Developing a risk assessment tool for prolonged postoperative ileus

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Despite advancements in surgical treatment over the past decade, prolonged postoperative ileus (PPOI) continues to remain a challenging entity following major abdominal operations. After abdominal surgery, a typical period of 4–5 days of reduced or abnormal intestinal function is considered a standard portion of the postoperative recovery phase (1). Extension of ileus beyond 5 days (alternatively postoperative day 4) has been termed "prolonged" and considered to be outside the window of standard recovery. While the term ileus has been broadly referred to a loss of gastrointestinal function involving the stomach, small intestine and colon, the etiology of this condition is multifocal. Bowel manipulation during surgery is thought to result in the release of nitric oxide, prostaglandins, and an inflammatory cell pathway, thereby leading to increased leukocyte migration to intestinal tissue, edema development, and subsequent loss of gastrointestinal propulsion (2). Surgical stress renders a neurogenic impact which limits MMC (migrating motor complex) patterns while also activating cortisol-based hormonal pathways which activate the aforementioned inflammatory cell pathway (3,4). Finally, opioid-based medications have been considered a prominent exogenous, pharmacological contributor to postoperative ileus through stimulation of enteric mu-receptors leading to constipation and bowel dysfunction (3). Patient risk factors for ileus occurrence include male gender, history of peripheral vascular disease, and prolonged operative duration (5). To date, conventional methods of abating prolonged ileus such as bowel rest through prophylactic nasogastric tube placement have demonstrated no significant reduction in occurrence or duration (6).

PPOI occurrence has been associated with increased occurrence of postoperative complications such as nosocomial infections, increased length of stay, and a dramatic increase in associated health care expenditure, estimated to be approximately $1 billion in annual cost for medical providers and hospitals (7). To date, PPOI risk assessment has largely been conducted for patients undergoing colorectal or gynecological operations; thus, prediction of PPOI occurrence in other domains of abdominal surgery such as foregut, hepatobiliary, pancreatic, and vascular operation remains unclear. In light of the significant complications associated with PPOI occurrence, there remains a pressing need for accurate risk prediction over a wide spectrum of abdominal operations.

Through analysis of a prospectively maintained database, Sugawara and colleagues have attempted to devise a PPOI stratification model through examination of 1,666 consecutive patients undergoing elective major abdominal operations (8). PPOI was defined as meeting two of five criteria on or after postoperative day 4: (I) nausea or vomiting over preceding 12 hours; (II) an inability to tolerate an oral diet over the prior 24 hours; (III) the absence of flatus over the prior 24 hours; (IV) abdominal distension on clinical exam; or (V) radiological identification of gastric distension, air-fluid levels, or dilated intestinal loops. Postoperative management consisted of an ERAS (enhanced recovery after surgery) pathway with an epidural analgesia and early carbohydrate supplementation (initiation of regular diet occurred on postoperative day 2 or 3). After exclusion of minor surgical interventions, ileus-associated operations, and emergent interventions, 841 patients were selected for evaluation. Of the entire cohort, foregut surgery composed 34.8%, colorectal surgery 35.8%, hepatobiliary surgery 19.7%, and vascular surgery at 7.4%.

Of the entire cohort, PPOI occurred in 8.8% of which colorectal operations composed the largest fraction at 52.1%. Compared to the non-PPOI group, male gender, tobacco use, performance status ≥2, and open surgical intervention were more common in the PPOI group. With respect to intraoperative characteristics, the PPOI group demonstrated significantly longer median operative duration, PPOI: 305 min (IQR, 242–484 min) *vs.* non-PPOI: 270 min (IQR, 211–358 min), P<0.01. With respect to postoperative outcomes, the PPOI group demonstrated longer duration of hospitalization with an elevated postoperative morbidity and incidence of major complications. On multivariate logistic regression, smoking, colorectal surgery, and open surgical intervention were found to be independent predictors for occurrence of PPOI. By employing these criteria, the authors have subsequently crafted a PPOI nomogram to serve as a prediction model with good discriminatory capacity (concordance index: 0.71).

In summary, Sugawara *et al.* have provided a novel approach towards PPOI risk assessment. Through emphasis on three primary risk factors: (I) open vs minimally-invasive intervention; (II) operative field (vascular, hepatobiliary, foregut, colorectal); (III) and tobacco history, this nomogram allows heath care providers to provide risk stratification among patients undergoing abdominal intervention. To date, the impact of laparoscopy in PPOI reduction has been well documented. On a cellular level, it is believed the laparoscopic environment limits inflammatory cell/mast cell activation, limiting ileus occurrence and duration (9). This pathophysiology corresponds to the fact that laparoscopic intervention minimizes surgical stress through limited bowel manipulation and peritoneal exposure. This benefit rendered by laparoscopy is quite notable as it occurs in spite of significantly longer operative duration which has been historically associated with ileus formation. Interestingly, once PPOI has occurred, ileus-related morbidity rates have been found to be equivalent regardless of laparoscopic or open index intervention. Nonetheless, analysis of multiple, large trials has consistently demonstrated strong association between laparoscopic intervention and early gastrointestinal recovery (10,11). As evidenced by the large impact of laparoscopy on the nomogram, a minimally-invasively approach should be considered the standard of care when appropriate for the patient (12).

Of the 4 operative fields reviewed in this study and included in the predictive nomogram, colorectal interventions were associated with the highest PPOI risk. To date, no contemporary studies have closely examined varying rates of ileus occurrence among surgical fields. The association of colorectal operation with higher PPOI occurrence may be attributable to multiple etiologies. In comparison to foregut and hepatobiliary intervention, colorectal surgery often requires extensive manipulation of the both the small and large bowel, thereby potentially leading to a more pronounced dysfunction of the MMC than foregut and hepatobiliary/pancreatic interventions. In spite of current standards for prophylactic oral and intravenous antibiotics, surgical site infection (SSI) rates continue to remain exceptionally high among colorectal patients (approximately 25%) which may ultimately induce a strong effect on PPOI occurrence (13). In reference, hepatobiliary SSI rates have been cited at 3.94% while gastrointestinal (foregut/midgut) SSI rates have been reported at approximately 3.3% (14,15). In general, colorectal operations have been associated with postoperative morbidity rates as high as 35% and morality rate ranging from 1-16.4%; both findings are significantly higher than other surgical subspecialties. This may ultimately be reflective of the colorectal patient demographic as well which has been associated with elevated age, significant medical comorbidities, and low preoperative albumin (16).

Tobacco use was listed by Sugawara and colleagues as the third independent predictor of PPOI occurrence and key factor in their nomogram. The impact of tobacco use on major abdominal surgery is multifactorial. Nicotine induces arterial vasoconstriction and renders a negative effect on cellular reparative mechanisms, predisposing patients to impaired healing and SSI (17). Respiratory comorbidities which may be secondary to prolonged tobacco use are independent predictors of PPOI as well (5). Moreover, active smokers were found to require elevated quantities of opiate narcotics in the first 72 hours following major surgery and may thus further increase PPOI incidence (18).

Though this model by Sugawara offers a unique method of predicting PPOI across multiple surgical specialties, a retrospective approach with minimal sample size ultimately limits inclusion to only three criteria to the nomogram. It is quite possible that with a larger population and elevated study power, additional criteria may come to fruition and be more closely assessed for integration in the current model. Additional factors that have previously been associated with reduction in PPOI in current literature warrant further analysis here as well. Foremost, incorporation of COX-2 inhibitors such as ketorolac has been associated with lower narcotic requirements and play a valuable role in ERAS pathways; stratification of patients based on receipt of NSAID therapy may allow further assessment of its impact against opioid therapy only on PPOI occurrence (19). Secondly, Sugawara *et al.* assessed regular diet initiation on either postoperative day 2 or 3. Utilization of early enteric nutrition has typically consisted of a near immediate administration of a regular diet which provides early stimulation of gastrointestinal hormones and intestinal motility; furthermore, it has been associated with reduction in PPOI and length of stay (20). Finally, evaluation of the impact of mu-antagonist therapy such as alvimopan is notably absent for this current analysis. Mu-antagonists allow selective inhibition of opioid-induced gut dysfunction while not crossing the blood-brain barrier and affecting opioid-induced analgesia. Meta-analysis of phase III trials involving application of alvimopan have illustrated significant reduction in time to first bowel movement and flatus (21).

In summary, Sugawara *et al.* have taken a pivotal step in establishing the first risk stratification model that allows medical providers to assess probability of PPOI occurrence in patients undergoing major abdominal surgery over multiple surgical specialties. Through further analysis in larger population sets, it is possible additional criteria can be identified that are suitable for this model and will further improve the external validity; although with these three current criteria, a strong concordance index has already been achieved. In theory, application of the model allows early determination of high-risk patient subsets that would ultimately benefit from evidenced-based components of the ERAS pathway such as immediate postoperative nutrition, multi-modal pain management including NSAIDs and epidural treatment, mu-antagonist therapy, and standard application of minimally invasive intervention when feasible. Prospective application of the nomogram and assessment of its ability to provide early identification and modification of PPOI risk will serve as the next step.

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Footnote

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