



## Research Article

# Risk factors and outcomes for early returns to the operating room following abdominal wall hernia repairs

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## ABSTRACT

**Background:** Risks of re-operation in ventral hernias in non-American populations and recurrence have been studied extensively. However, data on early risk factors for reoperation in North America are still lacking. The most recent NSQIP study, analyzing risk factors for reoperation of ventral hernias was extracted from 2005–2008 data. Since then, there have been major advances in ventral hernia repair techniques. Here, we identify risk factors and indications for re-operation within 30 days.

**Methods:** NSQIP ACS data from 2020–2022 were used in our analysis. Additional procedures that posed significant morbidity and mortality were excluded. Risk factors were analyzed with univariate and multivariable models to determine association with re-operation within 30 days. ICD10 codes for re-operation were also analyzed.

**Results:** Of 56,260 patients, 2.38 % returned to the OR within 30 days. Higher ASA, male gender, surgical site infection (SSI), smoking, ascites, age group > 70, dialysis patients, open surgeries and dehiscence were significantly associated with re-operation whereas outpatient surgery was protective in univariate and multivariable models ( $p < 0.01$ ). The most common indications for re-operation were surgical site occurrence (SSO) and recurrence of hernia. Mortality was significantly higher in the reoperation group, 3.29 %, compared to those patients that did not require early reoperation (0.36 %,  $p < 0.01$ ).

**Conclusions:** Mortality and early reoperation rates have decreased in the past decade in the U.S, which could be attributed to advancement in ventral hernia repair techniques. Our analysis of risk factors for reoperation supports findings in the broader literature. This study also suggests that SSO and recurrence of hernia are leading diagnoses for early reoperation.

## Introduction

Ventral hernias are characterized by an abnormal protrusion of intestine or other abdominal contents through a weakness in the anterior abdominal wall. The prevalence of ventral hernia in the United States has increased over the years, driven by the ongoing obesity epidemic and aging population [1]. As a result, larger hernias that are more challenging to treat surgically are also becoming more prevalent [2]. Ventral hernia repairs are among the most common procedures performed by general surgeons, but re-operation following recurrence is devastating to the patient and adds a lot of direct and indirect costs. Significant efforts have been made in the field of hernia surgery to understand risk factors for complications and advance techniques to optimize outcomes. Known risk factors for recurrence include smoking, incarcerated hernia, increased body mass index (BMI), prior hernia

repairs, surgical site infection (SSI), vertical incision, larger hernia defect size, and open wound [2,3,21–23].

Despite recent advances in surgical techniques, availability of more effective modern prosthetic materials, and an increased understanding of ventral hernias, rates of ventral hernia recurrence and re-operation are to range from 10–50 % and 2–6 %, respectively [4,20–22]. The most recent large data ventral hernia study in the U.S. was a NSQIP study from 2005–2008, analyzing risk factors for early and late reoperation of ventral hernias. Since then, there have been major advances in ventral hernia repair techniques. For example, the retro-muscular Rives-Stoppa technique, which was technically demanding in the first laparoscopic attempts, has gained popularity in recent years with the introduction of the “enhanced” or “extended” view total extra-peritoneal (eTEP) approach [5,6]. Additionally, the transversus abdominis release (TAR) creates myo-fascial advancement, which aids

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in the repair of larger defects [7,8]. Despite these recent advancements, there are still significant risk factors involved with ventral hernia repair re-operation, such as SSI, and others that were mentioned earlier.

Outside of the US, there are studies detailing the discrepancies in risk factors of ventral hernia re-operation. In the recent large data studies from the Nordic countries, women, bimodal distribution of age < 50 and > 80, patients with cirrhosis were associated with re-operation, mostly in the long term up to a decade. More recently in an eleven-year cohort study in Sweden from 2004–2014, male gender, older age, and concurrent surgery were risks associated with re-operation within 30 days. While these findings are valuable, there is yet to be an up-to-date study investigating these risk factors in the US using a large, national database, analyzing short term risk factors for re-operation. Early re-operation tends to be more life threatening compared to late re-operation. Here, risk factors for re-operation within 30 days and indications for early re-operation were analyzed.

Methods

The participant user forms from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) data from 2020–2022 were analyzed, and IRB exemption was obtained prior to beginning this study. Exclusion criteria included concurrent unrelated procedures, procedures performed by surgeons other than general or plastic surgeons. ASA scores were classified into low (1–2), moderate (3), high risk (4–5). Procedures were grouped into either laparoscopic or open repairs. CPT codes 49,654,49,655,49,656, 49,657, and 49,659 described laparoscopic repairs whereas 49,560, 49,561, 49,565, 49,566, 49,570, and 49,572 described open repairs. 49,568 is a code describing placement of mesh. However, this code is often used in conjunction with other CPT codes, including inguinal hernia repairs. Only concurrent codes with ventral hernias were included. Race was grouped into White, Black, Asian, and Hispanic. Surgeries completed in less than five minutes were excluded. BMI was also calculated in kg/m<sup>2</sup> based on weight and height. Ages were then grouped into 18–30, 30–50, 50–70, > 70, given that prior retrospective studies showed a bimodal distribution of the age in patients who were at higher risk for returning to the operating room [15,20]. Several risk factors in Table 2 were analyzed given previously known risk factors for recurrence and re-operation in prior studies.

Risk factors were analyzed with univariate and multivariable models using Chi-squared and Mann-Whitney tests to determine association between risk factors and early re-operation after a ventral hernia repair within 30 days. Some missing values in variables analyzed were excluded. This however was infrequent due to a highly well-maintained national database (Table 4). Collinearity was also assessed in the logistic regression model to ensure that each independent variable has unique influence on the dependent variable and is not highly interrelated to the other independent variables in the model. ICD-10 codes for re-operation were analyzed to determine the most frequent diagnoses for early re-operation. Due to a number of nonspecific, unclear diagnoses and missing ICD-10 codes, 110 patients who underwent re-operation were excluded. Surgical site occurrence (SSO) encompassed all types of wound complications such as surgical site infections, superficial wound hematoma, seroma, and dehiscence. It is unclear from the data set whether dehiscence was simply fascial dehiscence or skin dehiscence. Statistical analyses and data cleaning were completed using R and RStudio (Version 2023.06.1 + 524).

Results

70,702 patients were compiled, and 56,260 met inclusion criteria. The patient population in the study was predominantly female (55.4 %). The majority of cases were completed by general surgeons, 98.9 %, compared to only 1.1 % by plastic surgeons. The average BMI of patients was 32.8. 75.9 % of the study population classified themselves as White, non-Hispanic. 68.2 % of hernia repairs were done in an open

fashion, despite rapid development of laparoscopic and robotic techniques over the past decade. 1339 (2.4 %) patients returned to the OR within 30 days of surgery (Table 1).

Risk factors significantly associated with early re-operation only in univariate models were as follows: cases completed by plastic surgeons, obesity (BMI 30–40), morbid obesity BMI (>40), ages 30 and older, diabetes, chronic obstructive pulmonary disease (COPD), congestive heart failure, steroid use and incarcerated hernia (*p* < 0.01). Risk factors significantly associated with early re-operation in both univariate and multivariable analyses included: open surgery, ASA 3–5, inpatient

Table 1  
Demographics of patient population stratified by reoperation.

	Return to OR		Overall (N = 56,260)
	No (N = 54,921)	Yes (N = 1339)	
Age Mean (SD)	57.6 (14.1 %)	60.2 (12.9 %)	57.7 (14.1 %)
Inpatient	18,670 (34.0 %)	957 (71.5 %)	19,627 (34.9 %)
Gender (Male)	24,468 (44.6 %)	648 (48.4 %)	25,116 (44.6 %)
Surgical Specialty			
General Surgery	54,326 (98.9 %)	1312 (98.0 %)	55,638 (98.9 %)
Plastics	595 (1.1 %)	27 (2.0 %)	622 (1.1 %)
Mean Body Mass Index (BMI)	32.7 (7.71)	34.2 (8.57)	32.8 (7.73)
Surgical Approach			
Laparoscopic	17,629 (32.1 %)	266 (19.9 %)	17,895 (31.8 %)
Open	37,292 (67.9 %)	1073 (80.1 %)	38,365 (68.2 %)
Race			
White	41,655 (75.8 %)	1028 (76.8 %)	42,683 (75.9 %)
Black	7640 (13.9 %)	196 (14.6 %)	7836 (13.9 %)
Asian	744 (1.4 %)	12 (0.9 %)	756 (1.3 %)
Hispanic	4882 (8.9 %)	103 (7.7 %)	4985 (8.9 %)
ASA			
Low Risk (1)	24,847 (45.2 %)	386 (28.8 %)	25,233 (44.9 %)
Moderate Risk(2–3)	28,201 (51.3 %)	849 (63.4 %)	29,050 (51.6 %)
High risk (4–5)	1873 (3.4 %)	104 (7.8 %)	1977 (3.5 %)
Dehiscence	101 (0.2 %)	124 (9.3 %)	225 (0.4 %)
Surgical Site Infection (SSI)	1329 (2.4 %)	166 (12.4 %)	1495 (2.7 %)
Operative Time (mean in minutes) SD (minutes)	112 (83.0)	163 (106)	114 (84.0)
Steroid	3384 (6.2 %)	107 (8.0 %)	3491 (6.2 %)
Dialysis	551 (1.0 %)	33 (2.5 %)	584 (1.0 %)
Hypertension	27,542 (50.1 %)	808 (60.3 %)	28,350 (50.4 %)
Heart Failure	1390 (2.5 %)	63 (4.7 %)	1453 (2.6 %)
Ascites	390 (0.7 %)	27 (2.0 %)	417 (0.7 %)
Chronic Obstructive Pulmonary Disease (COPD)	2803 (5.1 %)	119 (8.9 %)	2922 (5.2 %)
Smoking	8402 (15.3 %)	255 (19.0 %)	8657 (15.4 %)
Diabetes	9933 (18.1 %)	303 (22.6 %)	10,236 (18.2 %)
Length of Stay (days)	1.68 (4.86)	0.534 (24.7)	1.65 (6.13)
Recurrent	1583 (2.9 %)	33 (2.5 %)	1616 (2.9 %)
Reducible	29,579 (53.9 %)	624 (46.6 %)	30,203 (53.7 %)

surgeries, smoking, ascites, dialysis, SSI, dehiscence, and male gender, age group > 70, hemodialysis patients, increased operative time, ( $p < 0.05$ , Fig. 1). A more complete analysis of various risk factors is shown in Table 2. Collinearity of the regression model was also calculated to ensure minimal bias and appropriate selection of variables in the multivariable analysis. As visualized in Table 2, collinearity of all the independent variables in the multivariable model are 1–2. The mortality rate was significantly higher in the re-operative group 3.29 %, compared to the non-reoperative group 0.36 % ( $p < 0.001$ ).

The most frequent diagnosis for re-operation was surgical site occurrence (SSO) which included infection, dehiscence, seroma and superficial hematoma at 25 %. Unrelated surgeries were the second most frequent diagnosis at 13 %. These included surgeries or procedures for diagnoses unrelated to the index ventral repair such as fractures, nephrolithiasis, appendicitis, cholecystitis, and breast malignancy. Following SSO, the most common diagnoses for reoperation related to the index procedure were recurrence of ventral hernia, small bowel obstruction, and intra-abdominal hematoma, 12 %, 11 %, 11 % respectively. Table 3 shows a complete list of diagnoses leading to re-operation.

## Discussion

Recurrence of ventral hernias most often occur within 2 years of repair [9], although recent data from the Abdominal Core Health Quality Collaborative suggested that this time period may extend to 5 years [21]. Reoperation rates in longer term studies, vary from 4–6.6 % in at least a one year follow up period [10,11]. However, re-operation rates within 30 days were lower and more morbid. The current re-operation, mortality, dehiscence, and SSI rates were all lower than those reported by Stey et al. [11] a similar study analyzing risk factors and re-operation from an earlier NSQIP dataset using hernia data from 2005–2008: 2.4 % vs 3.8 %, 0.4 % vs. 1.4 %, 0.4 % vs. 1.4 %, 2.6 % vs. 4.8 % respectively. As demonstrated here, the rates of post operative morbidity were higher in the United States almost a decade ago when minimally invasive techniques of ventral hernia repair were still in their infancy. In this present study, recent technical advances in ventral hernia repair techniques likely improved the landscape of abdominal wall hernia repair outcomes. Despite advances in minimally invasive surgery in the realm of hernia repairs, 69.3 % of ventral hernia repairs were still performed via open incision across the nation.

This study analyzed diagnoses associated with early re-operation, which were more urgent in nature with more devastating sequela compared to diagnoses for long-term re-operation. The most common risk factor for later re-operation in prior literature was recurrence of hernias usually without obstructive symptoms, whereas the most common diagnoses for *early* re-operation in this study included surgical site occurrence (which included seroma, SSI, local hematoma and dehiscence), recurrence of hernia, small bowel obstruction, and intra-abdominal hematoma in decreasing order of frequency [22]. Some of these diagnoses require urgent intervention and if not intervened swiftly can lead to increased mortality. In light of these findings, surgeons can more easily identify candidates who will likely require re-operation based on diagnosis on re-presentation.

Equally important are pre and perioperative risk factors which may help surgeons select the appropriate candidate for surgery and optimize modifiable risk factors prior to surgery to maximize favorable outcomes. Significant risk factors for early return to surgery in multivariable models included open surgery, moderate (3) to high-risk ASA (4–5), age groups >70, inpatient surgeries, smoking, ascites, dialysis patients, SSI, wound dehiscence, and male gender. Variables that were only significant in univariate analysis included cases completed by plastic surgeons, BMI (30 or higher), diabetes, COPD, congestive heart failure, steroid use, and incarcerated hernias. Numerous previous studies have cited female gender to be associated with recurrence and increased 30-day adverse events [2,16,20]. Contrary to other studies, male gender in the current study was a risk factor for re-operation, which was also reported in a large cohort Swedish cohort study [16].

Several of these other risk factors make intuitive sense. Higher ASA is associated with more significant comorbidities. The ASA classification is a predictor of overall health status, and its significance in the multivariable analysis underscores the fact that patients with comorbidities and poor general health are at a higher risk for complications following ventral hernia repair. It has also been identified in prior studies to be associated with recurrence [24–26]. However, in Bhardwaj et al. [21], this association was not seen.

Outpatient surgeries were less likely to undergo early re-operation because these patients at baseline had fewer comorbidities without urgent or emergent need for repair [18]. Inpatient surgeries for hernia repairs tend to be urgent, typically secondary to incarceration or strangulation with or without bowel obstruction. It is widely known in literature that patients who underwent emergency repairs were at

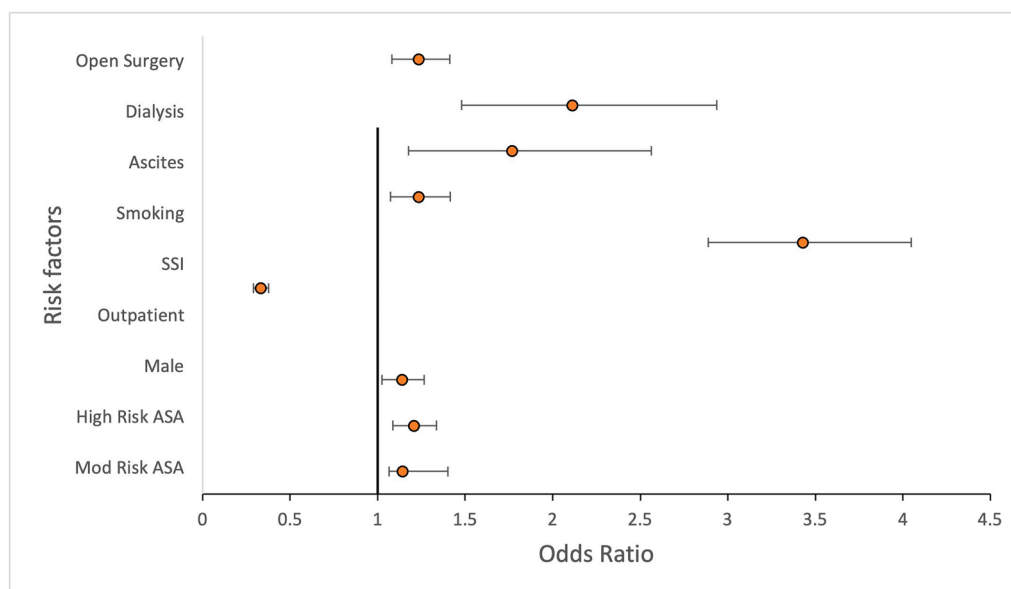


Fig. 1. Significant risks for re-operation in both univariate & multivariable models.

**Table 2**  
Risk factors associated with early reoperation.

N = 56,260		Univariate		P-value	Multivariable	
		OR	95 % CI		OR	95 % CI
Race	White			$p = 0.13$		
	Black	1.04	0.89–1.21		1.01	0.86–1.20
	Asian	0.64	0.34–1.09		0.72	0.38–1.23
	Hispanic	0.84	0.68–1.03		1.05	0.83–1.28
BMI Class				$p < 0.001$		
	Overweight (25–30)	1.02	0.84–1.24		0.95	0.78–1.18
	Obese (30–40)	1.21	1.01–1.45		1.02	0.84–1.24
	Morbidly Obese (>40)	1.64	1.35–2.01		1.14	0.92–1.43
ASA Group				$p < 0.001$		
	Moderate (3)	1.93	1.71–2.18		1.22	1.06–1.40
	High Risk (4–5)	3.62	2.89–4.48		1.42	1.08–1.85
Male Gender		1.16	1.04–1.29	$p = 0.0057$	1.21	1.08–1.35
Age Group				$p < 0.001$		
	30–50	1.57	1.04–2.51		1.19	0.77–1.93
	50–70	2.19	1.47–3.47		1.37	0.90–2.22
	70+	2.41	1.59–3.84		1.59	1.03–2.60
Outpatient		0.21	0.18–0.23	$p < 0.001$	0.33	0.28–0.37
Diabetes		1.33	1.16–1.51	$p < 0.001$	0.96	0.83–1.11
Surgical Site Infection (SSI)		5.70	4.79–6.74	$p < 0.001$	3.52	2.91–4.23
Chronic Obstructive Pulmonary Disease (COPD)		1.81	1.49–2.19	$p < 0.001$	1.20	0.97–1.49
Smoking		1.30	1.13–1.49	$p < 0.001$	1.24	1.06–1.44
Ascites		2.89	1.91–4.20	$p < 0.001$	1.67	1.06–2.51
Congestive Heart Failure (CHF)		1.91	1.46–2.45	$p < 0.001$	1.16	0.87–1.52
Dialysis		2.50	1.72–3.52	$p < 0.001$	1.97	1.31–2.85
Steroid		1.32	1.08–1.61	$p = 0.007$	0.99	0.80–1.23
Surgical Approach (Open)		1.90	1.67–2.19	$p < 0.001$	1.24	1.07–1.44
Dehiscence		55.35	42.33–72.66	$p < 0.001$	36.41	27.28–48.80
Plastic Surgery		1.88	1.25–2.73	$p = 0.002$	1.08	0.70–1.60
Reducible Hernia		0.75	0.67–0.83	$p < 0.001$	1.03	0.91–1.15
Recurrent hernia repair		0.86	0.59–1.19	$p = 0.41$		

**Table 3**  
Indications for reoperation.

Re-operation Diagnosis	N = 1232	Frequency
Surgical Site Occurrence (SSO)	306	24.84 %
Unrelated	165	13.39 %
Hernia	147	11.93 %
Hematoma	141	11.44 %
Small bowel obstruction (SBO)	133	10.80 %
Bowel perforation	109	8.85 %
Bleeding	74	6.01 %
Intraabdominal abscess	24	1.95 %
Mesenteric ischemia	14	1.14 %
Pain	15	1.22 %
Ileus	8	0.65 %
Other	8	0.65 %

increased risk of early re-operation [2,3,18].

The majority of ventral hernia repairs in the country were still performed open. As evident in the analysis, open surgery was a significant risk factor in early reoperation, also seen in a recent Swedish study [15]. Open procedures are more commonly employed in larger hernias, often in cases requiring component separation and/or transversus abdominis release, which comes with a host of possible complications. However, Howard et al. [22] observed an increased rate of recurrence and re-operation in a 10 year follow up with minimally invasive techniques. Other large recent studies did not show the same effect but did observe an increase in 5-year recurrence in robotic repairs, which may be attributed to a small sample size and employment of bridging mesh rather than primary fascial repair or release [21]. Fry et al. [28] also observed an increased risk of long-term ventral hernia recurrence in a 10-year cohort from 2010–2020 among repairs completed robotically. There appears to be conflicting evidence on whether open technique is a risk factor for reoperation and recurrence compared to other minimally

**Table 4**  
Collinearity analysis of multivariable regression.

Variables	Variance Inflation Factor
Body Mass Index (BMI)	1.27
Gender	1.05
ASA Group	1.42
Age group	1.25
Operative time	1.19
Race	1.07
Surgical Approach	1.11
Diabetes	1.08
Surgical Specialty	1.02
Ascites	1.06
COPD	1.10
Congestive Heart Failure	1.08
Smoking	1.09
Dehiscence	1.01
Surgical site infection (SSI)	1.04
Steroid	1.04
Dialysis	1.08
Inpatient	1.30
Reducible Hernia	1.07

invasive techniques, especially with robotic techniques. This may represent a lack of recent data during which optimization of robotic ventral hernia techniques have exponentially grown. Despite the controversy, this study supports the notion that minimally invasive techniques, which have also been associated with fewer SSIs and shorter recovery times, may be preferable when feasible, despite an earlier study by Eker et al. [14], highlighting in their randomized controlled trial that laparoscopic repairs of incisional hernias resulted in more wound complications and higher recurrence rate, although not significant [12–14].

The presence of surgical site infection (SSI) and its strong association

with re-operation cannot be overstated. SSIs led to a cascade of complications that can compromise the integrity of the hernia repair leading to recurrence [15,18,21]. Our data align with the broader literature emphasizing the critical nature of infection control in postoperative care [11].

Some patient related risk factors undoubtedly are major contributors to risk of early re-operation, but technical failure resulting in hernia recurrence with bowel obstruction or intra-abdominal hematoma is difficult to measure and quantify. A re-operation secondary to a small bowel obstruction can be a result of mesh slippage, which is a true technical failure or an early inflammatory adhesive band, an inevitable and unpredictable consequence of surgery. There are many nuances in ventral hernia repair that are unable to be stratified in this analysis. For instance, in laparoscopic repairs, some surgeons prefer primary fascial sutures with mesh over a simple bridging mesh alone. Although with equivocal evidence, primary fascial sutures with mesh compared with a bridging mesh tend to have a significant reduction in recurrence, bulging, rates of SSI, SSO with higher patient satisfaction in one randomized controlled trial and several observational studies [27]. Technical variability is a limitation of this study which can significantly affect outcomes.

Despite their association with early re-operation, when controlled for other factors in the multivariable model, variables significant only in univariate analysis would not be considered predictive of re-operation. Interestingly cases completed by plastic surgeons had significantly higher rates of re-operation only in univariate analysis. This difference was not seen in Yazid et al. [23] either in univariate or multivariable analysis. However, Yazid et al. [23], notably only included ventral hernia cases with component separation. The only significant difference found was that plastic surgeons were more involved in more contaminated wounds. Our population included hernias that were completed with and without component separation. With the significance seen in the univariate model, this may be due to the fact that plastic surgeons were typically involved in open, more complicated, component separation cases than those completed by general surgeons alone.

Another variable that was only significantly associated with early reoperation in the univariate model was presentation of a nonreducible hernia. Incarcerated hernias were identified as one of the risk factors for early reoperation in Stey et al. [11] on the contrary. It is still unclear why such a variable would be less significant in our study. Danzig et al [29], also did not observe an increase in morbidity rates, SSI, and recurrence between incarcerated vs non-incarcerated groups. One can speculate that the advancement in our techniques with mesh placed more liberally especially in clean-contaminated fields may have reduced early recurrence, and inevitably early reoperation.

A recurrent hernia repair is also not a factor in early reoperation in this study, although it may be a factor in long term recurrence [17,18]. Recurrent hernias tend to have poor tissue plains, copious of scar tissue and possibly further loss of fascia from mesh excision, all of which contribute to higher risk of recurrence [19].

Our analysis overall was limited by the data structure and collection despite the incredibly large sample size, resulting in exclusion of several variables that play a major role in ventral hernia outcomes. Variables such as hernia size, mesh type/position, and whether primary fascial sutures were placed in laparoscopic repairs which have been large contributing factors to recurrence, were not analyzed [21]. However, based on CPT codes, some characteristics of the hernias such as recurrence or incarceration were analyzed. Yet details regarding the number of episodes of recurrence were unavailable. This study also did not analyze long term outcomes and reoperation rates, excluding a number of patients who needed re-operation at a later stage where recurrence most often took place. As a result, this analysis would be underestimating the number re-operations after 30 days which were attributed to recurrence of hernias. Much more promising now with the new NSQIP dataset is the stratification of the robotic approach and size of hernia defects. This will help the surgical community further understand

the role of new techniques and the subtleties of mesh positioning.

## Conclusions

The rates of early re-operation and mortality were notably lower than those seen in prior studies. Risk factors for early re-operation were largely the same as risk factors for recurrence of ventral hernias with the exception of male gender, which was not clearly observed in other studies. This study focused on identifying risks for early-reoperation which could be devastating and likely extended beyond recurrence as the reason for re-operation. Indications most commonly associated with re-operation in the early period were also analyzed. The advances in laparoscopic, robotic and open techniques likely improved ventral hernia outcomes in regard to mortality, dehiscence, and rates of early re-operation. However, new unfavorable data on robotic ventral hernia repair outcomes are emerging. Long term studies are still needed to determine outcomes in utilization of the robot in ventral hernia repairs, since many surgeons are still early in their learning curve. Inconsistent age groups had been associated with early re-operation in the Swedish studies and this study, but that was likely due to selection bias. The most common diagnosis for early re-operation is surgical site occurrence, followed by recurrence of hernias, SBOs and intra-abdominal hematomas.

With higher mortality after early reoperation, this large data study can be a tool in assisting surgeons with patient selection and optimizing various modifiable risk factors prior to surgery. Moving forward with new CPT codes in 2023, stratifying our analysis by size will also be beneficial in eliminating confounding factors. Long term data would also be helpful in identifying if risk factors and diagnoses for re-operation are largely similar to those in early reoperation. The new NSQIP dataset from 2022 onwards also has data on robotic usage. Clear direction on whether laparoscopic or robotic repairs have any significant difference in outcomes is yet to be determined in current literature. Further analysis of robotic outcomes will be helpful in determining surgical approach in such a common condition with varying levels of complexity.

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## CRediT authorship contribution statement

**Saran Kunaprayoon:** Writing – original draft, Validation, Resources, Methodology, Funding acquisition. **Cole Brown:** Writing – original draft, Validation, Methodology, Formal analysis, Data curation. **Venu Bangla:** Writing – original draft, Resources, Methodology, Formal analysis, Data curation. **Tomer Lagziel:** Writing – review & editing, Resources, Methodology, Formal analysis, Data curation. **I. Michael Leitman:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

I. Michael Leitman, MD received financial support by the Marla Sue Golden Foundation. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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