

# Profile of preoperative fecal organic acids closely predicts the incidence of postoperative infectious complications after major hepatectomy with extrahepatic bile duct resection: Importance of fecal acetic acid plus butyric acid minus lactic acid gap

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**Background.** To investigate the association between preoperative fecal organic acid concentrations and the incidence of postoperative infectious complications in patients undergoing major hepatectomy with extrahepatic bile duct resection for biliary malignancies.

**Methods.** The fecal samples of 44 patients were collected before undergoing hepatectomy with bile duct resection for biliary malignancies. The concentrations of fecal organic acids, including acetic acid, butyric acid, and lactic acid, and representative fecal bacteria were measured. The perioperative clinical characteristics and the concentrations of fecal organic acids were compared between patients with and without postoperative infectious complications.

**Results.** Among 44 patients, 13 (30%) developed postoperative infectious complications. Patient age and intraoperative bleeding were significantly greater in patients with postoperative infectious complications compared with those without postoperative infectious complications. The concentrations of fecal acetic acid and butyric acid were significantly less, whereas the concentration of fecal lactic acid tended to be greater in the patients with postoperative infectious complications. The calculated gap between the concentrations of fecal acetic acid plus butyric acid minus lactic acid gap was less in the patients with postoperative infectious complications (median 43.5 vs 76.1  $\mu\text{mol/g}$  of feces,  $P = .011$ ). Multivariate analysis revealed that an acetic acid plus butyric acid minus lactic acid gap  $< 60 \mu\text{mol/g}$  was an independent risk factor for postoperative infectious complications with an odds ratio of 15.6; 95% confidence interval 1.8–384.1.

**Conclusion.** The preoperative fecal organic acid profile (especially low acetic acid, low butyric acid, and high lactic acid) had a clinically important impact on the incidence of postoperative infectious complications in patients undergoing major hepatectomy with extrahepatic bile duct resection. (Surgery 2017;■:■-■.)

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The authors received no financial or personal affiliation (including research funding) or other involvement with any commercial organization that has a direct financial interest in any matter included in this article.

This study was approved by the Ethics Committee of Nagoya University Hospital.

Accepted for publication April 5, 2017.

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0039-6060/\$ - see front matter

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<http://dx.doi.org/10.1016/j.surg.2017.04.022>

DESPITE RECENT IMPROVEMENTS IN PERIOPERATIVE PATIENT CARE, the high incidence of postoperative infectious complications (POICs) in patients undergoing hepatobiliary resection for biliary cancer remains a major problem.<sup>1-3</sup> We reported recently that pre- and postoperative administration of synbiotic agents decreased infectious complications after major hepatectomy with extrahepatic bile duct resection, mainly by correcting an imbalance on the intestinal microbial environment.<sup>3,4</sup> After these reports, we adopted routinely a perioperative synbiotic treatment in patients undergoing with this type of operation. Despite this treatment even in patients with synbiotic treatment, the incidence of POICs remains unsatisfactory.<sup>2</sup>

In another prior study, we demonstrated that the presence of bacteria in the mesenteric lymph nodes (MLN) sampled during the operation (a proof of bacterial translocation) was significantly correlated with the incidence of POICs.<sup>2,5</sup> Additionally, several reports indicated that the abnormality of intestinal microflora is associated with infectious complications in critically ill patients.<sup>4,6-8</sup> Fecal organic acids, especially small chain fatty acids (SCFAs) produced by intestinal microflora, are important in maintaining the integrity of the intestinal epithelium and the vascular endothelium<sup>9</sup> and to minimize bacterial translocation. Therefore, we hypothesized that the fecal concentration of organic acids may affect the intestinal integrity and have a subsequent impact on the incidence of POICs. Currently, however, there are no data regarding the association between preoperative fecal conditions and the incidence of POICs after major hepatectomy with extrahepatic bile duct resection.

In this study, we collected fecal samples before operation from patients who underwent a major hepatectomy with extrahepatic bile duct resection for biliary malignancies. All of the patients received preoperative and postoperative synbiotic therapy according to our institutional protocol. We investigated the association between the fecal profile (including the concentration of organic acids and pH) and the incidence of POICs.

## MATERIALS AND METHODS

This study involved 44 patients who were diagnosed preoperatively as having biliary malignancy (perihilar cholangiocarcinoma or gallbladder cancer involving the hepatic hilus) and were scheduled to undergo combined liver and extrahepatic bile duct resection with hepaticojejunostomy at the Nagoya University Hospital. These patients were part of a previous study<sup>2</sup> investigating the impact

of bacterial translocation (indicated by the detection of bacteria in the mesenteric lymph nodes sampled during operation) on postoperative short outcomes. All 44 patients received synbiotic treatment pre- and postoperatively as described in our previous report.<sup>3</sup> Written informed consent for participation was obtained from each patient before enrollment in this study, which was approved by the Human Research Review Committee of the Nagoya University Hospital. All patients received a regular diet preoperatively, and no patients received parenteral or enteral nutritional supplementation before operation.

**Perioperative patient management including synbiotic treatment and bile replacement.** Pre- and postoperative synbiotic treatment was performed as previously described.<sup>3,4</sup> Briefly, the following agents were administered orally as preoperative synbiotic treatment: one 80 mL bottle of Yakult 400 (Yakult Honsha, Tokyo, Japan) containing at least  $4 \times 10^{10}$  living *Lactobacillus casei* strain Shirota; one 100 mL bottle of MILMIL S (Yakult Honsha) containing at least  $1 \times 10^{10}$  living *Bifidobacterium breve* strain Yakult; and galactooligosaccharides (Oligomate S-HP, Yakult Honsha; 15 g/d). Patients underwent synbiotic treatment for at least 2 weeks before the operation. If the patients had biliary obstruction, biliary drainage by percutaneous transhepatic biliary drainage, endoscopic nasobiliary drainage, or an endoscopic biliary stent were performed. All the bile drained externally from the external biliary drainage catheter was replaced orally or via a nasoduodenal tube to maintain the intestinal integrity, as reported previously reported.<sup>10</sup> One day preoperatively, all patients underwent intestinal preparation with an iso-osmotic polyethyleneglycol solution (2,000 mL).

Prophylactic antibiotics were selected according to the preoperative surveillance bile culture if obtained preoperatively. When the bile culture was negative, a first- or second-generation cephalosporin was used. When the bile culture was positive, antibiotics were selected according to the susceptibility of the specific microorganisms. In patients with preoperative cholangitis, therapeutic antibiotics were administered and operative intervention was postponed until the symptoms subsided. No patients received preoperative oral administration of antibiotics. On the day of operation, all patients received a single, intravenous drip infusion of antibiotics 30 minutes before operation. The antibiotics were administered according to the kinetic half-lives of the antibiotics (every 3 hours in most cases) during the operation to maintain optimal concentrations in

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