



Reply to three Editorials by Luris N *et al.*, Sussmann N, and Vather R, *et al.*

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Response to: Lluís N, Biondo S. Prolonged postoperative ileus after colorectal surgery: still an unresolved problem. *Ann Laparosc Endosc Surg* 2018;3:15.

Shussman N. Prolonged postoperative Ileus: what should be done to improve patient outcome? *Ann Laparosc Endosc Surg* 2018;3:18.

Vather R, Bissett IP. Who will feel sick and bloated after their operation?—predicting post-operative ileus. *Ann Laparosc Endosc Surg* 2018;3:14.

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We are grateful to read three editorials by Lluís *et al.*, Sussmann, and Vather, *et al.* (1-3) for our recent study entitled “Perioperative factors predicting prolonged postoperative ileus after major abdominal surgery” in *Journal of Gastrointestinal Surgery* (4). We devised a nomogram to predict the development of prolonged postoperative ileus (PPOI) based on the multivariable logistic regression analysis for patients undergoing major abdominal surgery. The nomogram comprised three factors: operation type (upper gastrointestinal, colorectal, hepato-biliary-pancreatic, or vascular surgery), open/laparoscopic approach, and smoking history.

As Lluís *et al.* mentioned in their editorial (1), the definition of PPOI is heterogeneous, and its heterogeneity makes it difficult to compare different studies. Additionally, PPOI is not always clearly differentiated from delayed gastrointestinal functional recovery. A previous study reported that the gastrointestinal dysfunction was caused by the bowel resection (5). Further studies are needed to clarify the PPOI definition that is the most associated with the poor postoperative course.

In agree with the editorial by Shussman (2), our nomogram to predict PPOI included two unmodifiable factors (operation type and smoking history) and one modifiable factor (open or laparoscopic approach). A

laparoscopic approach avoids intestinal manipulation and decreases surgical stress (5), resulting in one day shorter recovery from the bowel dysfunction compared to open approach (laparoscopic approach, 4 days *vs.* open approach, 5 days) (5). Perioperative management after major abdominal surgery in our group is principally based on Enhanced Recovery After Surgery (ERAS) program. However, 8.8% of patients developed PPOI. We believe that our nomogram is helpful to predict patients with high PPOI probability and may help health providers to closely monitor such patients and to strictly perform evidence-based perioperative managements. Other interventions to reduce PPOI needs to be further investigated.

We totally agree with the editorial by Vather *et al.* (3). Our nomogram needs to be validated using an external cohort as our prognostic model is based on the cohort of one institution comprising Japanese patients. Although predictive models for PPOI were previously reported (6,7), most studies have targeted PPOI after colorectal surgery. The majority of abdominal surgery is for colorectal disease in the USA and Europe, whereas the rate of non-colorectal surgery is high in Asia including Japan. Indeed, our consecutive cohort included 293 (34.8%) gastrointestinal surgery and 166 (19.7%) hepato-biliary-pancreatic surgery. We are interested in the prognostic model for PPOI

after major abdominal surgery because it may be useful to identify high PPOI probability patients in outpatient clinics that cover not only colorectal surgery but also other abdominal surgeries. The strength of our study is to predict the development of PPOI for patients undergoing major abdominal surgery. Open approach (6,7) and smoking history (7) were reported to be predictive factors for PPOI after colorectal surgery, but it is important to note that the two factors were also independent predictors of PPOI regardless of surgery types.

The incidence of PPOI was reported to decrease by employing the ERAS protocols, a laparoscopic approach, and chewing gum use. We believe that it is useful to identify patients with high PPOI probability using predictive models. More importantly, the prevention and intervention of PPOI needs to be focused as future studies because our study showed that PPOI still developed 8.8% of patients who were managed mainly based on the ERAS protocols. To develop new treatments for PPOI, the mechanisms of PPOI should be further elucidated. Studies reported that postoperative bowel dysfunctions (impaired contractility, dysmotility, and gut wall edema) are caused by the inflammatory cascade initiation within the intestinal muscularis propria (8). The inflammatory cascade involves many proinflammatory and chemoattractive mediators [interleukin (IL)-6, IL-1 signaling] and the recruitment of inflammatory leukocytes [monocyte-derived macrophages (9)]. Consequently, mediators including nitric oxide (NO) directly inhibit smooth muscle contractility. Okamoto *et al.* focused on inhibiting the inflammatory response and suppressing NO production by injecting a single intraperitoneal injection of hydrogen-rich saline into mice (10). These PPOI-associated pathways will be targets for future treatments for PPOI.

In conclusion, PPOI is still a challenging problem, occurring from 2% to 54% (3), and increases postoperative morbidity and hospital stay/cost. We believe that the predictive model for PPOI is helpful to identify patients with high PPOI probability and may help health providers to closely monitor such patients and to strictly perform evidence-based perioperative managements. Additionally, further study is needed to develop useful prevention and treatment based on the mechanisms of PPOI.

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