Surgery for adhesive small-bowel obstruction is associated with improved long-term survival mediated through recurrence prevention: A population-based, propensity-matched analysis

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BACKGROUND: Adhesive small-bowel obstruction (aSBO) is among the most common reasons for admission to a surgical service. While operative intervention for aSBO is associated with a lower risk of recurrence, current guidelines continue to advocate a trial of nonoperative management. The impact of the increased risk for recurrence on long-term survival is unknown. We sought to explore the potential for improved survival with operative management through the prevention of admissions for recurrence of aSBO and the associated risks.

METHODS: This is a population-based retrospective cohort study using administrative data. We identified patients admitted to hospital for their first episode of aSBO from 2005 to 2014 and created a propensity-matched cohort to compare survival of patients managed operatively with those managed nonoperatively. To test whether survival differences were mediated by recurrence prevention, a competing risk regression was used to model the subdistribution hazard of death when accounting for the risk of recurrence. An instrumental variable approach was used as a secondary analysis to compare survival while accounting for unmeasured confounding.

RESULTS: There were 27,904 patients admitted for their first episode of aSBO between 2005 and 2014. The mean age was 61.2 years (std dev, 13.6), and 51% were female. Operative management was associated with a significantly lower risk of death (hazard ratio, 0.80; 95% confidence interval, 0.75–0.86), which was robust to instrumental variable analyses, and a lower risk of recurrence (hazard ratio, 0.59; 95% confidence interval, 0.54–0.65). When adjusting for the risk of recurrence, operative intervention was not associated with improved survival, suggesting that the survival benefit is mediated through prevention of recurrences of aSBO.

CONCLUSION: In patients admitted for their first episode of aSBO, operative intervention is associated with a significant long-term survival benefit. This survival benefit appears to be mediated through the prevention of recurrences of aSBO.

STUDY TYPE: Retrospective cohort study. (*J Trauma Acute Care Surg.* 2019;87: 636–644. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic study, Level II.

KEY WORDS: Small-bowel obstruction; adhesions; adhesive small-bowel obstruction; SBO; recurrence.

Adhesive small-bowel obstruction (aSBO) is a common reason for admission to hospital in developed countries, accounting for an estimated 20% of admissions for acute abdomen.[1–3] Approximately 70% to 80% of admissions for aSBO are managed without operative intervention,[4–7] and current guidelines advocate for a trial of nonoperative management in patients without signs of bowel ischemia or sepsis.[8–10] Improvements in computed tomography imaging and the introduction of water-soluble contrast studies have aided in identifying patients that will likely experience clinical resolution without operative intervention.[1,11–15]

Despite high rates of resolution with nonoperative management during individual episodes, aSBO is often a recurring, potentially chronic surgical illness.[16–21] The risks associated with an admission for aSBO are considerable, with one population-based study reporting in-hospital and 1-year mortality rates of 7% and 23%, respectively.[2] Moreover, several studies have demonstrated that nonoperative management is associated with an increased risk of recurrence of aSBO.[16–21] Although nonoperative management may result in resolution in any given admission for obstruction, the risk of recurrence and readmission may result in higher long-term risks as compared with operative management.

Despite the putative long-term benefit associated with preventing recurrent obstruction, the impact of operative intervention for aSBO on survival has not been well studied. We hypothesize that operative intervention for aSBO, through the prevention of recurrence, may have an overall survival benefit compared with nonoperative management. The purpose of this study was to compare the long-term survival between patients managed operatively for their first episode of aSBO and those managed nonoperatively.

METHODS

Study Design and Setting

We performed a population-based, retrospective cohort study of patients admitted to hospital in Ontario, Canada for their first episode of aSBO over 2005 to 2014. We compared the long-term survival of patients managed operatively for their first episode of aSBO to those managed nonoperatively. The single-payer health care system in Ontario facilitates the longitudinal following of a patient population with minimal loss to follow-up.

Data Sources

Administrative databases were made available through the Institute for Clinical Evaluative Sciences (ICES). Data from these databases was linked using unique encoded identifiers through ICES. The data sources utilized for this study have previously been validated for a wide range of surgical and nonsurgical diseases.[22–26]

Data sources for this study included the following: (1) the Discharge Abstract Database (DAD), an administrative database that uses discharge data for admissions to acute care hospitals; (2) the Registered Persons Database, an administrative database that captures demographic data for all residents of Ontario; (3) the Ontario Health Insurance Plan Claims Database, a database of all procedural billing codes submitted by physicians; (4) the

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National Ambulatory Care Reporting System, an administrative database of emergency room visits; (5) the Office of the Registrar General Database, an administrative database that captures data regarding all deaths that occur in Ontario; and (6) ICES-derived cohort databases for specific comorbidities (congestive heart failure, hypertension, myocardial infarction, chronic obstructive pulmonary disease, and diabetes mellitus).

Cohort

We identified a cohort of adult patients who were admitted for their first episode of aSBO. We limited the study to patients who were admitted for their first episode of aSBO to eliminate potential confounding associated with multiple previous admissions and/or procedures for aSBO. We identified all patients aged 18 years to 80 years with a primary diagnosis of either adhesive intestinal obstruction (ICD10: K56.5) or unspecified intestinal obstruction (ICD10: K56.6) based on their discharge abstract. We then excluded patients with any diagnosis codes associated with the admission that may be consistent with nonadhesive etiologies of SBO (Supplemental Digital Content 1, Table 1, http://links.lww.com/TA/B403). These exclusions included diagnosis codes for hernias, volvulus, ileus, gallstone ileus, and intra-abdominal malignancies. We used a 5-year look-back window to exclude any patients with a previous diagnosis of inflammatory bowel disease or abdominal radiation therapy. We also used the look-back window to exclude any patients with a previous admission for either adhesive intestinal obstruction or unspecified intestinal obstruction.

Exposure

The exposure of interest in this study was operative management for aSBO at the index admission. We identified operatively managed cases of aSBO using operative billing codes identified through claims data (Supplemental Digital Content 2, Table 2, http://links.lww.com/TA/B404). For the primary analysis, the study cohort was divided into two groups: those who underwent operative management for their first ("index") episode of aSBO and those treated nonoperatively.

Outcomes

The primary outcome for this study was mortality. We compared the long-term hazard of death between patients managed operatively and those managed nonoperatively and also estimated mortality as dichotomous outcomes (1, 3, and 5 years). We also reported the incidence of recurrence between the two exposure groups and compare the overall hazard of recurrence between the two groups.

Covariates

We considered patient- and hospital-level characteristics that may confound the relationship between operative intervention and mortality in our multivariable analyses. Patient characteristics including patient age, sex, socioeconomic status (income quintile), comorbidity burden, and the rurality of a patient's home residence were included in analysis. Income quintile was determined using census data and was based on the median income of a patient's residential postal code. Patient comorbidities used as covariates for analysis included chronic obstructive pulmonary disease, congestive heart failure, diabetes mellitus, hypertension, and myocardial infarction within the 2 years prior to admission. We measured rurality using Rurality Index of Ontario, which is calculated using population density as well as the distance to the nearest basic and advanced referral centers. We dichotomized Rurality Index of Ontario into "rural" or "urban" as has been validated previously.[27] We also considered hospital characteristics in our multivariable analyses, including the number of beds at the admitting institution and whether the institution had a designation as a teaching hospital.

Analytic Approach

We performed descriptive statistics to compare baseline characteristics of patients who underwent operative management at the index admission and those managed nonoperatively. Due to the large sample size, we compared baseline characteristics using standardized differences, which are not sensitive to sample size. A standardized difference of 10% or greater was determined *a priori* to represent a significant difference.[28,29]

Propensity Score Matching

A propensity score-matched approach was utilized to account for treatment-selection bias.[30] Each patient's propensity to undergo operative management at the index episode was estimated using a logistic regression model that included all patient- and hospital-level covariates.[31] Patients who underwent operative management were then matched one-to-one with those who were treated nonoperatively by propensity score using a "greedy" algorithm and a caliper width of 0.2 of the standard deviation of the logit of the propensity score.[32,33] Balance diagnostics were performed by calculating the standardized difference between the matched groups.

Using the matched cohort, we plotted Kaplan-Meier survival curves comparing management strategies and performed log-rank tests to statistically compare the curves. We used a Cox Proportional Hazards model to estimate the association between the choice of management strategy and the hazard of death. Proportional hazard assumptions for all Cox models were verified.

We also compared mortality as dichotomous outcomes (1-, 3-, and 5-year mortalities) between the treatment groups in the matched cohort using McNemar's test to account for the matched nature of the treatment groups.

Secondary Analyses

Instrumental Variable Analysis

We anticipated that confounding by indication may exist in the form of surgery being offered to patients who are more likely to survive. Factors associated with confounding by indication may be unmeasured, particularly given the administrative nature of the data, and therefore would not be adjusted for in a propensity-matched analysis.

We used an instrumental variable approach to evaluate the long-term mortality associated with operative intervention at the index aSBO episode. An ideal instrumental variable is one that is closely associated with the intervention of interest but is not associated with the outcome of interest (except through the exposure variable). Instrumental variable analyses aim to simulate a randomized controlled trial using observational data in that, much like trials, allocation

to the treatment/instrument group is closely associated with the intervention but unrelated to outcome.[34,35] In this way, instrumental variable analyses account for both measured and unmeasured confounders.

We utilized a "provider-preference" instrument defined as the probability that a patient would undergo operative management of aSBO at each hospital.[36] All patients managed for aSBO at the same hospital were assigned the same value of the instrumental variable. Provider-preference instruments, such as this one, are effective instrumental variables in that they are closely associated with the exposure of interest, but not associated with the outcome of interest.

The instrument was evaluated by dividing the cohort of patients into quartiles based on the instrument value and comparing patient baseline characteristics across the quartiles to ensure balance in known potential confounders. We utilized a two-stage endogenous model with full-information maximum likelihood bivariate probit estimation to estimate the mortality benefit associated with operative intervention while adjusting for patient- and hospital-level covariates as well as the instrumental variable.[37] Separate models were used for each endpoint (1-, 3-, and 5-year mortalities). For each model, only patients admitted early enough in the study period to facilitate full follow-up for that endpoint without right censoring were included. All models were tested for correlation between the instrument and the intervention of interest and for endogeneity using the correlation parameter (Rho >0.05 suggests that treatment selection bias did not have a significant effect on outcome).

Competing Risk Regression

We hypothesized that differences in survival between patients managed operatively and those managed nonoperatively were mediated through the prevention of recurrent aSBO. However, death and recurrence are competing events as survival is a necessary precondition to experiencing a recurrence. To test this hypothesis we utilized a Fine and Grey[38] competing risk regression in which we estimated the subdistribution hazard for death while accounting for the competing risk of recurrence. In this model, the subdistribution hazard of death is estimated under the assumption that no patients experience recurrence of aSBO. This analysis was performed using the propensity-matched cohort previously described.

If operative intervention was associated with improved survival, persistence of a survival benefit using the competing risk model would suggest that the survival benefit is not mediated through the prevention of recurrence. However, should adjustment for the competing risk of recurrence significantly reduce the magnitude of the survival benefit, it is likely that the survival benefit is mediated through recurrence prevention.

All analyses were performed using SAS Enterprise Guide, version 7.1 (SAS Institute, Cary, NC). Results were considered statistically significant if p is less than 0.05.

RESULTS

Over the study period, 27,904 patients were admitted to hospital with their first episode of aSBO. The mean patient age was 61.2 years (std dev, 13.6) and 51.1% of patients were female. There were 6,186 (22.2%) patients that underwent operative intervention for their aSBO. Overall, patients who underwent operative intervention were more likely to be female, had fewer comorbidities, were more likely to live in urban areas, and were treated at larger hospitals (Table 1). There were 5,482 (19.6%) patients who experienced at least one recurrence of aSBO during follow-up. The maximum follow-up period was 10 years, and the median follow-up was 3.6 years (interquartile range, 1.4–6.5 years).

After matching patients managed operatively with those managed nonoperatively by propensity score, the resulting cohort consisted of 12,322 patients with 6,161 patients in each treatment group. Balance diagnostics suggested that the matched cohort was well-balanced with respect to all patient- and hospital-level covariates (Table 1).

Primary Analysis

Kaplan-Meier survival curves comparing operative and nonoperative management for the first episode of aSBO are shown in Figure 1. The log-rank test comparing these curves suggested a statistically significant survival benefit associated with operative management ($p < 0.001$). Using a Cox Proportional Hazards model for the hazard of death among patients in the propensity-matched cohort, operative intervention during the index admission was associated with a significantly lower hazard of death (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.74–0.86). This hazard ratio is somewhat greater than the adjusted hazard ratio associated with operation found in the unmatched cohort of 27,904 patients (HR, 0.75; 95% CI, 0.70–0.80), suggesting that propensity-score matching likely mitigated some degree of confounding by indication.

When we examined 1-year, 3-year, and 5-year mortalities as dichotomous outcomes, operative intervention was associated with a significantly lower probability of mortality at all time points ($p < 0.001$ for all) (Fig. 2). Operative intervention was also associated with significantly lower odds of 1-year, 3-year, and 5-year mortalities compared with nonoperative management with odds ratios of 0.77, 0.76, and 0.77 for 1-year, 3-year, and 5-year mortalities, respectively (95% CI, 0.68–0.87, 0.69–0.84, and 0.70–0.84, respectively) compared with nonoperative management.

There was no significant difference between operative management and nonoperative management with respect to 30-day mortality (4.2% vs. 4.0%, $p = 0.65$).

Secondary Analysis—Instrumental Variable Approach

Evaluation of the instrumental variable demonstrated that it was closely associated with the independent variable (operative intervention, $p < 0.001$, Supplemental Digital Content 3, Fig. 1, http://links.lww.com/TA/B405) and patient-level covariates were well balanced across quartiles of the instrumental variable (Supplemental Digital Content 4, Table 3, http://links.lww.com/TA/B406).

Adjusted analysis using the instrumental variable demonstrated that operative management was associated with a significantly lower risk of 1-year (OR, 0.67; 95% CI, 0.49–0.91) and 3-year mortality (OR, 0.66; 95% CI, 0.48–0.90). Operative management also appeared to be associated with a lower risk of 5-year mortality that approached significance (OR, 0.75; 95% CI,

TABLE 1. Baseline Characteristics of Unmatched and Matched Cohorts

	Unmatched Cohort			Matched Cohort		
	Nonoperative Management (n = 21,718)	Operative Management (n = 6,186)	Standardized Difference	Nonoperative Management (n = 6,161)	Operative Management (n = 6,161)	Standardized Difference
Mean age (std dev), y	61.5 (13.4)	60.2 (14.3)	0.10	61.1 (13.6)	60.2 (14.3)	0.06
Female sex, %	49.2%	57.8%	0.17	59.4%	57.8%	0.03
Comorbidities, %						
• MI (previous 2 years)	1.2%	0.6%	0.06	0.6%	0.6%	0.01
• HTN	55.9%	50.4%	0.11	51.9%	50.4%	0.03
• CHF	10.3%	7.7%	0.09	6.9%	7.7%	0.03
• DM	26.2%	20.3%	0.14	19.7%	20.3%	0.02
• COPD	25.6%	22.1%	0.08	20.8%	22.1%	0.03
Income quintile, %						
• 1st (lowest)	21.1%	20.9%	<0.01	20.7%	20.9%	0.01
• 2nd	20.8%	20.1%	0.02	20.4%	20.1%	0.01
• 3rd	20.2%	19.1%	0.03	19.3%	19.2%	<0.01
• 4th	19.3%	20.7%	0.03	20.5%	20.7%	0.01
• 5th	18.1%	19.0%	0.02	19.1%	19.0%	<0.01
Rural residence, %	8.6%	5.5%	0.12	4.5%	5.4%	0.04
Teaching hospital, %	40.8%	47.8%	0.14	47.3%	47.8%	0.01
Large hospital (beds > 250), %	23.5%	26.2%	0.06	24.7%	26.1%	0.03

0.52–1.08), but was underpowered due to the smaller sample size of this subgroup (Fig. 3). In all models, the treatment selection parameter was p less than 0.001, suggesting that the instrument was well correlated with the treatment variable of interest and the correlation parameter (Rho) was p greater than 0.05, suggesting that treatment selection bias did not significantly affect outcome.

Recurrence and Death

Among patients in the propensity-matched cohort, the 5-year cumulative incidence of recurrence was significantly lower among patients managed operatively than among patients managed nonoperatively (11.2% vs. 19.1%; $p < 0.001$).

We performed a competing risk regression using the propensity-matched cohort, in which we estimated the subdistribution hazard of death while adjusting for the competing risk of recurrence. After adjustment, surgery during the index episode was no longer associated with a significantly lower incidence of death (HR, 0.94; 95% CI, 0.86–1.02), however, strongly associated with recurrence (HR, 0.59; 95% CI, 0.54–0.65). This finding suggests that much of the original hazard reduction

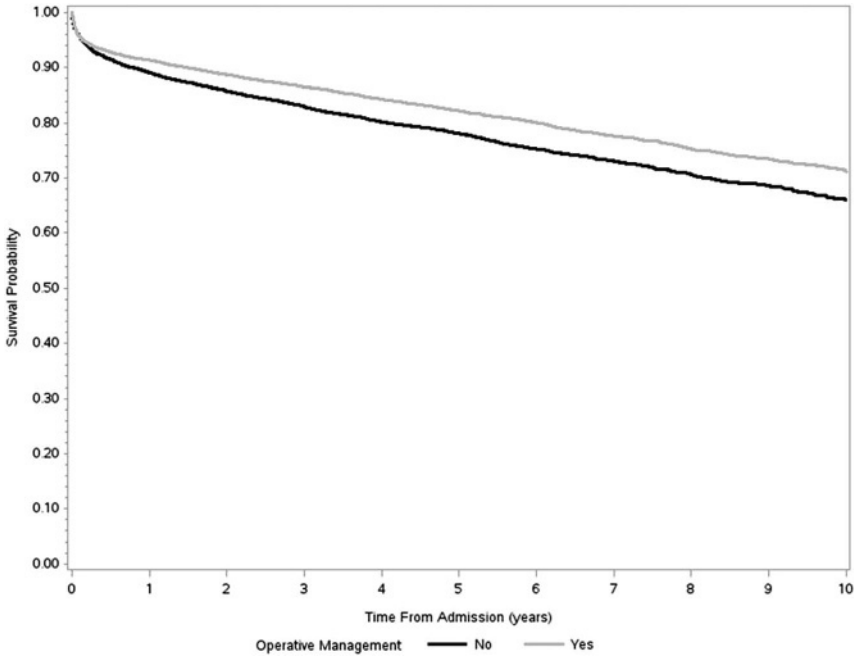

Figure 1. Kaplan-Meier survival curves for operative and nonoperative management.

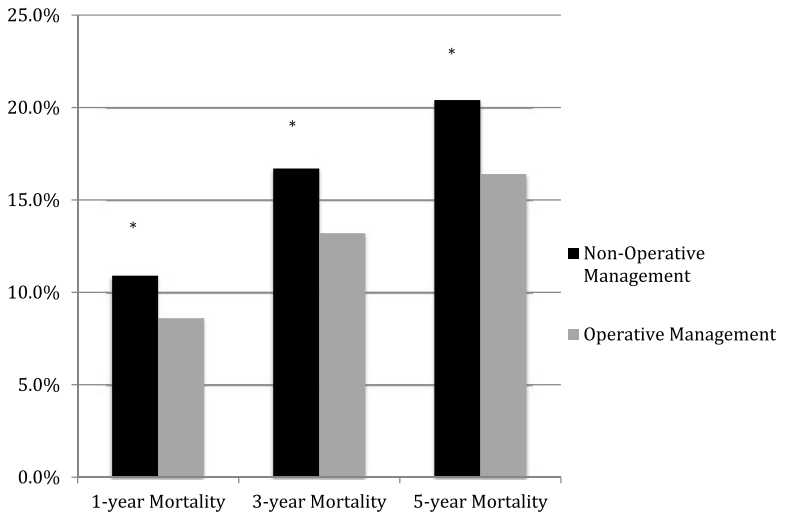

Figure 2. Long-term mortality in matched cohort. *$p < 0.001$.

associated with surgery (noted previously in the Cox proportional hazards model [HR, 0.80]) was in fact mediated through recurrence prevention.

DISCUSSION

In this population-based cohort study, we found that operative intervention for aSBO at the index admission is associated with an overall survival benefit compared to nonoperative management. When adjusting for recurrences, there was no significant survival benefit associated with operative intervention, suggesting that the survival benefit associated with surgery is largely mediated through recurrence prevention.

Approximately 20% of patients admitted with aSBO experience a recurrence, with the majority of recurrences occurring within 5-years of the index episode.[2,16] With each episode of aSBO, the risk for subsequent additional episodes increases and the time between episodes decreases.[16,19,39,40] Therefore, nonoperative management of aSBO not only increases the risk for a single recurrence, but sets patients on a path in which they are more likely to experience multiple recurrences. The risks associated with each readmission for aSBO are significant, with a short-term mortality of 4% to 7%.[2,41–44] The results of the present study suggest that, through the prevention of recurrences of aSBO, operative management may result in an overall survival benefit.

Current guidelines for the management of aSBO recommend a trial of nonoperative management in conjunction with a water-soluble contrast study to identify patients likely to resolve without operative intervention.[8–10] The current guidelines prioritize the individual admission and getting patients through each individual admission without surgery. At present, approximately 70% to 80% of patients admitted with aSBO are managed nonoperatively.[4–7] However, unlike many surgical illnesses, aSBO is often recurrent and the long-term outcomes should be considered in clinical decision making. The

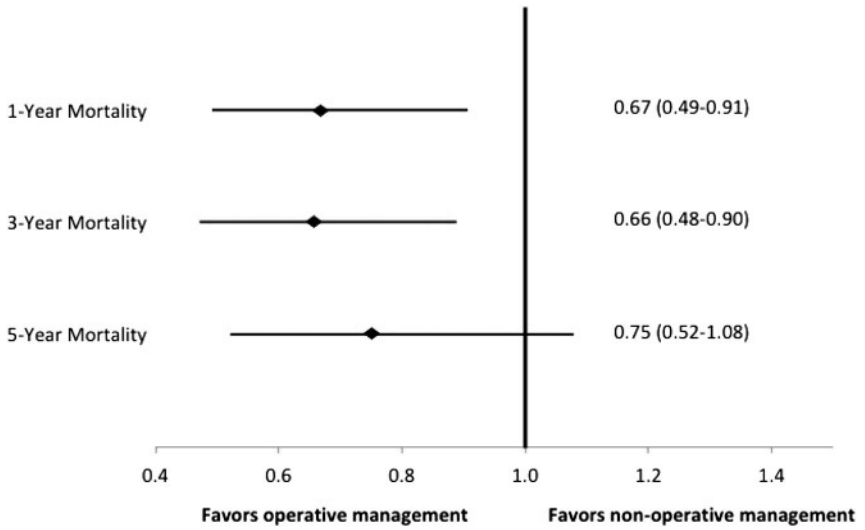

Figure 3. Odds of mortality with operative management (instrumental variable analyses). *$p < 0.001$ for each episode.

findings of this study suggest that the trial of nonoperative management advocated for in current guidelines may have a long-term harm with respect to patient survival.

While we have demonstrated that operative management is associated with improved survival at the population level, decision making ultimately occurs at the level of the individual patient. There are likely certain subpopulations of patients with aSBO for whom the risks of operative intervention may exceed the potential long-term benefits. The administrative data that was used lacked the granularity necessary to highlight some of these subpopulations. Clinical judgment in the balancing of the risks and benefits of operative and nonoperative management at the bedside of individual patients remains a critical aspect of care. The findings of the present study may serve to inform that judgment.

The available data was limited with respect to prior surgical history, imaging and bloodwork associated with the aSBO admission, and the use of water-soluble contrast studies. Interpretation of our results should consider these limitations. The data regarding the use of water-soluble contrast studies has suggested that its use results in a lower proportion of patients being managed operatively. Based on the existing evidence about the recurrence patterns of aSBO, we expect that the increased use of water-soluble contrast studies and the associated increase in the proportion of patients managed nonoperatively, will likely result in an increased risk of recurrence. The findings of our study suggest that this increased risk of recurrence may result in shorter survival. Ultimately long-term studies of the risk of recurrence with water-soluble contrast studies are needed. The impact of water-soluble contrast studies on the incidence of recurrence and the associated effect on survival will be important factors in determining its role in the management of aSBO.

The use of administrative data sets has the inherent limitations of misclassification bias and unmeasured confounding. Misclassification of nonadhesive etiologies of SBO as adhesive obstructions was of concern. We validated our algorithm with a chart review in a randomly selected sample cohort and had a positive predictive value of 88% associated, suggesting validity of our cohort. Moreover, a similar approach to the identification of adhesive SBO has been previously used by other groups[45] as well as our own.[4,16,46]

Particular care was taken to mitigate potential misclassification bias with respect to the inappropriate inclusion of malignant bowel obstructions. In addition to broadly excluding all patients with cancer-related diagnostic codes, we also noted similar short-term survival between patients managed operatively and those managed nonoperatively. Given the extremely poor survival following malignant obstruction, and this subgroups increased likelihood to receive nonoperative management, this finding suggests that the nonoperative treatment group was not contaminated with a significant proportion of patients with malignant obstruction. Moreover, the short-term mortality in both groups resembled previously reported rates for adhesive SBO and was substantially less than that reported for malignant SBO.[2,47,48]

We addressed measured confounding and unmeasured confounding using a variety of quasi-experimental methods. Our finding that operative intervention is associated with a survival benefit in patients with aSBO was robust and consistent across multiple analytic approaches. While only a randomized controlled trial can fully account for unmeasured confounding, the findings of instrumental variable analyses have been shown to have excellent concordance with randomized controlled trials of the same interventions.[49]

Finally, it should be noted that instrumental variable analyses estimate the effect size of an intervention in the "marginal subpopulation"—the subgroup of patients for whom measured covariates did not determine treatment allocation. While this subpopulation often represents patients for whom data to inform clinical decision making may be most valuable, the effect size estimated by instrumental variable analyses should be considered with this in mind.

This study benefited from a large, population-based sample with minimal selection bias for entry into the cohort. Given the universally accessible health care system in Ontario, we were able to follow patients longitudinally with minimal loss to follow-up. Additionally, the analytic approach utilized multiple statistical methods to address measured and unmeasured treatment selection bias as much as possible using observational data. Ultimately, long-term prospective studies that are able to capture granular clinical data are needed to evaluate the role of operative management for aSBO on long-term survival.

CONCLUSION

In patients admitted for their first episode of aSBO, operative intervention is associated with a significant long-term survival benefit mediated through prevention of recurrences.

AUTHORSHIP

R.B. participated in the literature search, study design, data analysis and interpretation, writing. A.N. participated in the study design, data interpretation, critical revisions. B.H. participated in the study design, data interpretation, writing, critical revisions. N.L.H. participated in the study design, data interpretation, critical revision. P.P. participated in the data interpretation, critical revision. P.K. participated in the study design, data interpretation, writing, critical revisions.

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R.B. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The data used for this study are housed and maintained by ICES and the Ministry of Health and Long-Term Care of Ontario; access to data for the purposes of reproducibility must be approved and granted by those bodies. The authors will share any analytic material, including the SAS code, upon request. This study plan was registered with the Institute for Clinical Evaluative Sciences, which is independent of the study team.

DISCLOSURE

The authors declare no conflicts of interest.
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