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Blood Galectin-3 Levels Predict Postoperative Complications after Colorectal Cancer Surgery

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Background: Recent studies suggested that galectin-3 may act as a pro-inflammatory damage-associated molecular pattern. The aim of this study is to investigate the association between blood galectin-3 and postoperative complications (POC) after colorectal cancer (CRC) surgery.

Methods: Blood samples were taken from 35 patients with CRC before surgery, immediately after surgery, and on postoperative days (POD) 1, 3, 5, and 7. Blood galectin-3 and interleukin-6 levels were measured by commercially available ELISA. Patients were divided into those with (POC group) and without POC (no-POC group).

Results: Significantly higher galectin-3 levels were observed pre- and postoperatively in the POC group (n=10) compared with those of the no-POC group (n=25). Galectin-3 levels on POD1 showed the best predictive potential for POC (cut-off: 3.18 pg/mL, area under the curve: 0.868).

Conclusions: These results indicate that increased perioperative blood galectin-3 levels may be associated with POC after CRC surgery. (J Nippon Med Sch 2019; 86: 142–148)

Key words: colorectal cancer, galectin-3, postoperative complication, surgery

Introduction

The incidence of colorectal cancer (CRC) in Japan is increasing, and CRC was recognised as the commonest cancer in 2015[1]. Although surgical resection has been a mainstay for the treatment of CRC, high rates of postoperative complications (POC) (about 30%) and mortality (about 4%) are reported, despite improvements in surgical techniques and perioperative management[2,3]. Recent studies demonstrated that POC were associated with poorer long-term outcomes after CRC surgery[4–7], and prevention of POC is thus a critical issue for surgeons. But prevention is difficult, because multiple risk factors promote the occurrence of POC, such as comorbidities, surgical procedures, operation time, and transfusion of blood[8–11]. Recent interest has focused on perioperative pro-inflammatory immunological host responses as distinct predictive biomarkers for POC after CRC surgery[12–16].

Galectin-3 is a 31-kDa chimeric galectin characterized by a single C-terminal carbohydrate recognition domain (CRD) and an N-terminal aggregating domain that interacts with non-carbohydrate ligands to allow the formation of oligomers[17,18]. The functions of galectin-3 are diverse, including roles in cell migration, adhesion, apoptosis, and inflammatory and immunomodulatory activities. Studies have shown that galectin-3 is associated with several inflammatory diseases, such as sepsis and airway inflammation[18–20]. Galectin-3 was recently shown to provoke the inflammatory responses in sepsis, and has emerged as a 'damage-associated molecular pattern (DAMP)'[21]. However, the influence of galectin-3 on surgical outcomes following gastrointestinal surgery is unknown. We evaluated the association between blood galectin-3 levels and the development of POC after elec-

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https://doi.org/10.1272/jnms.JNMS.2019_86-302
Journal Website (http://www2.nms.ac.jp/jnms/)

Table 1 Clinical characteristics of patients with and without postoperative complications and results of univariate analyses

Variables	No POC group (n=25)	POC group (n=10)	*P* value
Sex (male/female)	16/9	7/3	1.000
Age (years)	67.2±1.6	68.4±2.7	0.711
BMI (kg/m^2)	22.6±0.6	22.4±1.0	0.800
Comorbidity (yes/no)	15/10	7/3	0.709
ASA score (1/2/3)	12/13/0	3/7/0	0.458
Tumor location (Colon/Rectum)	13/12	3/7	0.285
Pathological stage (JSCCR) (0/I/II/III/IV)	2/2/13/6/2	1/2/1/5/1	0.105
Surgical approach (open/laparoscopic)	1/24	2/8	0.190
Resection of other organ (yes/no)	1/24	1/9	0.496
Surgical duration (min)	270±19	364±39	0.046
Intraoperative blood loss (mL)	64±19	289±102	0.059
Preoperative blood exam			
White blood cells (counts/μL)	6,356±309	6,375±820	0.983
C-reactive protein (mg/dL)	0.5±0.1	0.7±0.5	0.679
IL-6 (ng/mL)	undetectable	undetectable	-
Albumin (g/dL)	3.9±0.1	3.7±0.1	0.246
Galectin-3 (ng/mL)	2.8±0.4	4.4±0.7	0.045

Values are expressed as mean ± SE. POC; postoperative complications, BMI; body mass index, ASA; American Society of Anesthesiologists, JSCCR; Japan Society for Cancer of the Colon and Rectum

Table 2 Details of postoperative complications

Clavien-Dindo grading	Postoperative complications	n
I	Superficial SSI	2
II	Minor anastomotic leakage	1
	Intraabdominal abscess	1
IIIa	Deep SSI	1
	Adhesional small bowel obstruction	1
IIIb	Major anastomotic leakage	2
	Adhesional small bowel obstruction	1
	Intraabdominal abscess	1

SSI: surgical site infection

tive CRC surgery.

Materials and Methods

Subjects

This single-institutional prospective study from January 2014 to December 2015 was conducted at the Department of Surgery of Nippon Medical School Chiba Hokusoh Hospital. Thirty-five patients with CRC with elective primary tumor resection were included in this study. Antibiotic prophylaxis was administered for all patients. Patients under eighteen years old, having ongoing infection, preoperative chemotherapy and/or radiation therapy, or severe organ dysfunction were excluded from this study. The approach of surgery, open or laparoscopic was determined by patient factors and the surgeons' decision. The study was performed based on the standards of the Helsinki Declaration. This study protocol was approved by the Ethics Committee of the institution (approval no. 562).

Postoperative complications were categorised by the Clavien-Dingo grading system[22]. Complications of grade ≥I occurring before the end of the individual follow-up period of 30 days postoperatively were defined as POC in this study. The included patients (n=35) were divided into either group based on the presence (POC group, n=10) or absence (no-POC group, n=25) of POC. Related clinical data were collected at chart review.

Blood Collection and Measurements

Blood samples were collected from the antecubital vein before (pre) and immediately after surgery (post), and on 1, 3, 5, and 7 postoperative days (POD) in the morning. White blood cell count, C-reactive protein (CRP), and albumin levels were routinely monitored at the institutional laboratory. The detection limit of CRP was 0.02 mg/dL. The serum was extracted by centrifugation at 2,000×*g* for 10 min at 4℃ and stored at −80℃. Blood galectin-3 and interleukin (IL)-6 levels were analysed by commercially available kits (DuoSet ELISA, R&D Systems, Minneapolis, MN, USA) at all the stated time

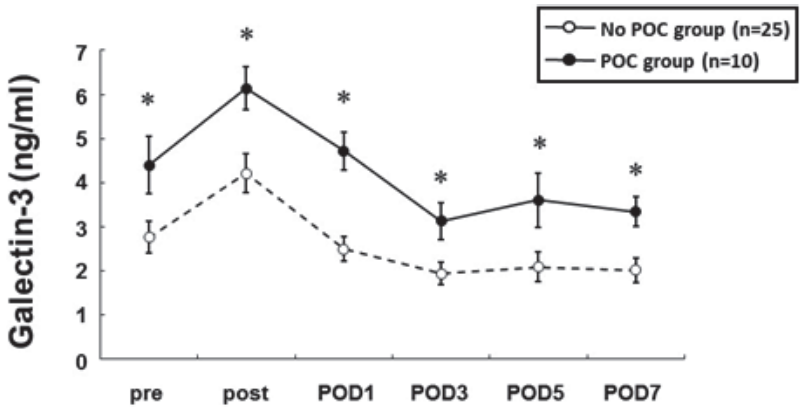

Fig. 1 Perioperative changes in blood galectin-3 levels in patients without (no-POC; open circles) and with POC (POC; closed circles). The data are expressed as mean ± SE. *P<0.05 *vs.* the no-POC group at the same time point.
POC; postoperative complication, pre; preoperative, post; immediately after surgery, POD; postoperative day.

points.

Statistics

Data were expressed as mean ± standard error (SE). Continuous variables were compared by Student's *t*-tests and Mann-Whitney *U* tests, and discrete variables were compared by χ^2 and Fisher's exact tests. Correlations were analysed using Spearman's tests. To identify the cut-off of perioperative galectin-3 in terms of POC, analysis of receiver operating characteristic (ROC) curve was performed. If the P value was <0.05, it was considered to be statistically significant. All statistics were performed using R, version 3.1.0 (Vienna, Austria).

Results

Baseline Characteristics of Patients

The clinical characteristics of the 35 patients are shown in **Table 1**. The POC group had a significantly longer surgical duration (P=0.046) and tended to have greater intraoperative blood loss (P=0.057) than the no-POC group. No significant differences were observed in preoperative WBC, CRP, and albumin concentrations between the two groups, but galectin-3 levels were significantly higher in the POC group than the no-POC group (P= 0.045). Preoperative IL-6 levels were undetectable in both groups.

Among the patients with POC, six had complications ≥ grade III and four with grade IIIb complications required re-operations. Details of POC are shown in **Table 2**. The median time to POC diagnosis was POD5 (range: 3−16).

Perioperative Changes in Galectin-3

Patients in the POC group showed a significant increase of preoperative galectin-3 levels than the no-POC group (**Table 1**). Galectin-3 levels increased immediately after surgery in both groups and then recovered (**Fig. 1**). Galectin-3 levels immediately after surgery were significantly higher than preoperative levels in both groups, while levels in the POC group were significantly higher than the no-POC group throughout all perioperative periods.

Perioperative Inflammatory Responses

The perioperative changes in pro-inflammatory markers, including WBC, CRP, and IL-6, are summarized in **Table 3**. Preoperative WBC and CRP levels were equivalent in the POC and no-POC groups, but both parameters were significantly higher in the POC group on POD 5 and 7. However, no significant differences in IL-6 levels were observed throughout the entire perioperative period, because of the high degree of individual variation.

Evaluation of Galectin-3 as a Predictive Marker for POC

ROC curve analyses of blood galectin-3 levels pre, post, and on POD1 versus POC are shown in **Figure 2**. Levels at all three time points showed relatively high predictive potentials for POC (>0.7 of the area under the ROC curve (AUC)). Among these, the POD1 value showed the best predictive performance (cut-off: 3.18 pg/mL, AUC: 0.868, 95% confidence interval [CI]: 0.745−0.991), with a sensitivity and specificity of 68.0% and 90.0 %, respectively.

Table 3 Perioperative inflammatory responses related to postoperative complications

	Pre		Post		POD1		POD3		POD5		POD7	
Variables	No POC	POC	No POC	POC	No POC	POC	No POC	POC	No POC	POC	No POC	POC
White blood cells (counts/μL)	6,356±309	6,375±820	9,419±555	10,251±1,389	9,015±666	10,093±1,129	7,181±503	9,854±1,231	6,119±433	10,421±1,021*	5,880±351	9,498±1,062*
C-reactive protein (mg/dL)	0.5±0.1	0.7±0.5	0.6±0.2	0.7±0.3	6.1±0.8	7.5±1.1	0.5±0.1	11.8±1.7	4.1±0.7	9.0±2.7*	2.0±0.4	9.9±2.0*
IL-6 (ng/mL)	ud	ud	122.1±23.1	257.6±79.7	133.0±23.1	187.1±53.7	9.8±3.3	26.2±11.3	6.6±4.4	27.3±16.0	2.1±0.9	80.9±67.9

Values are expressed as mean ± SE. ud: undetectable. *P<0.05 vs. No POC group

Discussion

The results of this study demonstrate that high perioperative blood galectin-3 levels are associated with POC after CRC surgery. We also showed that surgical stress transiently increased blood galectin-3 levels immediately after surgery, with gradual recovery of levels thereafter.

Galectins comprise a group of evolutionarily conserved proteins present in vertebrates, invertebrates, and fungi[23]. Fifteen mammalian galectins have been discovered to date, all including a characteristic CRD of about 130 amino acids, through which they can bind β-galactosides. Galectin-3 is classified in the chimera-type group, with a C-terminal CRD and a large N-terminal protein-binding domain[24]. The distribution of galectin-3 is wide-range throughout the body, including in the digestive and urogenital tracts, lungs, and heart. Also, galectin-3 is abundantly expressed in myeloid cells (monocytes, macrophages, dendritic cells, neutrophils) and in epithelial and endothelial cells[25,26]. It is located predominantly in the cytoplasm, and can be secreted extracellularly following stimulation with various agents such as lipopolysaccharide, under both physiological and pathophysiological conditions. Extracellular galectin-3 is involved in various functions, including immunity against pathogens and in both acute and chronic inflammation[25]. Recent studies have demonstrated that galectin-3 can recognize microbial structures as a pathogen-recognition receptor, as well as having pro-inflammatory properties eliciting infiltration of neutrophils and other immune cells, and that it can also be released as a DAMP. Regarding its role as a DAMP, Mishra *et al*.[21] recently reported that galectin-3 was released in the lungs of mice in a *Francisella novicida* lethal sepsis model, and elicited neutrophil infiltration, inflammatory cytokine release, vascular injury, and the release of various inflammatory mediators from neutrophils.

Blood galectin-3 level has been broadly applied as a biomarker in a number of inflammatory diseases, such as cancers, heart failure, stroke, rheumatoid arthritis, and sepsis[9,19,20,23,24,27]. Mueller *et al*.[24] reported an approximately 2.7-fold increase in blood galectin-3 levels in human sepsis than healthy controls. Oever *et al*.[23] also reported that galectin-3 levels were higher in patients with infections (viral respiratory infections, bacterial sepsis, and candidaemia) than controls or patients with non-infectious inflammatory diseases (gout or autoinflammatory syndrome). The ability of galectin-3 to segregate between an infection and non-infectious inflammation is superior to

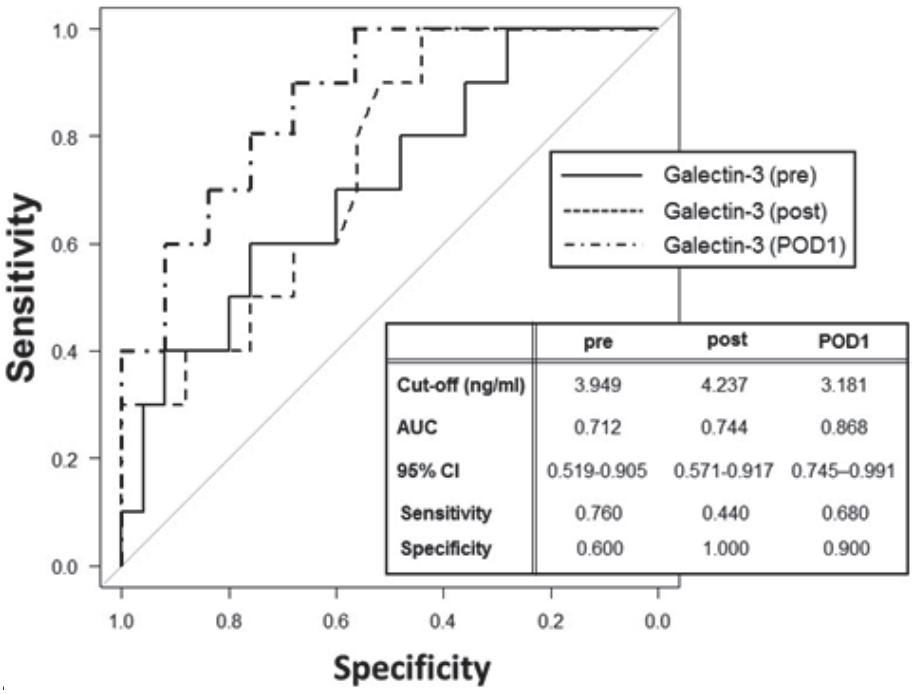

Fig. 2 Receiver operating characteristic curve analyses of blood galectin-3 levels versus POC.
POC; postoperative complication, pre; preoperative, post; immediately after surgery, POD; postoperative day, AUC; area under the curve, CI; confidence interval

CRP; but, galectin-3 could not segregate between bacterial and *Candida* sepsis. Interestingly, galectin-3 levels were 2-fold higher in patients with Gram-negative than Gram-positive infections, though the difference was not significant[23]. The immunological characteristics of galectin-3 may explain the postoperative increase in blood levels in patients with POC in the current study. Notably, nine of the 10 patients with POC had infectious complications. Furthermore, Gram-negative enterobacteria, such as *Enterococcus faecalis*, *Escherichia coli*, and *Pseudomonas aeruginosa*, are known to be isolated predominantly from surgical site infections and could be responsible for causing inflammation[26].

The early detection of POC would aid clinical decision-making and provide significant opportunities to achieve better patient outcomes. Pro-inflammatory and immunological blood biomarkers have recently received much attention in relation to their abilities to predict POC after CRC surgery[12–16]. CRP is used routinely as a pro-inflammatory marker to monitor postoperative condition, and has been widely reported to predict POC after CRC surgery[14,28,29]; however, its best predictive potential is based on levels measured on POD3 or 4[14,28,29], which is relatively late for effective interventions given the usual diagnostic period for POC (POD 5 in our study cohort). Retting *et al*.[15] recently reported that higher IL-6 blood levels on POD1 provided the best predictive value for POC after major abdominal surgery compared with CRP, tumor necrosis factor-α, and leukocyte count. However, the predictive potential of IL-6 on POD1 in the current study was relatively low (AUC: 0.67) compared with that for galectin-3 (AUC: 0.868). Neither CRP nor IL-6 levels demonstrated any predictive value in our study cohort.

It should be noted that the significant difference of blood galectin-3 levels was observed preoperatively, which could imply an important and intrinsic pathophysiological difference between the two groups. The POC group had a slight increase of preoperative CRP levels (but not statistically significant) without any evidence of infection. This result suggested that patients in the POC group were preoperatively under "low-grade chronic inflammation condition", which is associated with dormant pathological conditions, such as visceral obesity, arteriosclerosis, and diabetes mellites. These disease conditions are reported to have higher blood levels of galectin-3 than control patients[30,31]. The preoperative low-grade chronic inflammation condition could be a trigger for an exaggerated hyperinflammation induced by surgical stress and result in the occurrence of POCs[32,33].

The results of our study offer several potential clinical benefits. In the case of patients with blood galectin-3 levels below the cut-off value, surgeons can be reassured

that POC are unlikely to occur, thus allowing immediate patient discharge. In contrast, higher galectin-3 levels can alert surgeons to the possibility of POC at an early stage, allowing the patient to be reassessed and managed accordingly.

This observational study had certain limitations: 1) this was a single-institution study with a small cohort of patients, which may have affected the predictive potential of the marker to discriminate between the presence and absence of POC; 2) POD1 blood samples were collected at different times after surgery, because the starting time of surgery varied; 3) the degree of surgical stress may differ among different procedures.

In conclusion, surgical stress may increase blood galectin-3 levels and high perioperative blood galectin-3 levels may be associated with POC after CRC surgery. Future studies with larger sample sizes are warranted to clarify the predictive value of galectin-3, its role in the pathophysiology of POC, and its potential in terms of therapeutic interventions for POC.

Acknowledgements: This study was financially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (15K10037: Matsuda A). We thank Susan Furness, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Conflict of Interest: All authors have no conflict of interest to declare.

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(Received, July 8, 2018)
(Accepted, January 22, 2019)