairs, the CDC recommends surveillance for deep surgical site infections up to 90 days. Limiting endpoints to 30 days likely underestimates the true incidence of SSI and fails to measure the impact on late outcomes, which may include mesh infection and hernia recurrences.

Variability also exists in the reporting of other SSOs. Some studies define seroma as a sterile fluid collection identified on imaging studies or noted on physical exam. However, such definitions may overrepresent minor complications that are likely to resolve spontaneously without any intervention. Many have advocated for reporting of SSOPI. For instance, large seromas may cause discomfort and require drainage. Similarly, small separations of a wound may close spontaneously, whereas a large wound separation may significantly delay wound healing and require prolonged wound care. The identification of clinically meaningful wound outcomes is an active area of research without a clear consensus among hernia researchers (79).

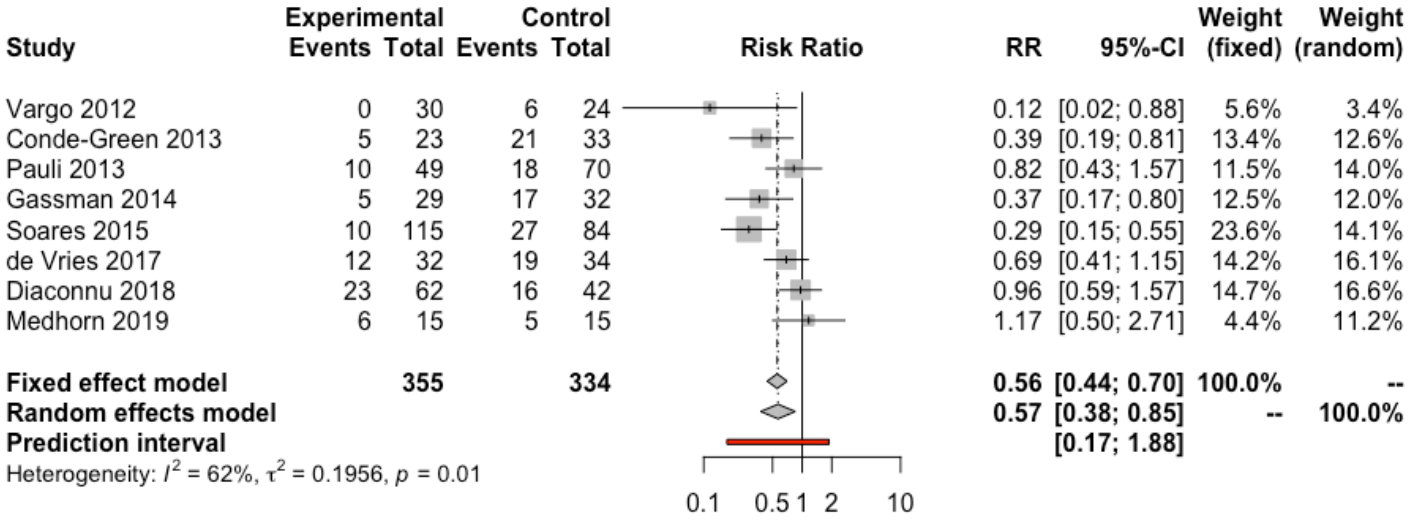

Figure 1 - Meta-analysis of retrospective and non-randomized prospective cohort studies comparing incisional negative pressure wound therapy (iNPWT).

CHAPTER 2: THESIS OBJECTIVES

1. The primary objective of this thesis is to evaluate the effectiveness of iNPWT in the prevention of surgical site infection after complex incisional hernia repair in high-risk patients.
2. The secondary objective of this thesis is to assess the validity of wound outcomes (surgical site infection and surgical site occurrences) after incisional hernia repair at various time-points in order to determine an adequate length of follow-up.

CHAPTER 3: THE EFFECT OF INCISIONAL NEGATIVE PRESSURE WOUND THERAPY ON THE INCIDENCE OF SURGICAL SITE INFECTION AFTER COMPLEX INCISIONAL HERNIA REPAIR, A MATCHED COHORT ANALYSIS

3.1 PREAMBLE TO MANUSCRIPT 1

At the onset of this study, iNPWT had been proposed as a means to reduce the incidence of SSI and SSO in closed surgical incisions after IHR. The evidence supporting iNPWT in other surgical specialties was promising. However, recent systematic reviews maintained that higher quality RCTs were still needed to support its use, especially given its higher costs compared to the standard of care. Consensus guidelines regarding the use of iNPWT recommended limiting its use to only high-risk patients. Still, the effectiveness of iNPWT for laparotomy wounds had yet to be clearly demonstrated in RCTs, and studies regarding iNPWT in IHR were limited to retrospective and non-randomized prospective series.

In 2018, iNPWT became widely available at our institution and was used at the surgeons' discretion in patients at high-risk for wound infection. We sought to evaluate the effectiveness of iNPWT compared to standard sterile dressings among patients undergoing complex IHR at our institution. To address confounding introduced by iNPWT's use at the surgeon's discretion, we planned a matched cohort analysis, with the intention of matching patients who received iNPWT to historical controls who were likely to have received the intervention had it been available prior to 2018.

In manuscript 1, we report the results of a matched cohort analysis comparing the incidence of SSI at 30 days among patients receiving iNPWT versus standard sterile dressings after complex incisional hernia repair. In the supplementary material accompanying manuscript 1, we include the results of sensitivity analyses regarding the effect of loss to follow-up on our results and impact of bias introduced by the use of iNPWT at the surgeon's discretion (see appendices 1 and 2). In appendix 3, we presented the results

of an updated meta-analysis of the retrospective and non-randomized prospective studies evaluating iNPWT in complex IHR.

MANUSCRIPT 1: IMPACT OF INCISIONAL NEGATIVE PRESSURE WOUND THERAPY ON SURGICAL SITE INFECTION AFTER COMPLEX INCISIONAL HERNIA REPAIR: A RETROSPECTIVE MATCHED COHORT STUDY

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3.2 ABSTRACT

INTRODUCTION: Incisional negative pressure wound therapy (iNPWT) may reduce surgical site infections (SSI), which can have devastating consequences after incisional hernia repair. Few comparative studies investigate the effectiveness of this wound management strategy in high-risk patients undergoing complex hernia repair. The objective of this study is to determine the effect of iNPWT on the incidence of SSI after complex incisional hernia repair.

METHODS: All adult patients undergoing open incisional hernia repair at a single center from 2016-2019 were reviewed. A commercial iNPWT dressing was used at the discretion of the surgeon. Patients were grouped by type of dressing; iNPWT and standard sterile dressings (SSD). Coarsened exact matching was used to create balanced cohorts for comparison using age, sex, American Anesthesiologist class, wound classification, and surgical urgency. The primary outcome was the composite incidence of superficial and deep SSI within 30 days. Secondary outcomes included non-infectious surgical site occurrences (SSO), overall complications, length of stay (LOS), emergency department visits and readmission at 30 days.

RESULTS: 134 patients underwent complex hernia repair, with 85 patients included after matching (34 iNPWT and 51 SSD). Composite incidence of superficial and deep SSI was 19.3% (11.8% vs. 27.5%, p=0.1.07), with significantly lower rates of deep SSI in patients receiving iNPWT (2.9% vs. 17.6%, p=0.045). After accounting for residual differences between groups, iNPWT was associated with decreased incidence of composite SSI (RR 0.36, 95%CI [0.16, 0.87]). Median LOS was longer in patients with iNPWT (7 vs. 5 days, p=0.001). There were no differences in SSO, overall complications, readmission, or emergency department visits.

CONCLUSION: In patients undergoing incisional hernia repair, the use of iNPWT was associated with a lower incidence of SSI at 30 days. Future studies should focus on cost-effectiveness of iNPWT, its impact on long-term hernia recurrences, and the identification of patient selection criteria in this population.

3.3 INTRODUCTION

Patients undergoing complex incisional hernia repair (IHR) are at high risk for a range of wound complications[1]. In these procedures, the incidence of wound complications including surgical site infection (SSIs) ranges from 15%-46% [2]. Together these complications are called surgical site occurrences (SSOs) and include SSI, hematoma, seroma, wound dehiscence, and enterocutaneous fistula. The consequences of these wound complications can be devastating, especially in the context of complex IHR with prosthetic mesh. SSI is associated with hernia recurrence, and mesh infection will often require reintervention, long-term antibiotic therapy, protracted wound-care, and possible mesh excision [3, 4]. These outcomes are costly [5, 6] and associated with poor quality of life[7].

Negative pressure wound therapy (NPWT) was developed in the 1990s to assist in wound healing. It consists of a sealed foam dressing through which suction is applied via tubing to draw exudate and liquid material from the wound. NPWT has been widely used to treat open and chronic wounds [8]. Since the early 2010's, the use of incisional negative pressure wound therapy (iNPWT) on closed surgical incisions has been proposed as a means to reduce surgical site occurrences, including SSI. At least two proprietary iNPWT systems are commercially available and in clinical use today. However, the effectiveness of iNPWT has yet to be established [9-11]. In complex IHR, evidence regarding the use of iNPWT is equivocal and of low quality overall. Despite the lack of evidence, iNPWT remains of particular interest as a wound management strategy given the high incidence of SSOs and their potentially devastating consequences. iNPWT may be most effective in patients at higher risk of wound complication, and may be cost-effective when the SSI incidence is as high as 16%[12]. Further evidence to guide selection criteria for this intervention is needed, especially in resource conscious settings. The objective of this study is to estimate the impact of iNPWT on the incidence of superficial and deep SSI in a matched-cohort of adult patients undergoing complex IHR.

3.4 METHODS

STUDY DESIGN

We performed a retrospective matched cohort analysis of patients undergoing complex IHR repair at a single university hospital from January 2016 to December 2019. The study was approved by the institution's Research Ethics Committee and access to patient charts was obtained from the institution's Director of Professional Services in lieu of individual informed consent of participants. No industry funding or outside sponsorship was provided for this study. We included adult patients undergoing open IHR involving component separation or mesh greater than 16x9cm, and who met criteria for "complex abdominal hernia" as per a consensus based definition by Slater et al[13]. Both emergency and elective cases were included. Stoma and dirty cases were included as iNPWT was also employed at the surgeon's discretion in these scenarios. Day surgeries, cases without primary wound closure at the time of surgery, and patients with post-operative follow-up less than 30 days were excluded.

SURGICAL TECHNIQUE

Complex IHR were performed by a total of 7 surgeons with practice interest in hernia surgery. All patients received pre-operative antibiotics. The choice of repair was decided according to hernia characteristics and surgeon expertise, with a preference for retro-rectus repair when possible. Where tension-free approximation of the facia was not achieved, component separation was routinely performed to ensure facial closure with mesh reinforcement. Bridging repairs were avoided, with transversus abdominis release (TAR) being the preferred method of component separation if required. In the beginning of the study period, anterior component separation with external oblique release (EOR) was also performed. Mesh reinforcement was used in almost all cases, with a preference for extraperitoneal placement. In an extraperitoneal position, self-fixating Parietex™ ProGrip™ mesh (Medtronic, Mansfield, MA) was most common, while Parietex™ composite mesh was most commonly used in the intraperitoneal position. Where permanent synthetic mesh could not be used, slowly

resorbing GORE®BIO-A® Tissue Reinforcement (Gore Medica, Flagstaff, AZ) or absorbable VICRYL® mesh (Ethicon, Cincinnati, OH) was used. Skin flaps were performed as needed, and concomitant musculocutaneous flaps or panniculectomy were performed by a plastic surgeon in selected cases. Surgical drains were routinely placed in sub-fascial and subcutaneous planes and removed on follow-up when drainage was minimal. Skin was most commonly closed with skin clips and abdominal dressings were placed immediately after closure.

INTERVENTION

A proprietary negative pressure dressing (PREVENA™ incision management system, KCI San Antonio, TX) was available since October 2018 and was used at the discretion of the surgeon. Non-proprietary negative pressure dressings were also constructed with available NPWT supplies. Patients with these 'home-made' dressings were included in the iNPWT group and recorded as 'home-made'. All iNPWT dressings were placed directly to closed skin (without any penetrating inter-digitations), and were removed 5-7 days post-operatively. Standard sterile dressings (SSD) consisted of non-adherent sterile gauze secured with an adhesive border or adhesive tape. SSD were placed in the OR and removed on post-operative day 2. Post-operative antibiotics were not routinely given, except in the presence of active infection.

OUTCOMES AND COVARIATES

Conventional demographics, comorbidities as per the Charlson Comorbidity Index, and operative characteristics were collected. Risk factors for surgical site occurrences including obesity, smoking within 1 year, diabetes, chronic obstructive pulmonary disease (COPD), immunosuppression, presence of stoma, prior hernia repairs, and history of wound infection were collected. Operative details including technique of component separation, and mesh use, material, and position were recorded. The creation of a new stoma, the use of closed suction drains, the involvement of a plastic surgeon were also recorded. Cases were identified as including a 'skin flap' in all anterior component separations and in

procedures where the development of a skin flap via subcutaneous undermining was mentioned specifically by the surgeon in the operative note. A 'tissue flap' denoted the use of myocutaneous flap for tissue coverage performed by a plastic surgeon.

Risk of surgical site infection was assessed using the 3-level Modified Hernia Grading Scale (MHGS) scale [2] and Ventral Hernia Risk Scores (VHRS) for SSI and SSO [14]. The MHGS was adapted from the 4-level Ventral Hernia Working Group (VHWG) grading scale [1] and classifies open hernia repairs into three grades depending on the presence of patient-level risk factors and surgical contamination: grade 1 (low risk); grade 2 (co-morbid patients); and grade 3 (contaminated cases). The VHRS for SSI is a prospectively validated risk score that was found to more accurately predict SSO and SSI compared to the VHWG grade [2, 15]. The VHRS ranges from 0 to 16 points for SSI and 0 to 15 points for SSO. Points are calculated based on the presence of 6 risk factors (use of a mesh implant, concomitant hernia repair, creation of skin flaps, American Anesthesiologist (ASA) class 3 or greater, Body Mass Index (BMI) 40 or greater, and wound class 4) and used to categorize into risk groups.

The primary outcome was a composite measure of superficial and deep SSI within 30 days, following the Center for Disease Control definitions[16, 17]. The composite measure included wound infection involving only skin and subcutaneous tissue (superficial) or the muscle and fascia layers of the abdominal wall (deep). Intraabdominal infection were classified as "organ/space SSI" as per CDC definitions, and were not included in the composite outcome. Secondary outcomes included non-infectious SSOs, overall complications, length of stay (LOS), emergency department visits, and readmission within 30 days. Late SSIs and hernia recurrence beyond 30 days were also collected, with follow-up until 180 days post-operatively.

COARSENED EXACT MATCHING AND STATISTICAL ANALYSIS

Statistical analysis was performed in R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) and coarsened exact matching (CEM) was performed using the CEM package [18]. Similar to other matching methods, CEM is used to control for confounding introduced by imbalances in baseline patient-level characteristics between treatment and control groups [19, 20]. Compared to propensity score matching, CEM may produce less variance and bias in estimates of causal effect [21]. Matching also served to account for selection and confounding bias introduced by the use of iNPWT at the surgeon's discretion. Patients were grouped by type of dressing used: iNPWT vs. SSD. Selecting among patients operated prior to the availability of iNPWT, we used CEM to create balanced cohorts for comparison using age, sex, ASA class, wound contamination, and surgical urgency.

Chi-squared or Fisher's Exact tests and Student's T-tests or Kruskal Wallis tests were performed for comparison of categorical and continuous variables respectively. For 30-day outcomes, multiple logistic regression was performed to account for additional differences between groups that may have introduced confounding. Clinically relevant variables were tested in a step-wise approach to select a model using a Bayesian information criterion. The final model included iNPWT treatment, technique of component separation, VHRS for SSI, and smoking exposure. Risk ratios were estimated using marginal standardization from logistic regression. For outcomes beyond 30 days, Kaplan-Meier curves were used to describe SSI occurrence and log-rank tests were used to compare cumulative probabilities of SSI between groups. A cox proportional hazard model was used to evaluate iNPWT as a predictor of SSI after adjusting for technique of component separation, smoking exposure, and body mass index (BMI).

Sensitivity analysis for loss to follow-up was performed. Survival analysis was repeated after including cases with less than 30 days of follow-up. To evaluate the consequence of missed SSIs among cases lost to follow-up, multiple logistic regression was repeated after reclassifying iNPWT cases lost to follow-up

as having developed deep or superficial SSI within 30 days. Regression models were adjusted for VHRS for SSI, procedure duration, and smoking exposure in this analysis.

3.5 RESULTS

Among 245 ventral hernia repairs performed during the study period, 134 met the criteria for complex IHR. An additional 9 cases were excluded due to failure to achieve abdominal wall or skin closure at the time of surgery, and 11 cases were excluded due to inadequate follow-up. A total 114 cases were included prior to matching (Figure 1). Overall, the incidence of composite SSI in the cohort was 19.3% at 30 days. Median follow-up was that 164 days, 19% with follow-up beyond 1-year, and 6% beyond 2-years.

After CEM, a total of 85 patients were retained in the matched cohort, with 34 patients receiving iNPWT and 51 matched controls receiving SSD. The groups were similar with respect to age, sex, BMI, and ASA scores, and comorbidities (Table 1). Certain individual risk factors for wound complications were somewhat more prevalent in the iNPWT group. These included diabetes and smoking in the year of surgery, although these did not reach statistical significance. Prior wound infection was more common in the iNPWT group, as was the frequency of multiple prior hernia repairs. All matched cases were performed on an elective basis (Table 2). Contamination class were similar, the use of closed suction drains, tissue flaps was similar between groups.

Procedure durations were longer in the iNPWT group, with more patients undergoing posterior component separation and extraperitoneal mesh placement. The creation of skin flaps was also more common in the iNPWT group. The distribution of MHGS was similar between groups, although VHRS for SSO differed between groups with a larger proportion of patients receiving iNPWT in higher risk-groups (Table 3).

At 30 days postoperatively, the crude incidence of the composite SSI outcome was 21.1% with no statistically significant difference between the iNPWT and SSD groups in the matched cohort (Table 4). The incidence of deep SSI, however, was significantly lower in the iNPWT group (2.9% vs. 17.6.%, p=0.045). Overall the incidence of non-infectious SSOs were similar between groups, as were interventions for wound complications. Median length of stay was longer among patients receiving iNPWT (7 vs 5 days, p=0.001). There was no difference in all complications, mortality, hospital readmissions, or emergency department visits. Results of multivariate logistic regression are shown in Table 3. After adjusting for the technique of component separation, VHRS for SSI, and smoking exposure, iNPWT predicted a lower incidence of composite SSI (RR 0.37 95%CI [0.15 - 0.87]).

The incidence of SSI beyond 30 days was 11.8% in the matched cohort (Table 4). There were no differences in late SSOs or hernia recurrence at 180 days. On Kaplan-Meier analysis, SSI did not significantly differ between groups in either the matched or unmatched cohorts with follow-up up to 180 days (Figure 2). In multiple Cox proportional hazards regression, after adjusting for possible confounders, iNPWT was not significantly associated with SSI when late cases were included (Table 5). Among 18 patients with SSI at 30 days, 1 patient (4.5%) had a sterile seroma drained prior to developing infection. Among those with SSI beyond 30 days, 2 patients (16%) had a prior sterile intervention for seroma.

Among 11 cases excluded due to less than 30 days of follow-up, 9 received SSD and 2 received iNPWT. After the inclusion of these cases in matching and survival analysis supported the association between iNPWT and decreased incidence of deep SSI at 30 days (Figure 3). Sensitivity analysis for the impact of missed SSIs in cases lost to follow-up suggested a preserved association between iNPWT and decreased SSI incidence, even when assuming the maximal effect of this potential bias (RR 0.45, 95% CI[0.20 – 1.01]).

3.6 DISCUSSION

iNPWT is a novel wound management strategy that has been used in complex IHR and other abdominal operations [10, 22, 23]. However, evidence regarding its effectiveness in IHR remains equivocal and of low quality. This study evaluated the effectiveness iNPWT among patients undergoing complex IHR at a university hospital, where iNPWT was used at the discretion of the operating surgeon. In this retrospective matched-cohort analysis, we found a significantly decreased incidence of deep SSI among patients receiving iNPWT compared to SSD in matched historical controls at 30 days.

NPWT has been widely adopted in the management of open wounds[8]. More recently, iNPWT has been proposed as an effective strategy in the prophylaxis of SSIs and wound complications for closed surgical wounds. The application of negative pressure is thought to stimulate wound healing through several mechanisms. Negative pressure may improve capillary circulation and oxygen delivery at the wound site [24] while removing excess exudate and debris from the wound. The iNPWT's barrier may also promote sterility and a favorable environment for healing. Mechanical offloading of tension at the wound site may also promote apposition of the wound edges, and is of particular relevance in large abdominal incisions associated with complex IHR [25]. A role for iNPWT in preventing intraabdominal infection is not supported by these mechanisms. However, the abdominal wall fascia and the potential spaces created during IHR are continuous with more superficial layers of the wound, and an effect of iNPWT at level of the deep soft tissues of an incision is plausible. The reduction in deep SSI observed in the study is consistent with these proposed mechanisms of action and supports a role for iNPWT in the prevention of SSI after complex IHR.

Our results were consistent with other published retrospective studies in this population. A recent meta-analysis of 11 studies evaluating iNPWT on wound complications in complex IHR reported a 50% reduction in SSI and wound separation in a pooled analysis [22]. The review included a predominance of small retrospective studies (9 retrospective studies) and two RCTs involving oncologic resections. The

results of these RCTs may not applicable to complex incisional hernia repair, as the wound associated with IHR differ importantly from a standard midline laparotomy incisions used in oncologic resection, including undermining and use of mesh. We identified eight studies that have specifically investigated iNPWT in the context of IHR since 2012. Four studies supported an effect of iNPWT in reducing SSI [26-29]. With the exception of one case series of 199 cases, these studies were small retrospective studies that compared iNPWT to historical controls. All but one reported consecutive cases by a single surgeon, which strengthened their internal validity. Only two provided estimates of effect size and measures of confidence. Four studies found no difference in SSI with iNPWT [30-33]. These include two studies with more than 100 cases. All four used iNPWT at the surgeon's discretion, and most included cases performed by different surgeons and using different approaches. This variability may have introduced bias but may also lend to the external validity of their results.

Together, these studies had several limitations, including a heterogeneity in surgical approach, patient characteristics, and iNPWT design and duration. However, these limitations reflect real-world challenges in the implementation and evaluation of surgical interventions. Confounding and selection bias remain limitations in several of these studies. In a resource conscious setting, iNPWT may be targeted to patients who are thought to benefit most—that is, patients with risk factors for SSI. In this context, the use of iNPWT at the discretion of the surgeon precludes a direct before-and-after comparison. Several studies have avoided this source bias by reporting consecutive series performed by a single surgeon [28, 29, 34, 35], however others make no explicit attempt to account for this.

In this study, we attempt to mitigate the effect of selection and confounding bias by employing a matched cohort analysis, selecting controls from a cohort whose surgery was performed prior to the availability of a proprietary iNPWT device at our institution. Residual difference between the iNPWT and SSD groups after matching appeared to favor a lower risk of SSI among the controls, thereby underestimating the effect of iNPWT. In other words, patients in whom iNPWT was selected were at

higher risk of SSI compared to patients who received SSD. Based on clinical judgement and salient differences between groups, we performed regression analysis adjusting for technique of component separation, VHRS for SSI and smoking exposure. Even after accounting for these variables, iNPWT was associated with an estimated 11.4% absolute reduction in SSI compared to SSD and number needed to treat of 9.

Our regression analysis suggests that iNPWT may be effective across all MHGS grades, however, we were limited by sample size and number of events to meaningfully estimate effects across strata of hernia grade. Other studies, including a case comparative study of 199 consecutive cases by Soares et al, found that iNPWT reduced SSI only in higher grade hernias (MHGS Grade 2 and 3) [29]. This group has subsequently published two case series demonstrating dramatic reductions in SSI (5.2%) and SSO (12.9%) using their HVAC system in high-risk patients [34, 35]. Large comparative studies are needed to evaluate the effect of iNPWT across different risk profiles in order to identify patients who benefit the most from this intervention.

Duration of follow-up ranges from 30 days[26, 28, 30, 34] to a median of 190 days [33] among studies evaluating iNPWT in complex IHR. Although follow-up does not discernibly influence the distribution of outcomes across studies, few discuss the timing of SSI and SSO occurrence. Soares et al noted that 90-day follow-up was a particular strength of their study[29], and Vargo et al noted that all wound complications requiring intervention in their series occurred more than 4 weeks post-operatively[26]. In our study, 35% of all SSIs occurred beyond 30 days, and the differences in SSI incidence between groups was no longer significant on Kaplan-Meier and regression analysis after extending follow-up from 30 to 180 days. Non-infectious SSOs, wound-related interventions, and readmissions were similar between groups in both analyses. These results may suggest that iNPWT improves short term SSI incidence, but may not translate into better long-term outcomes. Ensuring follow-up beyond 30 days should be considered in subsequent evaluations of iNPWT in IHR.

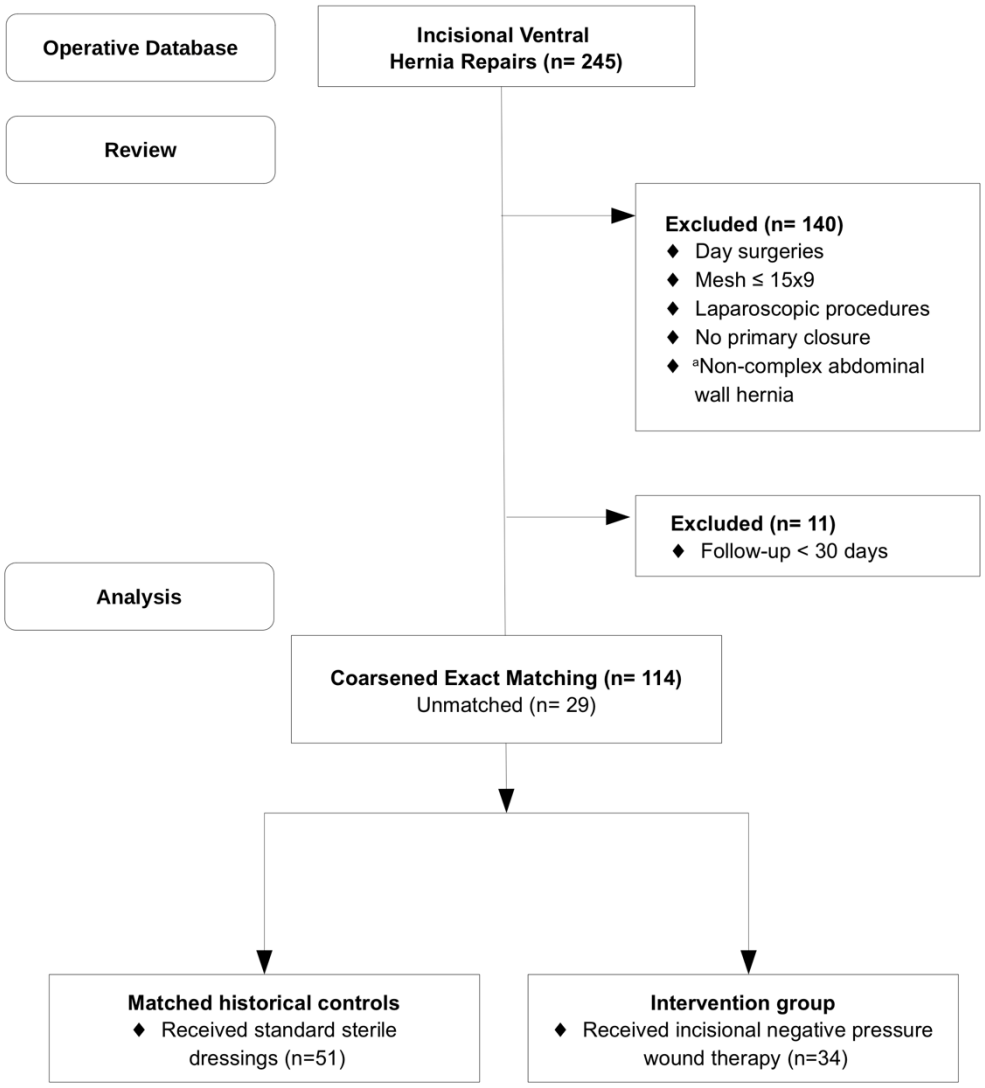
Our study was limited by its retrospective and observational design. Despite the promising results of prior retrospective studies of iNPWT in other abdominal operations, subsequent large RCTs have failed to demonstrate that benefit [36-38]. Another important limitation of our study included the change in surgical technique over time. Similar to Pauli et al [30], we observed a shift in surgical technique over the course of the study period. Early in the study period, EOR and TAR each accounted for 50% of component separations performed, whereas the proportion of TAR increased to 80% of all component separations by 2019. EOR, which requires extensive skin flaps, has been excluded from some studies of iNPWT [30], while being the primary focus of others [29, 35]. Our study was neither designed nor powered to detect differences between component separation techniques. However, EOR was equivalent between groups, while TAR was performed significantly more often in the iNPWT group. This distribution of component separations between the matched groups would likely favor a higher incidence of SSI in the iNPWT group, thus negatively biasing the effect of iNPWT. Indeed, adjusting for component separation in regression analysis only strengthened the association between iNPWT and lower SSI incidence. Loss to follow-up is another potential limitation of this study. While most patients with a wound complication are likely to seek care, it is possible that certain patients from distant referral site were treated for SSI at another institution. However, a sensitivity analysis supported the association between iNPWT and the decreased incidence of SSI at 30days, which suggested that this potential source of bias was unlikely to influence the study's findings. Cost remains an important limitation to the use of iNPWT and evidence from cost evaluation studies of this intervention is limited[10]. Chopra et al estimated that iNPWT may be cost-effective and potentially cost-saving when SSI incidence is greater than 16% in the context of IHR[12]. Furthermore, cost analyses may only be relevant to the specific healthcare system or institution (both based on purchase cost of the device as well as the baseline incidence of SSIs), and therefore may not be widely generalizable.

3.7 CONCLUSION

In patients undergoing complex IHR, the use of iNPWT was associated with a lower incidence of deep SSI at 30 days. After adjusting for residual differences between groups, a significant association between iNPWT and a composite outcome of deep and superficial SSI was observed. Our results support the pursuit of further prospective evaluations of this intervention, including randomized trials where feasible. The incidence of late SSI beyond 30 days in this cohort underscores the need to include long-term follow-up in subsequent studies. Future studies should focus on the cost effectiveness of iNPWT in this population, and the identification of patient selection criteria for its use

3.8 Tables and Figures

FIGURE 1. FLOW CHART



Flow diagram of included and excluded cases. [a]Cases were excluded if they did not meet at least one criteria for "complex" abdominal wall hernia as per consensus definition by Slater et al 2014 [13] (defect size and location, patient history and risk factors, contamination and soft tissue condition, and clinical scenario).

TAB[...][...]LE 1. PATIENT DEMOGRAPHICS AND PRE-OPERATIVE CHARACTERISTICS

		Full Cohort			Matched Cohort		
	Total (N=114)	SSD (N=73)	iNPWT (N=41)	p-value	SSD (N=51)	iNPWT (N=34)	p-value
Age, years	60 (52, 69)	59 (52, 69)	61 (49, 66)	0.658	57 (52, 69)	59 (48, 66)	0.574
Female	52 (45.6%)	36 (49.3%)	16 (39.0%)	0.331	29 (50.9%)	13 (41.9%)	0.505
BMI, kg/m^2	31 (28, 37)	31 (28, 36)	31 (27, 38)	0.61	31 (28, 35)	31 (27, 38)	0.549
BMI > 30 kg/m^2	64 (57.7%)	41 (58.6%)	23 (56.1%)	0.844	34 (59.6%)	17 (54.8%)	0.821
ASA Class	3 (2, 3)	2 (2, 3)	3 (2, 3)	0.42	2 (2, 3)	3 (2, 3)	0.270
CCI	2 (1, 4)	2 (1, 3)	2 (1, 4)	0.837	2 (1, 3)	2 (1, 4)	0.771
Diabetes Mellitus	22 (19.3%)	11 (15.1%)	11 (26.8%)	0.144	8 (14.0%)	9 (29.0%)	0.099
Smoking in year prior	16 (14.0%)	8 (11.0%)	8 (19.5%)	0.263	7 (12.3%)	7 (22.6%)	0.233
Immunosuppressed	8 (7.0%)	4 (5.5%)	4 (9.8%)	0.455	3 (5.3%)	4 (12.9%)	0.236
Prior Hernia Repair	33 (28.9%)	24 (32.9%)	9 (22.0%)	0.283	17 (29.8%)	4 (12.9%)	0.115
Prior Wound Infection	24 (21.1%)	10 (13.7%)	14 (34.1%)	0.016	8 (14.0%)	8 (25.8%)	0.247
Existing Stoma	5 (4.4%)	2 (2.7%)	3 (7.3%)	0.349	1 (1.8%)	3 (9.7%)	0.123

Result presented as 'Median (IQR)' for continuous variables and 'n (percent)' for categorical variables.

SSD = standard sterile dressing; iNPWT = incisional negative pressure wound therapy; BMI = body mass index; ASA Class = American Society of Anesthesia Classification; CCI = Charlson Comorbidity Index.

TABLE 2. SURGICAL DETAILS

		Full Cohort			Matched Cohort		
	Total (N=114)	SSD (N=73)	iNPWT (N=41)	p-value	SSD (N=51)	iNPWT (N=34)	p-value
Emergency Surgery	9 (7.9%)	6 (8.2%)	3 (7.3%)	1.000	0 (0.0%)	0 (0.0%)	-
Procedure Duration, minutes	218 (136, 328)	159 (110, 310)	305 (232, 377)	< 0.001	187 (133, 318)	304 (240, 362)	< 0.001
Contamination Class ≥ 2 [a]	38 (33.3%)	22 (30.1%)	16 (39.0%)	0.409	11 (21.6%)	11 (32.4%)	0.316
Intraoperative Complications [b]	7 (6.1%)	4 (5.5%)	3 (7.3%)	0.701	3 (5.9%)	2 (5.9%)	1.000
Estimated Blood Loss, mL	200 (100, 350)	200 (75, 300)	200 (200, 500)	0.012	200 (100, 350)	200 (200, 500)	0.154
Component Separation				0.023			0.302
Posterior	33 (28.9%)	15 (20.5%)	18 (43.9%)		14 (27.5%)	15 (44.1%)	
Anterior	16 (14.0%)	10 (13.7%)	6 (14.6%)		7 (13.7%)	4 (11.8%)	
None	65 (57.0%)	48 (65.8%)	17 (41.5%)		30 (58.8%)	15 (44.1%)	
Mesh Used	107 (93.9%)	69 (94.5%)	38 (92.7%)	0.701	49 (96.1%)	32 (94.1%)	1.000
Mesh Material				0.865			0.639
Parietex Progrip™	68 (59.6%)	43 (58.9%)	25 (61.0%)		30 (58.8%)	22 (64.7%)	
Parietex™ Composite	30 (26.3%)	20 (27.4%)	10 (24.4%)		14 (27.5%)	8 (23.5%)	
Gore® Bio-A®	4 (3.5%)	3 (4.1%)	1 (2.4%)		3 (5.9%)	0 (0.0%)	
Mixed	1 (0.9%)	0 (0.0%)	1 (2.4%)		0 (0.0%)	1 (2.9%)	
Vycril®	4 (3.5%)	3 (4.1%)	1 (2.4%)		2 (3.9%)	1 (2.9%)	
Mesh Position				0.460			0.896
Intraperitoneal	30 (26.3%)	18 (24.7%)	12 (29.3%)		12 (23.5%)	9 (26.5%)	
Extraperitoneal	49 (43.0%)	29 (39.7%)	20 (48.8%)		25 (49.0%)	17 (50.0%)	
Onlay	26 (22.8%)	20 (27.4%)	6 (14.6%)		10 (19.6%)	6 (17.6%)	
Mixed	2 (1.8%)	2 (2.7%)	0 (0.0%)		2 (3.9%)	0 (0.0%)	
New Stoma	1 (0.9%)	0 (0.0%)	1 (2.4%)	0.36	0 (0.0%)	1 (2.9%)	0.400
Use of closed suction drains	91 (79.8%)	55 (75.3%)	36 (87.8%)	0.146	42 (82.4%)	30 (88.2%)	0.549
Creating of Skin flap	46 (40.4%)	22 (30.1%)	24 (58.5%)	0.005	15 (29.4%)	22 (64.7%)	0.002
Plastic Surgeon	24 (21.1%)	14 (19.2%)	10 (24.4%)	0.633	11 (21.6%)	10 (29.4%)	0.449

Tissue flaps	7 (6.1%)	5 (6.8%)	2 (4.9%)	1.000	2 (3.9%)	2 (5.9%)	1.000

Results presented s ‘n (percent)’ for continuous variables, ‘median (interquartile range)’ for categorical variables. SSD = standard sterile dressing, iNPWT = incisional negative wound pressure therapy

[a]Contamination class >2 indication clean-contaminated, contaminated, or dirty procedures following Centers for Disease Control definitions.

[b]Intraoperative complications include aspiration of gastric contents, bowel injury, cardio-respiratory complications, hemorrhage requiring transfusion, urinary injury, vascular injury, and others.

TABLE 3. RISK CLASSIFICATION AND RISK SCORES

		Full Cohort			Matched Cohort		
	Total (N=114)	SSD (N=73)	iNPWT (N=41)	p-value	SSD (N=51)	iNPWT (N=34)	p-value
MHGS Grade				0.196			0.695
Grade 1	37 (32.5%)	26 (35.6%)	11 (26.8%)		18 (35.3%)	10 (29.4%)	
Grade 2	54 (47.4%)	36 (49.3%)	18 (43.9%)		26 (51.0%)	17 (50.0%)	
Grade 3	23 (20.2%)	11 (15.1%)	12 (29.3%)		7 (13.7%)	7 (20.6%)	
VHRS for SSO[a]				<0.001			<0.001
I (0-1 points)	51 (44.7%)	42 (57.5%)	9 (22.0%)		30 (58.8%)	6 (17.6%)	
II (2-4 points)	49 (43.0%)	24 (32.9%)	25 (61.0%)		17 (33.3%)	24 (48.2%)	
III (4-15 points)	14 (12.3%)	7 (9.6%)	7 (17.1%)		4 (7.8%)	4 (11.8%)	
VHRS for SSI[b]				0.010			0.056
I (0 points)	69 (60.5%)	51 (69.9%)	18 (43.9%)		32(67.2%)	14 (41.2%)	
II (2-3 points)	25 (21.9%)	11 (15.1%)	14 (34.1%)		9 (17.6%)	12 (35.3%)	
III (4 points)	5 (4.4%)	4 (5.5%)	1 (2.4%)		4 (7.8%)	1 (2.9%)	
IV (5-10 points)	13 (11.4%)	5 (6.8%)	8 (19.5%)		4 (7.8%)	7 (20.6%)	
V (11-16 points)	2 (1.8%)	2 (2.7%)	0 (0.0%)		2 (3.9%)	0 (0.0%)	

Results presented s 'n (percent)' for continuous variables, 'median (interquartile range)' for categorical variables. MHGS = Modified Hernia Grading Scale; VHRS = Ventral Hernia Risk Score; SSO = surgical site occurrence; SSI = surgical site infection, SSD = standard sterile dressing, iNPWT = incisional negative pressure wound therapy. [a] VHRS for SSO and [b] VHRS for SSI are categorized into 3 and 5 risk groups, representing increasing risk, as per Berger et al 2013 [14].

TABLE 4. 30-DAY OUTCOMES

	Full Cohort				Matched Cohort			
	Total (N=114)	SSD (N=73)	iNPWT (N=41)	p-value	SSD (N=51)	iNPWT (N=34)	p-value	Adjusted RR (95% CI)
Surgical Site Infection								
Superficial/Deep	22 (19.3%)	18 (24.7%)	4 (9.8%)	0.082	14 (27.5%)	4 (11.8%)	0.107	0.36 (0.16 – 0.87)*
Superficial	15 (13.2%)	11 (15.1%)	4 (9.8%)	0.567	9 (17.6%)	4 (11.8%)	0.549	0.52 (0.18 – 1.45)
Deep	12 (10.5%)	11 (15.1%)	1 (2.4%)	0.053	9 (17.6%)	1 (2.9%)	0.045	0.19 (0.03 – 1.38)
Organ Space	2 (1.8%)	0 (0.0%)	2 (4.9%)	0.127	0 (0.0%)	2 (5.9%)	0.157	-
Any SSI	22 (19.3%)	17 (23.3%)	5 (12.2%)	0.216	14 (27.5%)	5 (14.7%)	0.194	0.45 (0.20 – 1.00)
Surgical Site Occurrences								
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	-
EC Fistula	2 (1.8%)	2 (2.7%)	0 (0.0%)	0.535	2 (3.9%)	0 (0.0%)	0.514	-
Wound dehiscence	18 (15.8%)	10 (13.7%)	8 (19.5%)	0.433	8 (15.7%)	7 (20.6%)	0.575	1.21 (0.54 – 2.68)
Seroma	28 (24.6%)	17 (23.3%)	11 (26.8%)	0.821	12 (23.5%)	8 (23.5%)	1.000	0.90 (0.41 – 1.97)
Any SSO	44 (38.6%)	26 (35.6%)	18 (43.9%)	0.426	19 (37.3%)	14 (41.2%)	0.821	0.92 (0.56 – 1.52)
Wound Interventions								
Antibiotic Therapy	23 (20.2%)	17 (23.3%)	6 (14.6%)	0.335	14 (27.5%)	5 (14.7%)	0.194	0.49 (0.21 – 1.14)
IR Drainage	12 (10.5%)	8 (11.0%)	4 (9.8%)	1.000	7 (13.7%)	3 (8.8%)	0.733	0.49 (0.13 – 1.76)
Wound Opened	14 (12.3%)	9 (12.3%)	5 (12.2%)	1.000	7 (13.7%)	4 (11.8%)	1.000	0.81 (0.32 - 2.04)
Reoperation	5 (4.3%)	5 (6.6%)	0 (0.0%)	0.093	4 (7.5%)	0 (0.0%)	0.101	-
Other Complications and Outcomes								
All Complication	48 (42.1%)	30 (41.1%)	18 (43.9%)	0.844	24 (47.1%)	14 (41.2%)	0.659	0.77 (0.48 – 1.23)
Length of Stay, days	6 (3, 8)	4 (3, 7)	7 (6, 10)	0.443	5 (3, 8)	7 (6, 10)	0.001	-
ED visit	20 (17.5%)	12 (16.4%)	8 (19.5%)	0.798	9 (17.6%)	5 (14.7%)	0.775	0.72 (0.28 – 1.89)

30-day Readmission	22 (19.3%)	15 (20.5%)	7 (17.1%)	0.806	13 (25.5%)	5 (14.7%)	0.286	0.51 (0.21 – 1.24)
30-day Mortality	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	-

Result presented s ‘n (percent)’ for continuous variables, ‘median (interquartile range)’ for continuous variables, and `relative risk (95% confidence interval)`. RR = relative risk of outcome between matched groups, adjusted for technique of component separation and smoking within the year prior to surgery and ventral hernia risk score for SSI. Relative risks estimated from logistic regression using the delta method. RR = relative risk, CI= confidence interval, SSD = standard sterile dressing; iNPWT = incisional negative pressure wound therapy; SSI = Surgical Site Infection; SSO = surgical site occurrence; EC Fistula = enterocutaneous fistula, IR = interventional radiology; ED = Emergency department.

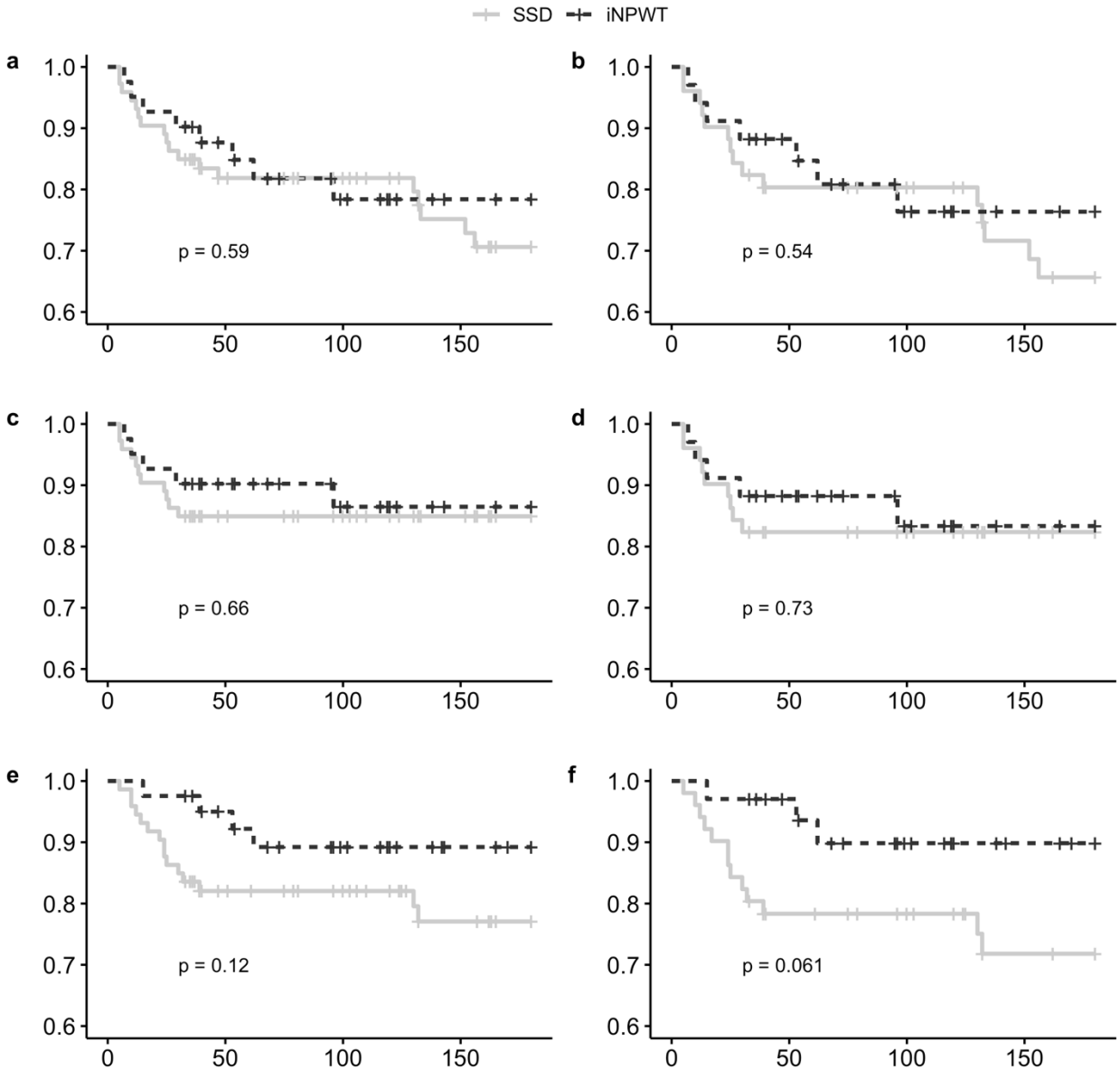
TABLE 5. OUTCOMES BEYOND 30 DAYS

	Full Cohort				Matched Cohort			
	Total (N=114)	**SSD (N=73)**	**iNPWT (N=41)**	**p-value**	**SSD (N=51)**	**iNPWT (N=34)**	**p-value**	**Adjusted HR (95CI%)**
Any SSI	12 (10.5%)	7 (9.6%)	5 (12.2%)	0.754	6 (11.8%)	4 (11.8%)	1.000	0.75 (0.30 – 1.85)
Superficial	1 (0.9%)	0 (0.0%)	1 (2.4%)	0.36	0 (0.0%)	1 (2.9%)	0.400	0.81 (0.27 – 2.44)
Deep	11 (9.6%)	7 (9.6%)	4 (9.8%)	1.000	6 (11.8%)	3 (8.8%)	0.735	0.34 (0.10– 1.2)
Organ Space	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	-
Any intervention	11 (9.6%)	7 (9.6%)	4 (9.8%)	1.000	6 (11.8%)	3 (8.8%)	0.735	-
Wound opened	7 (6.1%)	3 (4.1%)	4 (9.8%)	0.249	2 (3.9%)	3 (8.8%)	0.385	1.17 (0.38 – 3.61)
Antibiotics	9 (7.9%)	6 (8.2%)	3 (7.3%)	1.000	5 (9.8%)	2 (5.9%)	0.697	0.49 (0.19—1.27)
IR drainage	5 (4.4%)	4 (5.5%)	1 (2.4%)	0.653	3 (5.9%)	1 (2.9%)	0.647	0.17 (0.02– 1.43)
Reoperation	5 (4.4%)	4 (5.5%)	1 (2.4%)	0.653	4 (7.8%)	1 (2.9%)	0.644	0.20 (0.02 – 1.68)
ED Visit	11 (9.6%)	8 (11.0%)	3 (7.3%)	0.744	7 (13.7%)	2 (5.9%)	0.305	0.39 (0.11 – 1.43)
Readmission	13 (11.4%)	8 (11.0%)	5 (12.2%)	1.000	6 (11.8%)	4 (11.8%)	1.000	0.53 (0.17 – 1.72)
Hernia Recurrence	7 (6.1%)	2 (2.7%)	5 (12.2%)	0.096	2 (3.9%)	4 (11.8%)	0.212	4.61 (0.63 – 33.5)

Result presented s 'n (percent)' for continuous variables, 'median (interquartile range)' for continuous variables, and adjusted hazard ratios and 95% confidence intervals. Hazard ratios for iNPWT vs. SSD calculated using Cox Proportional Hazards Model adjusting for technique of component separation, smoking exposure 1 year prior to surgery, and body mass index. CI = confidence; MHGS = Modified Hernia Grading Scale; SSD = standard sterile dressing; iNPWT = incisional negative pressure wound

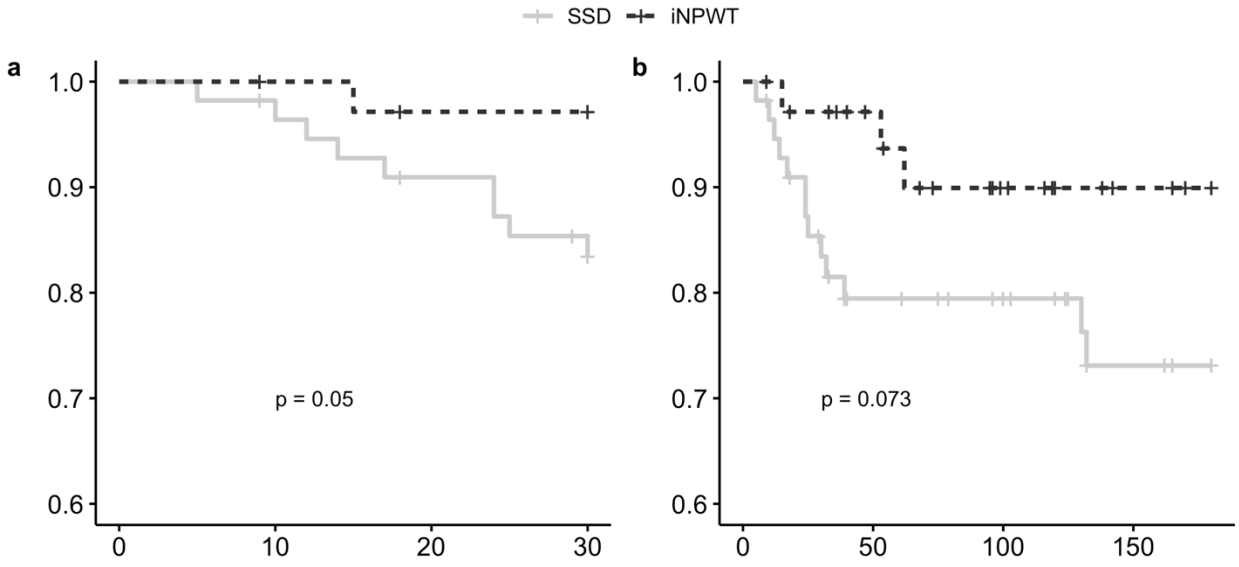
therapy, SSI=surgical site infection, IR drainage = drainage in interventional radiology, ED visit = emergency department visit.

FIGURE 2. KAPLAN MEIER CURVES FOR LATE SURGICAL SITE INFECTION



Kaplan Meier curves showing cumulative probability of follow-up without surgical site infections (SSI) vs time in days in the full cohort (FC) and in the matched cohort (MC). Follow-up is limited to 180 days. Cumulative probabilities are compared using the Log rank test and p-values are reported below the curves. **a** composite SSI in FC. **b** composite SSI in MC . **c** superficial SSI in F. **d** SSI in MC. **e** Deep SSI in FC. **f** Deep SSI in the matched cohort.

FIGURE 3.KAPLAN-MEIER CURVES FOR DEEP SSI OUTCOMES AFTER INCLUSION OF CASES LOST TO FOLLOW-UP



Kaplan Meier curves showing cumulative probability of follow-up without surgical site infections (SSI) vs time in days. Includes cases excluded from primary analysis due to less than 30 days of follow-up. Cumulative probabilities are compared using the Log rank test and p-values are reported below the curves. a deep SSI up to 30 days of follow-up. b deep SSI up to 180 days of follow-up. SSD = standard sterile dressing; iNPWT = incisional negative pressure wound therapy.

TABLE 6 – SENSITIVITY ANALYSIS FOR EFFECT MISSED SSI IN INPWT CASES LOST TO FOLLOW

	Adjusted RR and 95% CI		
30-day Outcomes	**No missed SSI**	**1 missed SSI (superficial)**	**2 missed SSIs (superficial + deep)**
Superficial/Deep SSI	0.30 (0.12 -0.78)	0.36 (0.15 – 0.85)	0.45 (0.20 – 1.01)
Superficial SSI	0.51 (0.18 – 1.50)	0.60 (0.23 – 1.62)	0.60 (0.23 -1.62)
Deep SSI	0.14 (0.02 – 1.10)	0.14 (0.02 – 1.10)	0.32 (0.07 – 1.41)

Results of a sensitivity analysis to evaluate the effect of missed SSI in iNPWT cases lost to follow-up on 30-day SSI outcomes. No SSIs were recorded in the group of 11 cases lost to follow-up, and only of these cases 2 received iNPWT. To simulate the maximal bias from missed SSIs among iNPWT cases, SSI outcomes were reclassified for these iNPWT cases. RR = relative risk of SSI associated with iNPWT, adjusted for procedure duration, VHRS for SSI, and smoking exposure.

3.9 DISCLOSURES

Dr. Feldman has received educational grants from Theator and Merck. Dr. Vassiliou has attended an educational course funded by KCI. Dr. Lee has received an investigator-initiated research grant from Johnson & Johnson.

Drs. Hopkins, Eustaches, Fried, Khwaja, Fata have no conflicts of interest or financial ties to disclose.

Ms. Ganescu, Cipolla, and Kaneva have no conflicts of interest or financial ties to disclose.

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3.11 SUPPLEMENTARY MATERIAL

APPENDIX 1. SENSITIVITY ANALYSIS FOR LOSS TO FOLLOW-UP

Table 1.1 – Demographics and risk factors of matched groups after the inclusion of cases with less than 30-days of follow-up.

	SSD (N=56)	iNPWT (N=36)	Total (N=92)	p value
Demographics				
Age, years	56 (52, 68)	61 (49, 66)	57 (51, 68)	0.996
Female	29 (51.8%)	14 (38.9%)	43 (46.7%)	0.286
BMI, kg/m^2	32 (28, 36)	31 (27, 38)	31 (28, 37)	0.984
BMI > 30 kg/m^2	35 (62.5%)	20 (55.6%)	55 (59.8%)	0.522
ASA Class	3 (2, 3)	3 (2, 3)	3 (2, 3)	0.543
CCI	2 (1, 3)	2 (1, 4)	2 (1, 3)	0.597
Diabetes Mellitus	7 (12.5%)	10 (27.8%)	17 (18.5%)	0.098
Smoking in year prior	8 (14.3%)	8 (22.2%)	16 (17.4%)	0.401
Immunosuppressed	3 (5.4%)	4 (11.1%)	7 (7.6%)	0.426
Prior Hernia Repair	18 (32.1%)	7 (19.4%)	25 (27.2%)	0.233
Prior Wound Infection	8 (14.3%)	11 (30.6%)	19 (20.7%)	0.070
Existing Stoma	(1.8%)	3 (8.3%)	4 (4.3%)	0.296

	SSD (N=56)	iNPWT (N=36)	Total (N=92)	p value
Surgical Details				
Emergency	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Procedure Duration	186 (128, 314)	304 (236, 366)	250 (158, 331)	< 0.001*
Contamination Class ≥ 2	12 (21.4%)	12 (33.3%)	24 (26.1%)	0.231
Intraoperative Complication	3 (5.4%)	3 (8.3%)	6 (6.5%)	0.675
Estimated Blood Loss	200 (100, 312)	200 (200, 500)	200 (100, 400)	0.089
Component Separation				0.100
None	33 (58.9%)	15 (41.7%)	48 (52.2%)	
Posterior	14 (25.0%)	17 (47.2%)	31 (33.7%)	
Anterior	9 (16.1%)	4 (11.1%)	13 (14.1%)	
Mesh Used	54 (96.4%)	34 (94.4%)	88 (95.7%)	0.643
Mesh Material				0.692
Parietex Progrip™	34 (60.7%)	23 (63.9%)	57 (62.0%)	
Parietex™ Composite	15 (26.8%)	9 (25.0%)	24 (26.1%)	

	SSD (N=56)	iNPWT (N=36)	Total (N=92)	p value
Vycril®	2 (3.6%)	1 (2.8%)	3 (3.3%)	
Gore® Bio-A®	3 (5.4%)	0 (0.0%)	3 (3.3%)	
Mixed	0 (0.0%)	1 (2.8%)	1 (1.1%)	
Mesh Position				0.876
Intraperitoneal	13 (23.2%)	10 (27.8%)	23 (25.0%)	
Extraperitoneal/Retrorectus	28 (50.0%)	17 (47.2%)	45 (48.9%)	
Onlay	11 (19.6%)	7 (19.4%)	18 (19.6%)	
Mixed	2 (3.6%)	0 (0.0%)	2 (2.2%)	
New Stoma	0 (0.0%)	1 (2.8%)	1 (1.1%)	0.391
Use of closed suction drains	46 (82.1%)	32 (88.9%)	78 (84.8%)	0.554
Skin flap	17 (30.4%)	24 (66.7%)	41 (44.6%)	0.001*
Plastic Surgeon	11 (19.6%)	11 (30.6%)	22 (23.9%)	0.371
Tissue flaps	2 (3.6%)	2 (5.6%)	4 (4.3%)	0.643
Risk Classification and Risk Scores				
MHGS Grade				0.617

	SSD (N=56)	iNPWT (N=36)	Total (N=92)	p value
Grade 1	19 (33.9%)	10 (27.8%)	29 (31.5%)	
Grade 2	30 (53.6%)	19 (52.8%)	49 (53.3%)	
Grade 3	7 (12.5%)	7 (19.4%)	14 (15.2%)	
VHRS for SSO[c]				< 0.001*
I (0-1 points)	33 (58.9%)	6 (16.7%)	39 (42.4%)	
II (2-4 points)	18 (32.1%)	26 (72.2%)	44 (47.8%)	
III (4-15 points)	5 (8.9%)	4 (11.1%)	9 (9.8%)	
VHRS for SSI[d]				0.012
I (0 points)	37 (66.1%)	14 (38.9%)	51 (55.4%)	
II (2-3 points)	9 (16.1%)	14 (38.9%)	23 (25.0%)	
III (4 points)	4 (7.1%)	1 (2.8%)	5 (5.4%)	
IV (5-10 points)	4 (7.1%)	7 (19.4%)	11 (12.0%)	
V (11-16 points)	2 (3.6%)	0 (0.0%)	2 (2.2%)	

Result presented as 'Median (IQR)' for continuous variables and 'n (percent)' for categorical variables. SSD = standard sterile dressing; iNPWT = incisional negative pressure wound therapy; BMI = body mass index; ASA Class = American Society of Anesthesia Classification; CCI = Charlson Comorbidity Index; MHGS = Modified Hernia Grading Scale; VHRS = Ventral Hernia Risk Score; SSO = surgical site occurrence; SSI = surgical site infection.

[a]Contamination class >2 indication clean-contaminated, contaminated, or dirty procedures following Centers for

Disease Control definitions. [b]Intraoperative complications include aspiration of gastric contents, bowel injury, cardio-respiratory complications, hemorrhage requiring transfusion, urinary injury, vascular injury, and others. [c]VHRS for SSO and [d]VHRS for SSI are categorized into 3 and 5 risk groups, representing increasing risk, as per Berger et al 2013 [14].

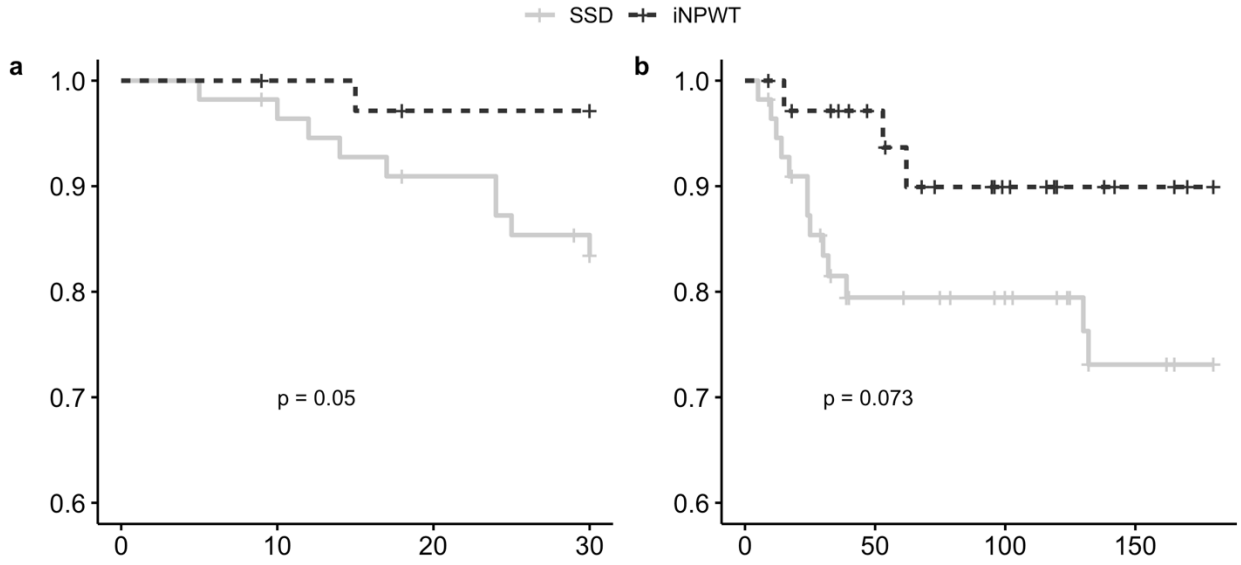
Table A1.2 – 30 day outcomes in a matched groups after the inclusion of cases with less than 30-days of follow-up.

	SSD (N=56)	**iNPWT (N=36)**	**Total (N=92)**	**p-value**
Surgical Site Infection				
Superficial/Deep	14 (25.0%)	6 (16.7%)	20 (21.7%)	0.441
Superficial	9 (16.1%)	5 (13.9%)	14 (15.2%)	0.617
Deep	9 (16.1%)	2 (5.6%)	11 (12.0%)	0.191
Organ Space	0 (0.0%)	2 (5.6%)	2 (2.2%)	0.151
Any SSI	14 (25.0%)	7 (19.4%)	21 (22.8%)	0.441
Surgical Site Occurrences				
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	
EC Fistula	2 (3.6%)	0 (0.0%)	2 (2.2%)	0.518
Wound dehiscence	8 (14.3%)	7 (19.4%)	15 (16.3%)	0.570
Seroma	13 (23.2%)	8 (22.2%)	21 (22.8%)	1.000
Any SSO	20 (35.7%)	14 (38.9%)	34 (37.0%)	0.826
Wound Interventions				

Antibiotic Therapy	14 (25.0%)	5 (13.9%)	19 (20.7%)	0.292
IR Drainage	7 (12.5%)	3 (8.3%)	10 (10.9%)	0.735
Wound Opened	7 (12.5%)	4 (11.1%)	11 (12.0%)	1.000
Reoperation	4 (7.1%)	0 (0.0%)	4 (4.3%)	0.153
Other Complications and Outcomes				
All Complication	25 (44.6%)	14 (38.9%)	39 (42.4%)	0.668
Length of Stay, days	5 (3, 7)	7 (6, 9)	6 (4, 8)	0.966
ED visit	9 (16.1%)	5 (13.9%)	14 (15.2%)	1.000
30-day Readmission	13 (23.2%)	5 (13.9%)	18 (19.6%)	0.298
30-day Mortality	0 (0.0%)	0 (0.0%)	0 (0.0%)	-

Result presented s ‘n (percent)’ for continuous variables, ‘median (interquartile range)’ for continuous variables, and `relative risk (95% confidence interval)`. SSD = standard sterile dressing; iNPWT = incisional negative pressure wound therapy; SSI = Surgical Site Infection; SSO = surgical site occurrence; EC Fistula = enterocutaneous fistula, IR = interventional radiology; ED = Emergency department.

Figure A1.1 – Kaplan-Meier curves for SSI outcomes in a matched Analysis with the inclusion of cases with less than 30-days follow-up



Kaplan Meier curves showing cumulative probability of follow-up without surgical site infections (SSI) vs time in days. Includes cases excluded from primary analysis due to less than 30 days of follow-up. Cumulative probabilities are compared using the Log rank test and p-values are reported below the curves. a deep SSI up to 30 days of follow-up. b deep SSI up to 180 days of follow-up.

Table A1.3 – Outcomes up to 180 days in a matched Analysis with the inclusion of cases with less than 30-days follow-up

	SSD (N=56)	**iNPWT (N=36)**	**Total (N=92)**	**p-value**	**Adjusted HR (95% CI)**
Superficial/Deep SSI	6 (10.7%)	4 (11.4%)	10 (11.0%)	0.638	0.40 (0.16 – 1.01)
Superficial	0 (0.0%)	1 (2.9%)	1 (1.1%)	-	0.61 (0.20 – 1.63)
Deep	6 (10.7%)	3 (8.6%)	9 (9.9%)	0.638	0.26 (0.07 – 0.96)
Organ Space	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	-
Any intervention	6 (10.7%)	3 (8.6%)	9 (9.9%)		
Wound opened	(3.6%)	3 (8.6%)	5 (5.5%)	0.638	1.01 (0.30 – 3.38)
Antibiotics	5 (8.9%)	2 (5.7%)	7 (7.7%)	0.265	0.39 (0.15 – 1.06)
IR drainage	3 (5.4%)	1 (2.9%)	4 (4.4%)	0.641	0.14 (0.02 – 1.29)
Reoperation	4 (7.1%)	1 (2.9%)	5 (5.5%)	1.000	0.06 (0.01 -0.92)
ED Visit	7 (12.5%)	2 (5.7%)	9 (9.9%)		0.35 (0.09 – 1.42)
Readmission	6 (10.7%)	4 (11.4%)	10 (11.0%)	0.641	0.52 (0.15 – 1.78)
Hernia Recurrence	2 (3.6%)	4 (11.4%)	6 (6.6%)	0.689	3.96 (0.52 – 30.38)

Result presented s ‘n (percent)’ for continuous variables, ‘median (interquartile range)’ for continuous variables, and adjusted hazard ratios and 95% confidence intervals for all outcomes up to 180 days follow-up. Hazard ratios for iNPWT vs. SSD calculated using Cox Proportional Hazards Model adjusting for procedure duration and VHRS for SSI. CI = confidence; SSD = standard sterile dressing; iNPWT = incisional negative pressure wound therapy,

SSI=surgical site infection, IR drainage = drainage in interventional radiology, ED visit = emergency department visit.

Table A1.4 – Sensitivity analysis for loss to follow

	Adjusted RR and 95% CI for iNPWT		
30-day Outcomes	**No missed SSI**	**1 missed SSI (superficial)**	**2 missed SSIs (superficial + deep)**
Superficial/Deep SSI	0.30 (0.12 -0.78)	0.36 (0.15 – 0.85)	0.45 (0.20 – 1.01)
Superficial SSI	0.51 (0.18 – 1.50)	0.60 (0.23 – 1.62)	0.60 (0.23 -1.62)
Deep SSI	0.14 (0.02 – 1.10)	0.14 (0.02 – 1.10)	0.32 (0.07 – 1.41)

Adjusted relative risk for SSI outcomes in patients receiving iNPWT compared to SSD in a matched cohort analysis, including patients with less than 30 days of follow-up. To simulate maximal bias from missed SSIs among iNPWT cases with less than 30 days of follow-up, these cases were reclassified as having developed SSI for this analysis. RR = relative risk, adjusted for procedure duration, VHRS for SSI, and smoking exposure. Relative risks are estimated from logistic regression using the delta method. CI= confidence interval.

APPENDIX 2. ANALYSIS OF CONCURRENT CASES PERFORMED WITH INCISIONAL NEGATIVE PRESSURE WOUND THERAPY OR STANDARDS STERILE DRESSINGS FROM JAN 2018 TO DEC 2019 WHILE A PROPRIETARY DRESSING WAS AVAILABLE

Table A2.1 Patient Demographics and Pre-operative characteristics

	SSD (N=23)	iNPWT (N=35)	Total (N=58)	p-value
Demographics				
Age, years	59 (54, 69)	62 (51, 68)	62 (51, 68)	0.973
Female	11 (47.8%)	14 (40.0%)	25 (43.1%)	0.597
BMI, kg/m^2	30 (29, 33)	33 (28, 39)	31 (29, 36)	0.034*

	SSD (N=23)	iNPWT (N=35)	Total (N=58)	p-value
BMI > 30 kg/m^2	11 (47.8%)	23 (65.7%)	34 (58.6%)	0.276
ASA Class	3 (2, 3)	3 (2, 3)	3 (2, 3)	0.670
CCI	3 (1, 4)	3 (1, 4)	3 (1, 4)	0.880
Diabetes Mellitus	2 (8.7%)	11 (31.4%)	13 (22.4%)	0.056
Smoking in year prior	3 (13.0%)	7 (20.0%)	10 (17.2%)	0.725
Immunosuppressed	2 (8.7%)	5 (14.3%)	7 (12.1%)	0.692
Prior Hernia Repair	8 (34.8%)	9 (25.7%)	17 (29.3%)	0.559
Prior Wound Infection	2 (8.7%)	12 (34.3%)	14 (24.1%)	0.031*
Existing Stoma	2 (8.7%)	3 (8.6%)	5 (8.6%)	1.000
Surgical Details				
Emergency	1 (4.3%)	3 (8.6%)	4 (6.9%)	1.000
Procedure Duration	123 (95, 182)	296 (224, 377)	218 (151, 326)	< 0.001*
Contamination Class ≥ 2	5 (21.7%)	14 (40.0%)	19 (32.8%)	0.167
Intraoperative Complication	2 (8.7%)	4 (11.4%)	6 (10.3%)	1.000

	SSD (N=23)	iNPWT (N=35)	Total (N=58)	p-value
Estimated Blood Loss	100 (50, 200)	200 (200, 400)	200 (100, 338)	0.014*
Component Separation				0.002*
None	18 (78.3%)	14 (40.0%)	32 (55.2%)	
Posterior	2 (8.7%)	18 (51.4%)	20 (34.5%)	
Anterior	3 (13.0%)	3 (8.6%)	6 (10.3%)	
Mesh Used	21 (91.3%)	32 (91.4%)	53 (91.4%)	1.000
Mesh Material				-
Parietex Progrip™	18 (78.3%)	22 (62.9%)	40 (69.0%)	
Parietex™ Composite	3 (13.0%)	8 (22.9%)	11 (19.0%)	
Vycril®	0 (0.0%)	1 (2.9%)	1 (1.7%)	
Gore® Bio-A®	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Mixed	0 (0.0%)	1 (2.9%)	1 (1.7%)	
Mesh Position				-
Intraperitoneal	3 (13.0%)	8 (22.9%)	11 (19.0%)	
Extraperitoneal/Retrorectus	12 (52.2%)	18 (51.4%)	30 (51.7%)	

	SSD (N=23)	iNPWT (N=35)	Total (N=58)	p-value
Onlay	6 (26.1%)	6 (17.1%)	12 (20.7%)	
Mixed	0 (0.0%)	0 (0.0%)	0 (0.0%)	
New Stoma	0 (0.0%)	1 (2.9%)	1 (1.7%)	1.000
Use of closed suction drains	17 (73.9%)	31 (88.6%)	48 (82.8%)	0.173
Skin flap	5 (21.7%)	22 (62.9%)	27 (46.6%)	0.003*
Plastic Surgeon	2 (8.7%)	10 (28.6%)	12 (20.7%)	0.099
Tissue flaps	0 (0.0%)	2 (5.7%)	2 (3.4%)	0.513
Risk Classification and Risk Scores				
MHGS Grade				0.144
Grade 1	10 (43.5%)	7 (20.0%)	17 (29.3%)	
Grade 2	9 (39.1%)	17 (48.6%)	26 (44.8%)	
Grade 3	4 (17.4%)	11 (31.4%)	15 (25.9%)	
VHRS for SSO[c]				< 0.001*
I (0-1 points)	16 (69.6%)	7 (20.0%)	23 (39.7%)	
II (2-4 points)	6 (26.1%)	22 (62.9%)	28 (48.3%)	

	SSD (N=23)	iNPWT (N=35)	Total (N=58)	p-value
III (4-15 points)	1 (4.3%)	6 (17.1%)	7 (12.1%)	
VHRS for SSI[d]				-
I (0 points)	18 (78.3%)	13 (37.1%)	31 (53.4%)	
II (2-3 points)	5 (21.7%)	13 (37.1%)	18 (31.0%)	
III (4 points)	0 (0.0%)	1 (2.9%)	1 (1.7%)	
IV (5-10 points)	0 (0.0%)	8 (22.9%)	8 (13.8%)	
V (11-16 points)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

Result presented as 'Median (IQR)' for continuous variables and 'n (percent)' for categorical variables. SSD = standard sterile dressing; iNPWT = incisional negative pressure wound therapy; BMI = body mass index; ASA Class = American Society of Anesthesia Classification; CCI = Charlson Comorbidity Index; MHGS = Modified Hernia Grading Scale; VHRS = Ventral Hernia Risk Score; SSO = surgical site occurrence; SSI = surgical site infection. [a]Contamination class >2 indication clean-contaminated, contaminated, or dirty procedures following Centers for Disease Control definitions. [b]Intraoperative complications include aspiration of gastric contents, bowel injury, cardio-respiratory complications, hemorrhage requiring transfusion, urinary injury, vascular injury, and others. [c]VHRS for SSO and [d]VHRS for SSI are categorized into 3 and 5 risk groups, representing increasing risk, as per Berger et al 2013 [14].

Table A2.2 30 Day Outcomes

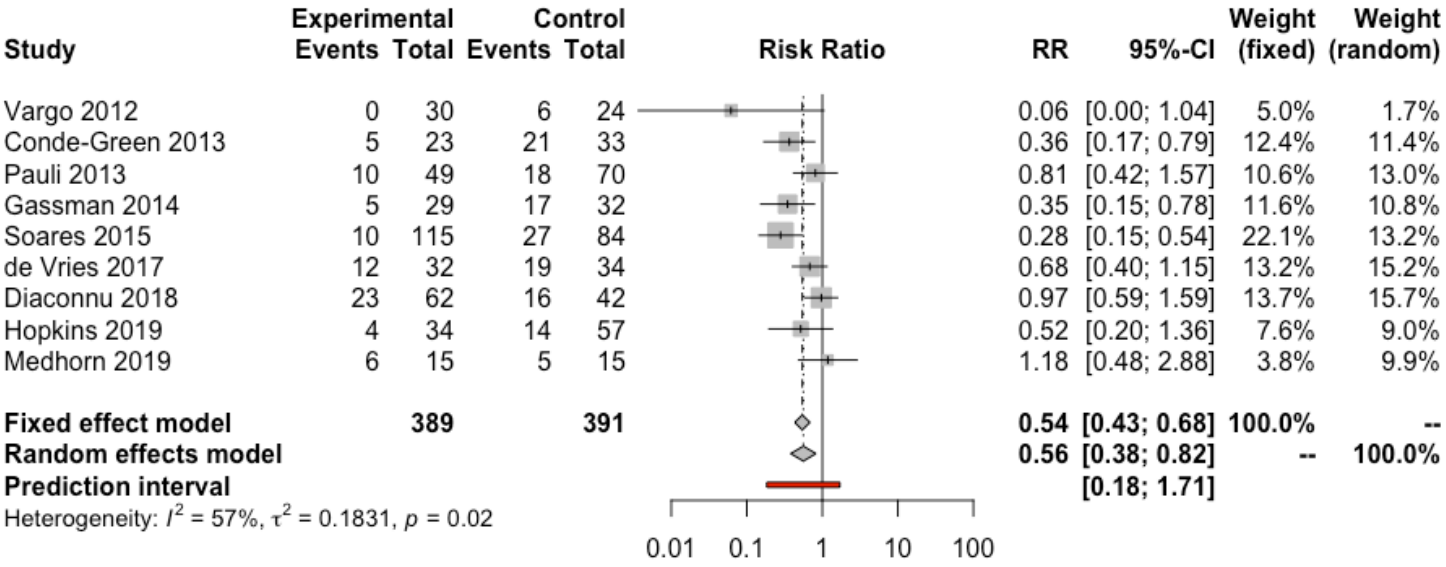
30-Day Outcomes

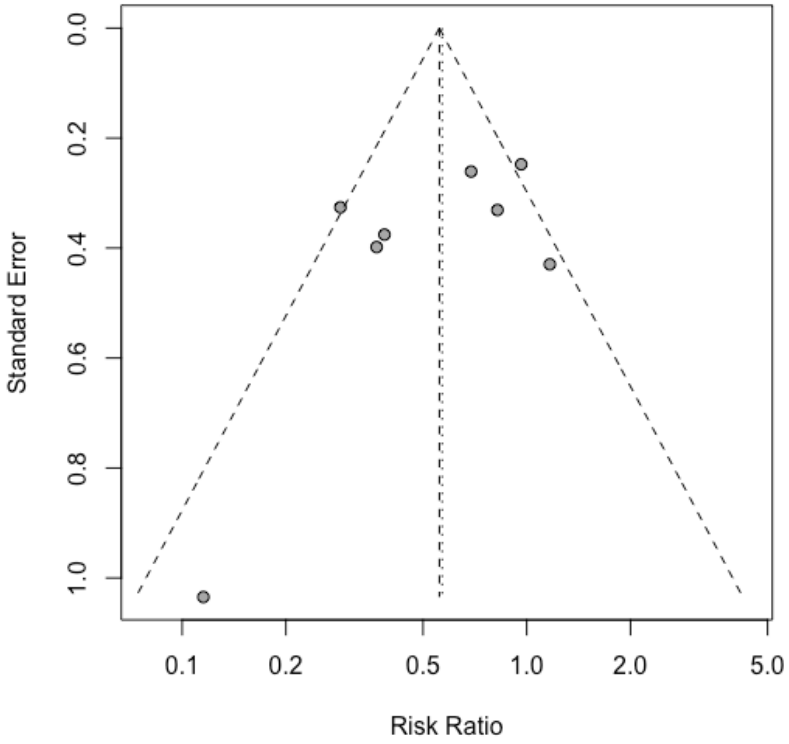
	SSD (N=23)	iNPWT (N=35)	Total (N=58)	p-value	Adjusted RR (95% CI)
Surgical Site Infection					
Superficial/Deep	3 (13.0%)	4 (11.4%)	7 (12.1%)	1.000	0.21 (0.08 – 0.59)
Superficial	1 (4.3%)	4 (11.4%)	5 (8.6%)	0.639	0.70 (0.26 – 1.90)
Deep	2 (8.7%)	1 (2.9%)	3 (5.2%)	0.556	0.25 (0.06 – 1.14)
Organ Space	0 (0.0%)	2 (5.7%)	2 (3.4%)	0.513	-
Any SSI	3 (13.0%)	5 (14.3%)	8 (13.8%)	1.000	0.39 (0.17 – 0.92)
Surgical Site Occurrences					
Hematoma	1 (4.3%)	0 (0.0%)	1 (1.7%)	0.397	-
EC Fistula	0 (0.0%)	0 (0.0%)	0 (0.0%)		-
Wound dehiscence	2 (8.7%)	6 (17.1%)	8 (13.8%)	0.458	0.98 (0.40 – 2.40)
Seroma	7 (30.4%)	11 (31.4%)	18 (31.0%)	1.000	1.14 (0.51 – 2.58)
Any SSO	9 (39.1%)	16 (45.7%)	25 (43.1%)	0.787	0.89 (0.52 – 1.53)
Wound Interventions					
Antibiotic Therapy	2 (8.7%)	6 (17.1%)	8 (13.8%)	0.458	0.42 (0.17 – 1.02)
IR Drainage	1 (4.3%)	4 (11.4%)	5 (8.6%)	0.639	0.48 (0.13 – 0.18)

Wound Opened	2 (8.7%)	5 (14.3%)	7 (12.1%)	0.692	0.63 (0.23 – 1.75)
Reoperation	1 (4.3%)	0 (0.0%)	1 (1.7%)	0.397	-
Other Complications and Outcomes					
All Complication	7 (30.4%)	15 (42.9%)	22 (37.9%)	0.413	0.62 (0.38– 1.03)
Length of Stay, days	3 (2, 5)	7 (6, 10)	6 (3, 8)	0.723	-
ED visit	3 (13.0%)	7 (20.0%)	10 (17.2%)	0.725	0.69 (0.24 – 1.99)
30-day Readmission	2 (8.7%)	7 (20.0%)	9 (15.5%)	0.295	0.48 (0.18 – 1.28)
30-day Mortality	0 (0.0%)	0 (0.0%)	0 (0.0%)		-

Result presented s ‘n (percent)’ for continuous variables, ‘median (interquartile range)’ for continuous variables, and `relative risk (95% confidence interval)`. RR = relative risk, adjusted for procedure duration, VHRS for SSI, and smoking exposure. Relative risks estimated from logistic regression using the delta method. RR = relative risk, CI= confidence interval, SSD = standard sterile dressing; iNPWT = incisional negative pressure wound therapy; SSI = Surgical Site Infection; SSO = surgical site occurrence; EC Fistula = enterocutaneous fistula, IR = interventional radiology; ED = Emergency department.

APPENDIX 3. UPDATED META-ANALYSIS OF STUDIES EVALUATION INCISIONAL NEGATIVE PRESSURE WOUND THERAPY FOR THE PREVENTION OF SURGICAL SITE INFECTION AFTER INCISIONAL HERNIA REPAIR





CHAPTER 4: FOLLOW-UP BEYOND 30-DAYS IS REQUIRED TO ADEQUATELY DETECT WOUND OUTCOMES AFTER INCISIONAL HERNIA REPAIR

4.1 PREAMBLE TO MANUSCRIPT 2

The results of manuscript 1 supported the effectiveness of iNPWT in reducing the incidence of SSI at 30 days after IHR. However, we noted that a considerable proportion of wound events occurred after 30 days, and that iNPWT's effect was no longer observed when we included these late outcomes in survival analysis. While 30-day wound outcomes have been routinely used in many surgical quality surveillance programs and comparative effectiveness studies, cohort studies had demonstrated that a considerable number of wound events do occur more than 30 days after IHR. It is possible, therefore, that a considerable number of clinically relevant outcomes could be missed when using 30-day wound outcomes to evaluate iNPWT or other interventions intended to prevent SSI after IHR. In the context of a clinical audit of all IHR repairs performed at our institution from 2016-2019 inclusively, we sought to determine an appropriate follow-up time for wound outcomes after IHR. In Manuscript 2, we assessed the validity of wound outcomes after IHR using 30, 60, and 90-day endpoints, and characterized the salient risk factors for wound complications among patients at our institution using cox-proportional hazards regression.

MANUSCRIPT 2: FOLLOW-UP BEYOND 30-DAYS IS REQUIRED TO ADEQUATELY DETECT WOUND OUTCOMES AFTER INCISIONAL HERNIA REPAIR

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Manuscript planned for submission to Surgical Endoscopy pending acceptance at SAGES 2021 Meeting.

4.2 ABSTRACT

Introduction: Incisional hernia repair (IHR) carries a high risk of wound complications. Thirty-day outcomes are frequently used in comparative-effectiveness research, but may miss a substantial number of surgical site occurrences (SSO) including surgical site infection (SSI). The objective of this study was to determine an optimal length of follow-up to detect SSI after IHR.

Methods: All adult patients undergoing open IHR at a single academic centre from January 2016 to December 2019 were reviewed. The primary outcome was SSI up to 180 days. Secondary outcomes were SSO and hospital readmission. Time-to-event analysis was performed for outcomes at 30, 60, 90, and 180 days. Cox-proportional hazards regression was used to calculate the relative hazards of SSI for relevant risk factors.

Results: 235 patients underwent open IHR. Median follow-up time of 102 days. Mean age was 58 years, 50.9% female, 91% elective, 86% used mesh, 27% component separation, and 7.7% bowel resection. Using the Modified Hernia Grading Scale (MHGS), 32% were Grade 1, 55% Grade 2, and 13% Grade 3. Overall incidence of SSI was 15.8% with median time to occurrence of 23 days. Incidence of non-infectious SSO was 35.5%, and wound-related readmission was 12.8%. Sensitivity for outcomes at 30, 60, 90, and 120 days are presented in Table1. In Cox-proportional hazards regression stratifying for technique of component separation, smoking exposure (HR 2.76, 95%CI 1.19-6.39) and emergency surgery (HR 3.20, 95%CI 1.21-8.47) were independently associated with SSI after adjusting for hernia grade.

Conclusion: A considerable proportion of SSIs occurred beyond 30 days, but 90-day follow-up detected 92% of SSIs. Follow-up to 120 days captured only 83% of wound-related readmissions. These results have implications for the design of trials evaluating wound complication after IHR, as early endpoints may miss clinically relevant outcomes and underestimate the number needed to treat. Where possible,

we advocate 90-day outcomes for wound complications following IHR. Further research is needed to determine adequate end-points for the outcome of wound-related hospital readmissions.

ABSTRACT TABLE 1. SENSITIVITY OF OUTCOMES BY LENGTH OF FOLLOW-UP

	180-days	30-days		60-days		90-days		120-days	
Outcome	Total events	n	% Detected	n	% Detected	n	% Detected	n	% Detected
SSI	37	30	81.6	33	89.5	35	92.3	37	94.7
SSO	83	54	65.3	77	92.7	82	97.6	82	98.8
SSOPI	46	32	70.0	40	87.0	43	93.5	44	95.7
Readmission	30	14	46.7	23	76.7	25	83.3	25	83.3

Sensitivity for wound outcomes at 30 days, 60 days, 90 days, and 120 days, compared to the total number of events occurring up to 180 days.

Results presented as number of events (n) and the proportion of total events detected at each endpoint in percent.

4.3 INTRODUCTION

Incisional hernia repair (IHR) is associated with a high incidence of wound complications[1, 2]. These complications, which include surgical site infection (SSI) and other surgical site occurrences (SSO), can be costly, often requiring protracted wound care and additional interventions[3-5]. To evaluate interventions designed to prevent these complications, comparative-effectiveness studies rely on accurate classification of wound outcomes. When ascertainment and detection bias threaten the validity of these outcomes, comparative studies tend to overestimate the size of effect[6].

Thirty-day outcomes have frequently been used in the development of risk scores, in surgical quality surveillance, and in studies evaluating novel wound management strategies to reduce the incidence of SSI and SSO after IHR [7-9]. However, cohort studies have reported that a substantial number of deep SSIs and other SSOs occur beyond 30 days [10, 11], suggesting that this time-frame may be inadequate to capture the breadth of clinically relevant outcomes in this population

The objective of this study was to evaluate the validity of 30-day, 60-day, and 90-day wound outcomes to identify an appropriate endpoint for follow-up after IHR.

4.4 METHODS

DESIGN AND STUDY POPULATION

We performed a retrospective cohort analysis of all open IHRs performed at single university hospital from January 2016 to Dec 2019. The study was approved by the institution's Research Ethics Committee, with permission from the Director of Professional Services to access patient charts in lieu of individual informed consent. This study received no outside support or industry funding. We included all adult patients undergoing abdominal IHR. To capture the range of clinical scenarios and SSI risk, we included both emergency and elective cases, as well as contaminated and dirty cases. Primary ventral hernias were excluded, as were cases that failed to achieve primary closure of the fascia and skin at the time of surgery. Follow-up time was defined as the time of surgery to the last documented follow-up or up to 180 days, whichever was earliest.

SURGICAL TECHNIQUE

The majority of procedures were performed by one of five surgeons with a practice interest in hernia surgery, however certain emergency cases were also performed by general surgeons on call in the department. The operative approach and surgical details (including mesh, component separation, drains, tissue flaps) were selected at discretion of the operating surgeon. Skin was most commonly closed with skin clips and abdominal dressings were placed immediately after closure. Sterile dry dressing was applied in most cases, however, VAC® dressing or a PREVENA™ device (KCI, San Antonio, TX) was applied to primary closed incisions in select patients at the surgeon's discretion.

COVARIATES AND OUTCOMES

Routine demographics and comorbidities as per the Charlson Comorbidity Index (CCI) were collected. Established risk factors for wound complication after ventral hernia repair were also recorded, including smoking exposure, obesity, diabetes mellitus, chronic obstructive pulmonary disease (COPD), immunosuppression (organ-transplant recipients, recent chemotherapy, or steroids), prior hernia repairs, history of wound infection, and stoma. Surgical details included procedure duration, intraoperative complications, blood loss, the use of mesh, mesh material and position, technique of component separation, use of closed-suction drains, undermining of subcutaneous tissue (creation of skin flaps), and the use of rotational myocutaneous flaps for tissue coverage (tissue flaps). Cases were classified using the 3-level Modified Hernia Grading Scale (MHGS) proposed by Kanter et al [12]. The Ventral Hernia Risk Scores (VHRS) for SSI and SSO developed by Berger et al [13] were also calculated for each case. Hernias were labelled as “complex” as per consensus based definition by Slater et al [14].

The primary outcome was the development of an incisional SSI up to 180 days. Definition of incisional SSI was based on the Centers for Disease Control (CDC) reporting guidelines[15, 16] (Berríos-Torres, Umscheid et al. 2017, Centers for Disease 2019). In brief, this included wound events involving the deep or superficial tissues of the incision and (1) the presence of purulent drainage, (2) a positive culture in the context of localized or systemic signs or symptoms of wound infection, (3) abscess or infectious signs identified on imaging, or (4) the diagnosis of wound infection recorded by the surgical team.

Secondary outcomes included non-infectious SSOs and hospital readmissions. Non-infectious SSOs included wound dehiscence that required wound packing or VAC placement, the formation of seroma, hematoma, and enterocutaneous fistula.

DATA ANALYSIS

Statistical analysis was performed in R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria). Time-to-event analysis was performed for outcomes at 30, 60, 90 days using the Kaplan Meier method. Established risk factors and risk scores for wound complication after ventral hernia repair were evaluated using Cox-Proportional Hazards regression for the outcomes of SSI, SSO, SSOIP, and unplanned hospital readmission. The final models were selected via an exhaustive model selection procedure using the Akaike information criterion. Model assumptions were tested using Schoenfeld's test and the evaluation of Martingale residuals for continuous variables.

4.5 RESULTS

Among 264 patients undergoing ventral hernia repair (VHR) during the study period, 234 patients underwent open IHR. Median follow-up time was 102 days (IQR 37 - 264 days). Demographics data and risk factors for SSI are presented in Table 1 and surgical details are presented in Table 2. MHGS and VHRS for SSI and SSO are summarized in Table 3.

The incidence of incisional SSI was 15.8% (n=37) with a median time to SSI of 23 days (IQR 12– 30). Seven SSIs occurred beyond 30 days (18.4% of SSIs). The incidence of SSO was 35.5% (n=83), with a median time to SSO of 24 days (IQR 15 – 37) and 34.9% of SSOs (n=29) occurring beyond 30 days. Outcomes up to 180 days are presented in Table 5. All seven patients experiencing late SSI were comorbid patients who underwent complex IHR. In 21% (n=8) of all SSIs, wound infection progressed from a prior SSO occurring within 30 days.

Among 37 SSIs at 180 days, 81.6% (n=30) were diagnosed at 30 days, 89.5% (n=33) at 60 days, and 92.3% (n=35) at 90days. The sensitivity for outcomes as follow-up was extended from 30 to 60 and 90 days are presented in Table 4. Among patients experiencing a SSI or SSO, 27% (n=26) were readmitted within 180 days and follow-up to 130 days was required to detect at least 90% of these readmissions.

Kaplan Meier Curves for these outcomes are shown in Figure 2. In Cox-proportional hazards regression stratifying for technique of component separation, smoking in the last year (HR 2.76, 95%CI 1.2-6.4) and emergency surgery (HR 3.20, 95%CI 1.21-8.47) were independently associated with SSI after adjusting for hernia grade. Hazard ratios from the Cox-proportional model are presented in Table 5.

4.6 DISCUSSION

Clinical-effectiveness studies rely on accurate outcome ascertainment in the evaluation of new interventions. In this analysis of wound outcomes in 235 IHRs, a considerable proportion of SSIs and SSOs occurred beyond 30 days. Only 81% of SSIs and 65% of SSOs occurring in within the first 6 months after surgery were detected at 30 days. However, with follow-up extended to 90 days, 92% of SSIs and 95% of SSOs were detected. Only 83% of wound-related hospital readmissions were detected at 90 days, and follow-up to 130 days was required to detect at least 90% of these readmissions. These results have implication for the design of comparative-effectiveness studies of interventions to prevent SSI and SSO after IHR.

Other studies have evaluated the follow-up and natural history of wound complications after open VHR. In a retrospective evaluation of long-term wound outcomes following 632 clean hernia repairs, Baucom et al reported that 30% of all SSOs occurred after thirty days in their cohort [17]. In a review of 1635 primary and IHRs—including emergent, and contaminated or dirty cases—by Holihan et al, 7.2% of cases developed SSI, of which 17.1% percent occurred beyond thirty days [10]. Notably, no risk factors were predictive of late vs. early SSI, with late infections developing even after simple repairs of primary hernias, and in patients without significant comorbidities or risk factors. In contrast, late SSIs in our cohort occurred only among comorbid patients undergoing complex IHR. While approximately 20% of all SSIs progressed from a prior SSO, only two patients with SSIs beyond 30 days (SSI diagnosed on day 63 and 96) had developed an SSO within the first 30 days of follow-up (SSO diagnosed on day 28 and 21

respectively), suggesting that the absence of SSO in the early follow-up period does not definitively rule out the occurrence of a late SSI.

In 2013, the CDC and NHSN updated the surveillance protocols for deep surgical site infection, modifying the reporting period to 90 days for selected procedures, including herniorrhaphy [15, 18]. Superficial incisional SSIs continue to be reported up to 30 days as per CDC definitions. The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) collects outcomes up to 30 days, including SSIs[19]. Many hernia-specific registries, including the European Registry of Abdominal Wall Hernias (EuraHS) and the American Hernia Society Quality Collaborative (AHSQC) require the reporting of 30-day "early" outcomes, but also include non-clinical follow-up to detect outcomes beyond 30-days [20-23]. Similarly, the European hernia society encourages the reporting of early and late wound outcomes, distinguishing late outcomes as those occurring after 30 days. Our results support the use of late outcomes in the design of comparative-effectiveness studies evaluating interventions to prevent SSO and SSI after IHR.

The use of incisional negative pressure wound therapy (iNPWT) in high-risk patients undergoing VHR has been the focus of several retrospective and non-randomized prospective cohort studies, in which iNPWT and similar wound management strategies have demonstrated effectiveness [7, 24-26]. Most studies used CDC definitions for SSI outcomes, although the timeframes defining these outcomes were often not explicitly stated or occasionally conflicted with CDC definitions.

We recently reported results of a retrospective matched cohort study favouring an effect of iNPWT in the prevention of deep and superficial SSI after complex IHR at 30 days. The estimated effect was consistent with prior studies of iNPWT in this high-risk population, however the effect was no longer significant with follow-up up to 180 days. To our knowledge, only a single randomized controlled trial has since been published evaluating iNPWT after VHR [27]. This RCT supported an effect of iNPWT in

reducing SSI, but only reported outcomes up to 30 days and was at risk of ascertainment bias because outcome assessors were not blinded to the treatment status of the participants. At least another two prospective randomized trials are registered or underway [28, 29]. These include a study with 30-day wound outcomes, and a study with 3-month wound, quality of life, and cost outcomes. Based on the results of the present study, as well as the others mentioned above [10, 17], the appropriate follow-up duration should be at least 90 days, and it would be interesting for these trials to report effectiveness at the different follow-up timepoints to evaluate for differential detection bias due to early end-points. Appropriate follow-up for hospital readmission may be longer still, perhaps beyond 120 days. While not within the scope of this study, further research could evaluate the length of follow-up needed to capture at least 90% of wound-related hospital readmissions after incisional hernia repair.

Our study is limited by its retrospective design and lack of prospective and systematic follow-up beyond routine clinical care. There may be ascertainment bias, as patients who do not experience a wound complication may have less follow-up, as many patients are followed-up as needed on an outpatient basis. Our institution services a large geographical area, and there may be patients that were diagnosed outside our centre. However, given the complex nature of many of these patients and the practice patterns in the province of Quebec, these patients would have likely been transferred back for definitive management. With only 37 SSI events in our cohort, we limited covariates in our regression model to the Modified Hernia Grading Scale (MHGS) and a small subset of clinically relevant variables or modifiable risk factors. We also noted a change in clinical practices during the study period, with a growing preference for component separation with transversus abdominis release versus anterior component separation. Regression models were stratified by technique of component separation to account for differences between these groups and to comply with the assumptions of proportional hazards.

4.7 CONCLUSION

A considerable proportion of SSIs occurred beyond 30-days after IHR. A 30-day SSI outcome detected only 81% of SSIs occurring within 6 months of IHR, however sensitivity improved to 92% by 90 days of follow-up. Early endpoints may miss clinically relevant outcomes after IHR and studies without longer follow-up should be interpreted with this limitation in mind. These results have implications for the design of trials evaluating interventions to prevent SSI/SSO after IHR. In the design of comparative effectiveness studies, early endpoints may underestimate the number needed to treat and overestimate required sample sizes. We advocate at least 90 days of follow-up for these outcomes after IHR.

4.8 TABLES AND FIGURES

FIGURE 1. FLOW CHART OF PARTICIPANT SELECTION

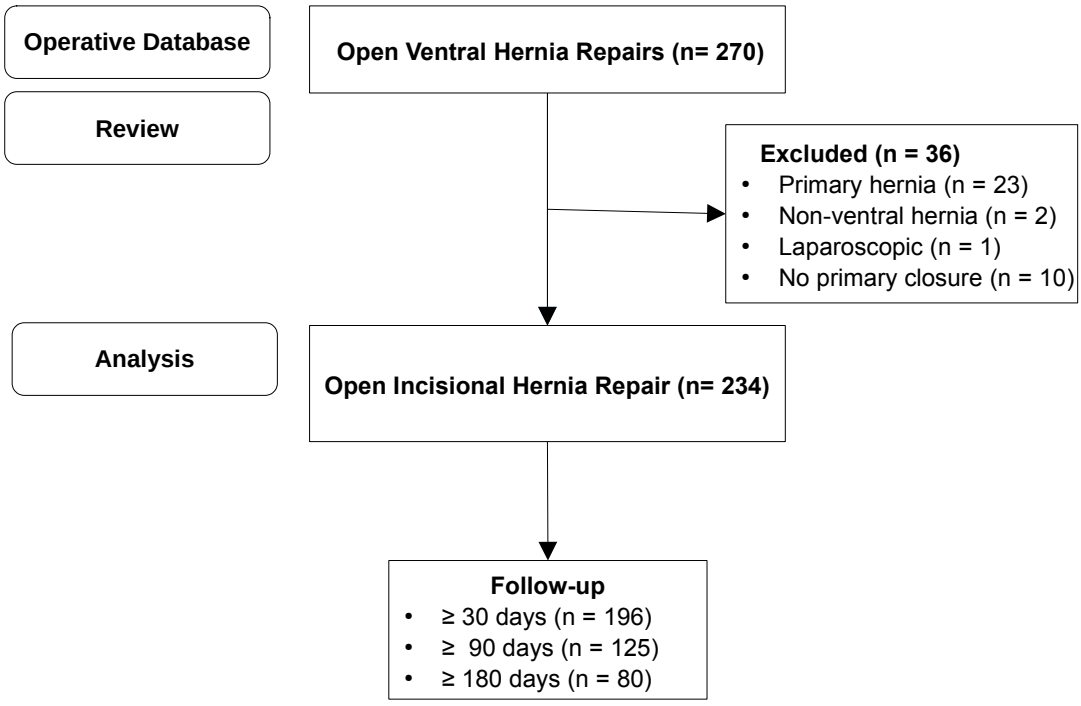


TABLE 1. PATIENT CHARACTERISTICS

	Total (N=234)
Age, years	60 (51, 68)
Female	119 (50.6%)
BMI, kg/m^2	30 (27, 35)
BMI > 30 kg/m^2	110 (47.0%)
ASA Class > 2	115 (49.1%)
CCI > 2	93 (39.7%)
Diabetes Mellitus	47 (20.1%)
Smoking in year prior	35 (15.0%)
Smoking actively	9 (3.8%)
Immunosuppressed	14 (6.0%)
Prior Hernia Repair	62 (26.5%)
Prior Wound Infection	27 (11.5%)
Existing or New Stoma	5 (2.1%)

Result presented as 'Median (IQR)' for continuous variables and 'n (percent)' for categorical variables.

BMI = body mass index; ASA Class = American Society of Anesthesia Classification; CCI = Charlson Comorbidity Index.

TABLE 2. SURGICAL DETAILS

Emergency Surgery	19 (8.1%)
Procedure Duration, minutes	131 (66, 252)
Contamination Class ≥ 2 [a]	30 (12.8%)
Estimated Blood Loss, mL	100 (0, 250)
Component Separation	
Posterior	41 (17.5%)
Anterior	23 (9.8%)
None	170 (72.6%)
Mesh Used	203 (86.8%)
Mesh Material	
Parietex Progrip™	156 (76.1%)
Parietex™ Composite	34 (16.6%)
Ventralex	4 (2.0%)
Gore® Bio-A®	5 (2.0%)
Vycril®	6 (2.9%)
Other	1 (0.5%)
Mesh Position	
Intraperitoneal	42 (20.7%)
Extraperitoneal	82 (40.4%)
Onlay	76 (37.4%)
Mixed	3 (1.5%)
Use of closed suction drains	136 (58.1%)
Creating of Skin flap	87 (37.2%)
Plastic Surgeon	29 (12.4%)
Tissue flaps	8 (3.4%)

Result presented as 'Median (IQR)' for continuous variables and 'n (percent)' for categorical variables.

[a]Contamination class >2 indication clean-contaminated, contaminated, or dirty procedures following Centers for Disease Control definitions.

TABLE 3. RISK SCORE

MHGS Grade	
Grade 1	75 (31.2%)
Grade 2	129 (55.1%)
Grade 3	31 (12.8%)
VHRS for SSO[a]	
I (0-1 points)	137 (58.5%)
II (2-4 points)	68 (29.1%)
III (4-15 points)	29 (12.4%)
VHRS for SSI[b]	
I (0 points)	157 (67.1%)
II (2-3 points)	43 (18.4%)
III (4 points)	8 (3.4%)
IV (5-10 points)	20 (8.5%)
V (11-16 points)	6 (2.6%)

Result presented as 'Median (IQR)' for continuous variables and 'n (percent)' for categorical variables.

MHGS = Modified Hernia Grading Scale; VHRS = Ventral Hernia Risk Score; SSO = surgical site occurrence; SSI = surgical site infection. VHRS for SSO and b VHRS for SSI are categorized into 3 and 5 risk groups, representing increasing risk.

TABLE 4. SENSITIVITY OF OUTCOMES BY LENGTH OF FOLLOW-UP

	180-days	30-days		60-days		90-days		120-days	
Outcome	Total events	n	% Detected	n	% Detected	n	% Detected	n	% Detected
SSI	37	30	81.6	33	89.5	35	92.3	37	94.7
SSO	83	54	65.3	77	92.7	82	97.6	82	98.8
SSOPI	46	32	70.0	40	87.0	43	93.5	44	95.7
Readmission	30	14	46.7	23	76.7	25	83.3	25	83.3

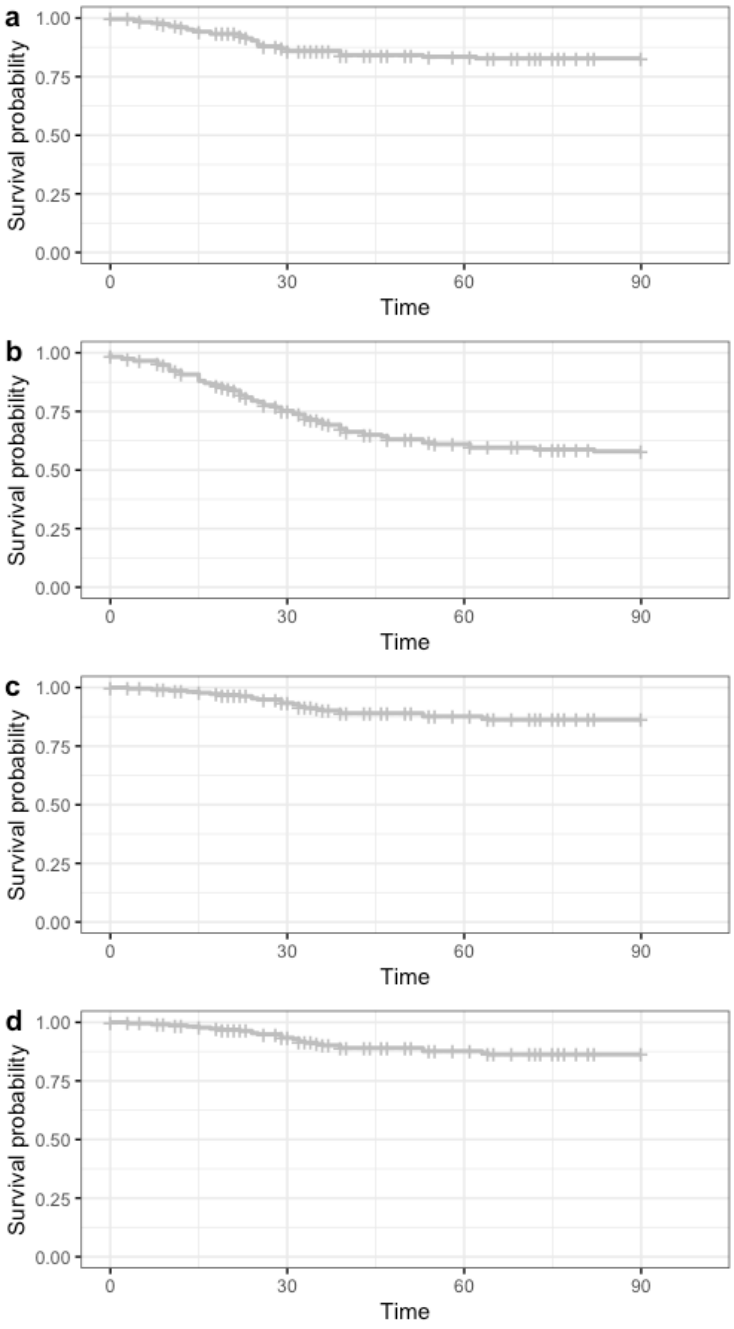
Sensitivity for wound outcomes at 30 days, 60 days, 90 days, and 120 days, compared to the total number of events occurring up to 180 days. Results present as number of events (n) and the proportion of total events detected at each endpoint in percent.

TABLE 5. COX PROPORTIONAL HAZARDS MODELS FOR SSI, SSO, SSOPI AND READMISSION

	SSI		SSO		SSOPI		Readmission	
Characteristic	HR[1]	95% CI[1]	HR[1]	95% CI[1]	HR[1]	95% CI[1]	HR[1]	95% CI[1]
MHGS								
Grade 1	—	—	—	—	—	—	—	—
Grade 2	0.79	0.19, 3.29	0.81	0.37, 1.75	1.02	0.30, 3.55	0.81	0.37, 1.75
Grade 3	1.25	0.28, 5.66	1.57	0.68, 3.62	1.95	0.53, 7.26	1.57	0.68, 3.62
Smoking Exposure	3.49	1.47, 8.33	1.00	0.51, 1.97	2.66	1.24, 5.70	1.00	0.51, 1.97
Obesity	2.82	1.05, 7.59	1.63	0.87, 3.06	2.31	0.99, 5.37	1.63	0.87, 3.06
Emergency Procedure	3.25	1.21, 8.75	0.74	0.29, 1.88	1.77	0.65, 4.82	0.74	0.29, 1.88

Relative Hazards estimated from a Cox-Proportional Hazards Models for the outcomes of surgical site infection, surgical site occurrence, surgical site occurrence requiring procedural intervention, and hospital readmission up to 180 days. Models are stratified by technique of component separation, adjusting for Modified Hernia Grading Scale, smoking exposure in the last year, and surgical urgency. SSI = surgical site infection, SSO = surgical site occurrence, SSOPI = surgical site occurrence requiring procedural intervention, HR = Hazard Ratio, CI = Confidence Interval, MHGS = Modified Hernia Grading Scale.

FIGURE 2. KAPLAN MEIER CURVES FOR SSI, SSO, SSOPI, READMISSION



Kaplan Meier curves showing cumulative probability of follow-up up to 90-days without **A** surgical site infections (SSI), **B** surgical site occurrence (SSO), **C** surgical site occurrences requiring procedural intervention**, D** hospital readmission for wound-related complications.

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CHAPTER 5: DISCUSSION

5.1 GENERAL FINDINGS

This thesis investigated the effectiveness of iNPWT after complex IHR and explored the validity of 30-day wound outcomes compared to longer follow-up after IHR.

In Manuscript 1, we presented the evaluation of iNPWT after complex IHR at our institution in a matched cohort study. iNPWT was associated with a decreased incidence of incisional SSI at 30 days. These results were consistent with prior studies and supported the effectiveness of iNPWT in preventing SSI in this population. In the supplemental materials included with Manuscript 1, we showed the results of a meta-analysis of studies identified in a recent systematic review (34), with the addition of our study and two others that had since been published (77,78,80). The pooled results were consistent with a decreased incidence of SSI among patients receiving iNPWT compared to SSD. Although these studies were limited by their retrospective or non-randomized designs, and by heterogeneity in patient populations, operative techniques, and other procedural details, they represented the best available evidence for the use iNPWT in IHR until the recent publication of a RCT published during the preparation of this thesis (81).

Manuscript 1 also reported late outcomes occurring beyond 30 days, as recommended by the European Hernia Society. At 180 days of follow-up, the association between iNPWT and decreased SSI incidence was no longer observed. Many of the prior studies on this topic also had a primary outcome of SSI up to 30 days, which prompted us to consider that a substantial number of clinically relevant outcomes may have been omitted as a consequence 30-day endpoints. Prior cohort studies suggested that wound outcomes do occur beyond 30 days after IHR, and in manuscript 2, we sought to examine the validity of wound outcomes at various lengths of follow-up. We assessed the validity of wound complications at 30 days compared to 60-day, 90-day, and 180-day endpoints. A 30-day endpoint detected only 81% of SSIs,

65% of SSOs, 70% of SSOPIs, and 46.7% of wound-related readmissions occurring within 6 months of IHR. These results indicated that 30-day endpoints likely omit clinically relevant wound complications after IHR, and support the reporting of wound outcome to at least 90 days in comparative effectiveness studies of interventions to prevent of SSI. An adequate length of follow-up for wound-related readmissions may be longer still, perhaps beyond 120 days, and further research is needed to evaluate this outcome.

5.2 SIGNIFICANCE OF FINDINGS

On Nov 12th 2020, the first RCT evaluating iNPWT in IHR was published in the in Annals of Surgery (81). The trial involved 136 patients with a midline incisional hernia of at least 4cm in width, repaired electively using a Rive-Stoppa technique, transversus abdominis release (TAR), or anterior component separation (ACS). After wound closure, patients were randomized to receive either a single-use NPWT device (PICO device) or a standard sterile dressing. The incidence of SSO and SSI at 30 days was significantly higher in the SSD group compared to iNPWT (SSO 29.8% vs 16.6%, SSI 8% vs 0%). The use of 30-day outcomes and the lack of blinding among outcome assessors remain important limitations to this trial. If clinical follow-up to 90 days is available for participants, reporting these outcomes to supplement these results would be interesting.

To our knowledge, no other RCTs have been published evaluating iNPWT in IHR. Two industry-sponsored trials were terminated in 2018, one reporting an insufficient incidence of SSI on interim analysis to achieve planned statistical power and the other due to the primary investigator changing institutions without transferring the trial. Although these were terminated early and are limited by the use of 30-day endpoints for wound outcomes, these trials have randomized a total of 131 participants to iNPWT vs standard sterile dressings, and it would be important to include their results in future systematic reviews and meta-analyses if available.

There are at least two active RCTs registered with clinical trials.gov. A search of the European, International, and the Cochrane-databases using the terms “hernia” and “negative pressure wound therapy” did not identify any other registered or ongoing trials. The earlier of these trials, by Blewett et al, is expected to be completed by July 2022. This multicentre RCT will include 110 patients undergoing elective or emergent VHR with factors for SSI and a defect size of at least 3cm. Participants will be randomized to iNPWT or SSD and followed for 90 days for a composite outcome of SSI, hematoma, seroma, wound dehiscence, hernia recurrence, and enterocutaneous fistula. Quality of life (QoL) and a patient-reported measure of abdominal wall function will be assessed up to 3 months post-operatively. Cost per quality-adjusted-life-year will be estimated based on the costs associated with length of hospital stay, complications, and interventions. The later of the two trials, by Latifi et al, is expected to be completed by February 2023. This trial randomizes 170 patients undergoing complex abdominal wall reconstruction (synonymous with complex VHR) or other major laparotomies at high risk of wound complications. Grossly contaminated or dirty procedures will be excluded. The primary outcome will be surgical site infection at 30 days, with secondary outcomes of hospital readmissions and cost at 30 days.

As pointed-out in prior systematic reviews, it will be important for subsequent RCTs to ensure the adequate blinding of outcome assessors (62,82). The use of shared outcome definitions specific to the hernia literature—including SSO, SSI, and SSOPI—will also be useful to minimize heterogeneity in future meta-analyses. Reporting late-outcomes up to at least 90 days will also add to the value of subsequent trial, especially considering that a substantial proportion of SSI and SSOPI after IHR occur beyond 30 days. Capturing these events should also add to the robustness of cost-analyses that could be performed alongside these trials.

The per unit cost of PREVENA has been reported at $495 USD, although this may vary by model and by location. Cost remains an important limitation to the use of iNPWT. A recent systematic review identified only two cost-effectiveness studies using RCT data (82). These studies were limited to

caesarean sections and hip and knee replacement surgery (83,84). Both studies concluded that iNPWT was likely cost-effective compared to standard sterile dressing, however these were derived from low to moderate evidence from single RCTs.

In IHR, Chopra et al used pooled results from retrospective cohort studies to estimate that iNPWT would be cost-effective when SSI incidence was greater than 13.5% and cost-saving when greater than 16% (85). While this would include high-risk patients undergoing complex incisional hernia repair, this estimate is limited by very low quality of the evidence. Robust cost analyses and QoL data should be included in future cohort studies from hernia registries as well as RCTs evaluating iNPWT.

Although RCTs are still underway, it is likely that many surgeons and institutions are already using iNPWT routinely. The ongoing evaluation of iNPWT and other interventions in the context of hernia-specific surgical quality surveillance will be of great value moving forward. VHR is a rapidly developing field that, in the face of high rates of SSO and hernia recurrence, has seen a rapid evolution in operative techniques and surgical technology. While experts agree on certain guiding principles of complex hernia repair, surgeons must weigh the advantages and disadvantages of a variety of surgical options that have yet to be assessed comprehensively in high quality RCTs.

Hernia specific registries have been developed and have been used increasingly in surgical research. These registries include the Americas Hernia Society Quality Collaborative (AHSQC), the European Registry of Abdominal Wall Hernias (EuraHS), and Danish Hernia Database (38,86,87). Wide participation in such registries is likely to provide opportunities to prospectively evaluate emerging and “state-of-the-art” interventions prior to RCTs. Another benefit of large registry data will be the development of high-performing risk models for incisional hernia repair that can be used to control baseline risk factors in cohort studies more robustly. The MHGS was developed in a cohort of less than 300 patients with a c-statistic of only 0.64 on external validation (47,88). The highest performing risk score, the HW-RAT (c-

statistic 0.71), was developed using NSQIP data from a total population or more than 60,000 ventral hernia repairs, although it remains to be externally validated (88). The performance of models from broader surgical databases—such as the ACS-NSQIP Universal Surgical Risk Calculator Model (c-statistic 0.817) (89)—suggests that hernia-specific models are likely to continue to improve as these registries grow. However, mechanisms to reliably detect wound outcomes beyond 30 days and other long-term outcomes such as hernia recurrence, will be important components of registries for effective clinical research.

5.3 DISCUSSION OF METHODOLOGY

A detailed discussion of the study designs and the limitations of this work is presented to supplement manuscripts 1 and 2.

5.3.1 STUDY DESIGNS

The studies presented in this thesis were performed in the context of a clinical audit of IHRs at a single university hospital over a 4-year period. In September 2018, an iNPWT dressings were made widely available to surgeons at our institution and were used at their discretion. This provided an opportunity to perform an audit of outcomes after IHR and evaluate the effect of iNPWT in preventing SSI in this population, while addressing certain biases that had not been accounted for in prior studies.

In a resource-conscious setting, surgeons are encouraged to use costly resources judiciously—that is, in patients who are likely to benefit the most. In the case of iNPWT, these would include comorbid patients undergoing procedures with a high risk of SSI. Below a certain threshold in SSI risk the number needed to treat will be high and the benefit of iNPWT is unlikely to justify its cost compared to standard sterile dressings. As SSI risk increases, it may also eventually breach a risk-ceiling beyond which iNPWT will no longer be effective. We suspected that only a subset of patients were targeted for this intervention and that a direct comparison of concurrent cases was likely to introduce confounding by indication, due to

the use of iNPWT at the discretion of the surgeon. At our institution iNPWT was most frequently used in patients with comorbidities and potentially contaminated wounds undergoing large incisional hernia repairs that involved extensive tissue dissections and mesh implantation. This observation supported our assumptions and our choice of our study population.

The details of our study design were informed by published recommendations regarding the use of iNPWT, established risk factors for SSI after IHR, and the clinical knowledge of our investigators. We identified several potential sources of bias and incorporated these into a directed acyclic graph (DAG), which is presented in Figure 2. Although this DAG is a simplification of the mechanisms and risk factors involved in the development of SSI after IHR, controlling for certain elements of surgical technique,

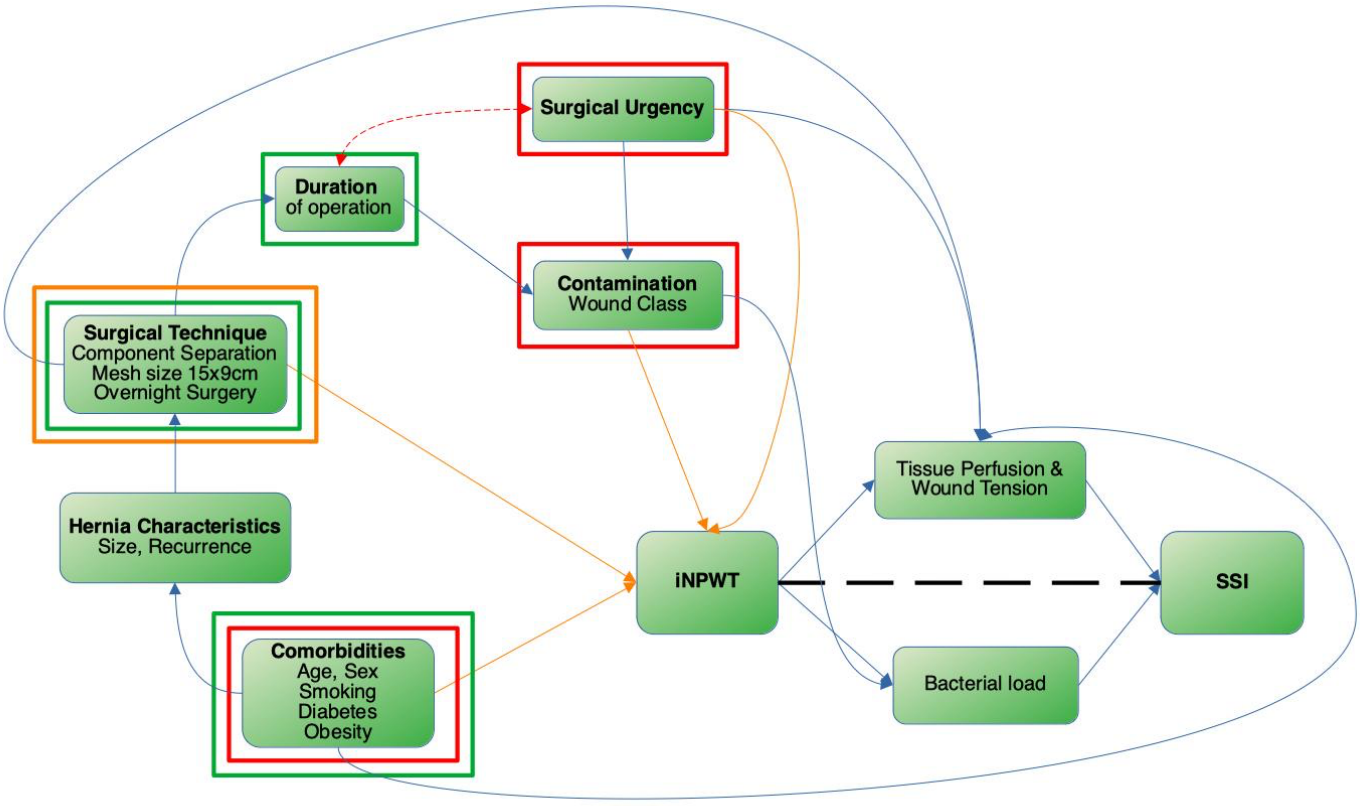

Figure 2 - A directed acyclic graph of risk factors and mediators affecting incisional negative pressure wound therapy (iNPWT) use and outcomes of SSI. Factors have been grouped where appropriate for simplicity. Boxes indicate factors controlled for by study design, where colour indicate the method (orange=restriction, red=matching, green=regression). Orange arrows indicate factors influencing the surgeon's preference to employ iNPWT. Blue arrows indicate relationship between risk factors and surgical site infection (SSI) via their respective mechanism or mediators.

patient-related factors, surgical urgency, and wound contamination was likely to account for much of the confounding we identified. We chose to (1) restrict our study to "complex" incisional hernia repairs, (2) match patients receiving iNPWT to historical controls based on factors that were likely to inform a surgeon's decision to use an iNPWT, and (3) perform regression analysis to address salient differences between groups that remained after matching.

To demonstrate the potential impact of confounding introduced by the use of iNPWT at the surgeon's discretion, we directly compared iNPWT to SSD in concurrent cases performed after Sept 2018, when iNPWT was available. The results are presented in a supplemental appendix to Manuscript 1. In that period, 60% of patients received iNPWT. Compared to those receiving SSD, these patients had higher BMIs, prevalence of diabetes, degrees of contamination, rates of component separations, risk scores for surgical site occurrences, and longer procedure durations. No crude difference in SSI outcomes was present between these groups, however, after adjusting for the same covariates used in our matched analysis, iNPWT was associated with a significant fewer SSIs (adjusted RR 0.21, 95%CI [0.08, 0.59]). These results suggested that a considerable amount of bias was present in the direct comparison of concurrent cases. However, without matching, this approach was also likely to exaggerate the effectiveness of iNPWT due to unmeasured bias from surgeons successfully selecting patients who were likely to benefit from the intervention.

5.2.2 ANALYSIS

Coarsened exact matching

In Manuscript 1, we used coarsened exact matching (CEM) to create balanced groups for comparison using risk factors that were routinely collected and readily available at the time of surgery: age, sex, American Society of Anesthesiologists (ASA) class, degree of wound contamination, and surgical urgency. The goal of matching was to create a control group of recent historical controls who would have likely received the intervention had it been available. Age and sex, while not identified in the

MHGS, are both risk factors for SSI (89). The ASA is a risk score that reflects the patients susceptibility to SSI and other complications based on the presence and the severity of physiologic derangements (90). Wound contamination class and surgical urgency are both well-established risk factors for SSI (91).

Similar to other matching procedures, CEM is a non-parametric method used to control for imbalances between treatment and control groups based on *a priori* choices by the investigators. (92,93). CEM also allows subsequent regression analyses to be performed, and compared to propensity score matching, CEM does not require iterative balance checking and re-matching, and may produce less varied and less biased estimates of causal effect, avoiding clinically unlikely causal-effect relationships driven by model-dependence (94).

Logistic Regression for 30-day Outcomes

In Manuscript 1, we used logistic regression to control for imbalances in baseline risk factors in our estimation of iNPWT effect on SSI incidence at 30 days. Logistic regression is a method used to control for confounding and to identify risk factors for SSI, including in the development of many hernia-related SSI risk scores (48,51,88). Logistic regression calculates odds ratio as an estimates of effect size for the intervention of interest. However, when effect sizes are large and events are relatively common, odds ratios are likely to represent an overestimate of the true effect size. For this reason, we chose to estimate the relative risk from the odds ratio using the delta method. The limitations of logistic regression are discussed further below.

Survival Analysis and Cox Proportional Hazards Regression

For late outcomes, we presented the results of time-to-event analysis for late outcomes using the Kaplan-Meier method and the log-rank test to compare the iNPWT and SSD groups. Kaplan-Meier curves provide a clear and familiar visual representation of wound events occurring over time. A log-rank test is a non-parametric test that compares survival distributions but cannot estimate the effect size or

account for confounding. We evaluated the impact of iNPWT on the hazard of SSI using a Cox proportional hazards model to adjust for salient clinical differences between the matched groups. Cox-proportional hazards models are a semi-parametric method to estimate the effect of multiple variables on the hazard rate. In this context, the hazard was the risk of a given patient experiencing a wound infection in the upcoming interval of time, provided they have yet to develop a wound infection. We tested the assumption of proportional hazards based on a visual assessment of Kaplan-Meier curves and the Schoenfeld's test. In manuscript 2, we stratified our model by technique of component separation to address a violation of proportional hazards.

Choice of regression covariates

We selected covariates for logistic regression and cox-proportional hazards regression based on a priori knowledge of risk factors summarized in a DAG presented in Figure 2. Our choice to include an established risk score in our models was influenced by the relatively few total events (37 SSI, 83 SSO, 46 SSOPI, 21 readmissions) and the limited number of covariates we could include in our model. In Manuscript 1, salient differences between groups after matching also influenced the choices of covariates. Multiple comorbidities have been shown to have a combined effects on the risk of SSOs after IHR (95), and although certain elements of the MHGS or VHRS for SSI may be redundant in a model including smoking exposure, we did not anticipate or observe any significant collinearity as a result. In fact, the failure of many risk scores to account for the interaction of multiple comorbidities has been a source of criticism regarding these classification systems (88).

5.4 LIMITATIONS

5.4.1 DEFINITIONS OF COMPLEX HERNIA REPAIR

We used established consensus definitions to identify "complex" hernia repairs (25). However, certain hernia characteristics were not reliably available in the medical record. For example, hernia size was not

routinely recorded in the operative note or clinic notes, and abdominal imaging—from which defect size could be measured—was not available for all patients. Rather than excluding cases with missing data or imputing missing values using statistical methods, we determined hernia complexity based on the details available in the surgeons' operative notes. Guided by the clinical knowledge of our investigators, we used a combination of mesh size greater than 15x9cm, overnight admission, and component separation to restrict our source population prior to matching in Manuscript 1.

5.4.2 OUTCOME DEFINITIONS

The outcomes reported in Manuscript 1 and 2 comply with definitions proposed by recent calls for investigators to standardize the reporting of wound outcome after VHR (40). After a review of the literature demonstrating considerably variability in highly cited publications in the VHR literature, Haskins et al proposed the used of the terms *SSI*, *SSO*, and *SSO requiring procedural intervention* (SSOPI), which follow definitions from the CDC, the VHWG, and the Abdominal Core Health Quality Collaborative (ACHQC) respectively. We chose a composite primary outcome of deep or superficial incisional SSI, as these were likely to influenced by iNPWT's proposed mechanisms of action. However, we also reported itemized tables of all SSIs, SSOs and wound interventions.

Even with a shared terminology, the reporting of SSOs likely varies across studies. In part, this is likely due to ambiguity around the severity of complications (79). Wound dehiscence, for example, encompasses partial to complete disruptions of a wound. A partial dehiscence may require only a short regimen of wound-packing while a more significant dehiscence—along a wound's entire length, for instance—may require a prolonged course of wound care and VAC therapy. While these scenarios may be classified similarly, they have different implications for resource use, healthcare costs, and quality of life. Reporting SSOPI has been one strategy to address this ambiguity and identify severe outcomes that required an intervention. Other outcomes such as *time to wound closure, quality of life*, *pain scores*, and patient-reported measures of abdominal wall function may also prove to be valuable, however these are

often more resource-intensive to collect. While some multi-institutional registries for VHR, such as the ACHQC, collect long-term SSO and patient-reported outcomes via email and telephone contact (87), collecting more detailed outcomes is often prohibited by the burden such reporting requirements would impose on participating surgeons and institutions.

5.4.3 LOSS TO FOLLOW-UP

In Manuscript 1, eleven of 125 patients (8.8%) undergoing complex incisional hernia repair were not followed up to 30 days post-operatively. We opted to exclude these patients and perform an analysis to measure the impact of excluding these cases, which is presented in the supplemental material accompanying manuscript 1. Two of the patients received iNPWT, nine received SSD, and none of them had a documented SSI by the end of their follow-up. While patients with complications are likely to seek care with their surgeon, we could not rule out that patients had sought care at another institution. Applying the overall SSI incidence of 17% to these ten patients, we anticipated a maximum of two SSI events in this group. We included then ten cases lost to follow-up and reclassified two patients receiving iNPWT as having developed a composite SSI within 30 days. This approach was meant to simulate a worst-case-scenario, whereby loss-to-follow-up introduced the maximum expected bias in favour of the null hypothesis. Even in this simulation, iNPWT appeared to be associated with a lower incidence of SSI (RR 0.45, 95% CI[0.20 – 1.01]). These results suggested that the findings in Manuscript 1 were likely valid despite an 8.8% loss to follow-up.

5.4.4 LOGISTIC REGRESSION

We used logistic regression to control for imbalances between treatment groups after matching. However, logistic regression is often limited in the study health-care acquired infections as it fails to account for exposure over time and requires a binary classification around an often arbitrary point in time (96).

A frequently used end-point for reporting SSI is 30 days, which likely follows from the definition of superficial SSI by the CDC (91). Similar to the ACS-NSQIP's 30-day outcomes, these definitions were developed in the context of quality surveillance programs, and chosen partly for the convenience of data collection (97). A considerable number of SSIs are known to occur after 30 days in IHR (98). In fact, in Manuscript 2, the median time-to-SSI was 23 days, with 19% of SSIs occurring after 30 days. These late events were almost exclusively deep incisional SSIs occurring in patients with complex hernias who had first experienced a non-infectious SSO. These results suggest that the super-infection of seromas, hematomas, and dehisced wounds may be a common mechanism in the development of SSIs that is poorly captured by a 30-day endpoint. As well, these SSIs may be associated with exposures occurring after surgery that are traditionally considered outcomes—i.e., length of hospital stay, time to wound closure, and procedural interventions. If iNPWT influences both the incidence and the timing of SSI, then inferences based on 30-day outcomes may be misleading.

Still, 30-day SSI outcomes are frequently reported in the literature and provide a simple and convenient comparisons across research studies and quality surveillance data. After comparisons of risk stratification methods to predict 30-day surgical outcomes, leaders at the ACS-NSQIP continued to base their models on logistic regression, after concluding it was simpler and produced nearly identical estimates compared to more advanced mathematical models (97).

As well, logistic regression will produce similar estimates to survival analysis provided that the outcomes are rare and effect sizes are small enough. However, we observed an overall SSI incidence of 14% after IHR, and iNPWT was associated with a 40% reduction in SSI incidence. In this circumstance, the odds ratios estimated by logistic regression would likely overestimate the true effect. Although negative binomial regression or a Poisson regression could be used to most accurately estimate the relative risk and risk difference (99,100), these models had failed to converge, and we chose to proceed with logistic regression analysis and estimation of the relative risk using the delta method.

5.4.5 SURVIVAL ANALYSIS AND INDEPENDENT CENSORING

The results of survival analysis in the context of this clinical audit should be interpreted cautiously. Survival analysis makes several assumptions, including the independence of observations, independence in censoring from the outcome of interest, and the uniformity probability of survival within the time intervals between events. These assumptions will often be met in the context of prospective cohort studies with systematic follow-up of all participants. In the context of a retrospective clinical audit, follow-up may vary depending on the surgeon's discretion, and may challenge the assumption of independent censoring in particular.

In Manuscripts 1, patients were censored at their last day of documented follow-up by the surgical team, up to a maximum of 180 days. The administrative censoring at 180 days equated to non-informative right-censoring. However, surgeons often follow patients actively until their wound has healed and the foreseeable risk of complications is low. Beyond this point, patients are instructed to present to the emergency department or to return to clinic only as needed. Thus, patients who are no longer actively followed are unlikely to experience a wound complication. Although most patients do reliably return to the emergency department or to clinic, some proportion are truly lost to follow-up and seek care at another institution or with another provider after experiencing a complication. We suspect that loss to follow-up was more prevalent among our patients from Northern Quebec. However, there were no differences in length of follow-up between intervention groups or based on place of residence. Any bias introduced by varying length follow-up should have been minimal.

However, censoring patients based on their last date of documented follow-up likely led to less precise estimates of hazards ratios for variables included in our model. An alternative approach would have been to define loss to follow-up at a pre-determined time after the last clinical encounter (101). A potential advantage of censoring at the last surgical follow-up, however, is that discharge from clinic may mark the end of a patient's time-at-risk for wound complication via mechanisms that are plausibly

related to iNPWT. Once a wound is healed without any deviation from a normal recovery, it is unlikely that the use of iNPWT could influence to any subsequent wound outcomes. This assumption is supported by results of Manuscript 2, in which late outcomes occurred uniquely among patients with complicated post-operative courses.

Approaches have been developed to measure the magnitude and direction of bias introduced by informative or random censoring, including inverse probability weighting (102,103) and multiple imputation (104). However, the challenges regarding independent censoring in this study are likely best addressed by prospective trials with systematic follow-up for all participants.

CHAPTER 6: CONCLUSION

The objectives of this thesis were to (1) evaluate the use of iNPWT to prevent SSI after complex IHR, and (2) assess the validity of wound outcomes at 30, 60, and 90 days to determine the optimal length of follow-up for these outcomes after IHR. In manuscript 1, we presented the results of a retrospective matched cohort study that found a decreased incidence of SSI among patients receiving iNPWT compared to a group of matched historical controls who received standard sterile dressing. In Manuscript 2, we reported that nearly 20% of SSIs occurring within 6 months of IHR were missed when using 30-day outcomes after IHR. Only 8% of these SSIs were missed with follow-up to 90 days. These results support the use of 90-day outcomes after incisional hernia repair. Together, the findings in this thesis support the ongoing evaluation of iNPWT in RCTs and quality surveillance programs with reporting of 90-day wound outcomes.

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