

# Risk Factors for Opioid-induced Constipation in Cancer Patients: a Single-institution, Retrospective Analysis

Yuko Kanbayashi (✉ [yuko.kanbayashi@ompu.ac.jp](mailto:yuko.kanbayashi@ompu.ac.jp))

Osaka Ika Yakka Daigaku <https://orcid.org/0000-0002-0095-2293>

Yuichi Ishizuka

Seirei Hamamatsu Byoin

Mayumi Shimizu

Seirei Hamamatsu Hospital: Seirei Hamamatsu Byoin

Shohei Sawa

Seirei Hamamatsu Hospital: Seirei Hamamatsu Byoin

Katsushige Yabe

Seirei Hamamatsu Hospital: Seirei Hamamatsu Byoin

Mayako Uchida

Doshisha Women's College of Liberal Arts: Doshisha Joshi Daigaku

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## Research Article

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# Abstract

**Purpose:** To identify risk factors for opioid-induced constipation (OIC).

**Methods:** This study retrospectively analysed 175 advanced cancer patients who were receiving pain treatment with opioids and were newly prescribed laxatives for OIC at Seirei Hamamatsu General Hospital between November 2016 and June 2021. For the regression analysis of factors associated with OIC, variables were extracted manually from medical charts. The effect of laxatives was evaluated 3 days after administration. The effect of laxatives was evaluated based on whether the OIC was improved. The OIC was defined based on Rome IV diagnostic criteria. Multivariate ordered logistic regression analysis was performed to identify risk factors for OIC. Optimal cut-off thresholds were determined using receiver operating characteristic analysis. Values of  $P < 0.05$  (two-tailed) were considered significant.

**Results:** Significant factors identified included body mass index (BMI) (odds ratio [OR] = 0.141, 95% confidence interval [CI] = 0.027–0.733;  $P = 0.020$ ), chemotherapy with taxane within 1 month of evaluation of laxative effect (OR = 0.255, 95%CI = 0.068–0.958;  $P = 0.043$ ), use of naldemedine (OR = 2.791, 95%CI = 1.220–6.385;  $P = 0.015$ ) and addition or switching due to insufficient prior laxatives (OR = 0.339, 95%CI = 0.143–0.800;  $P = 0.014$ ).

**Conclusion:** High BMI, chemotherapy including a taxane within 1 month of evaluation of laxative effect, no use of naldemedine and addition or switching due to insufficient prior laxatives were identified as risk factors for OIC in advanced cancer patients with cancer pain.

## Introduction

Opioid analgesics represent the standard of treatment for moderate-to-severe cancer pain [1, 2]. While definitely effective in managing cancer pain, opioid use is often limited by adverse effects, which can lead to their discontinuation following significantly negative impacts on quality of life (QOL) [2, 3]. Opioid-induced constipation (OIC) remains the most common adverse event associated with opioid use. OIC is common among advanced cancer patients, with a prevalence of approximately 51–87% in patients taking opioids for pain management [4–6]. Advanced cancer patients are likely to experience severe distress, reduced work productivity, poor QOL, and increased healthcare utilization. Pharmacological treatments involve the use of traditional laxatives and newer agents like peripherally acting mu-opioid receptor agonists (PAMORAs), including naldemedine [6–8]. On the other hand, some patients have insufficient OIC control even with these laxatives in clinical practice. This retrospective study was thus undertaken to identify risk factors for OIC to help guide future strategies toward improving QOL in cancer patients receiving pain treatment with opioids.

## Patients And Methods

### Study Period and Participants

This study retrospectively analysed 208 cancer patients newly prescribed laxatives for OIC at Seirei Hamamatsu General Hospital between November 2016 and June 2021. All study protocols were approved by the Medical Ethics Review Committee at Seirei Hamamatsu General Hospital (approval no. 3310) and the Faculty of Pharmacy at Osaka Medical Pharmaceutical University (approval no. 0088).

## Extraction of Variables

Variables associated with alleviation of OIC were extracted from clinical records and used for regression analysis. Variables extracted were factors potentially affecting OIC: demographic data (age, height, weight, body surface area [BSA], body mass index [BMI]), Eastern Cooperative Oncology Group Performance Status (ECOG-PS), daily dosage of opioid in morphine-equivalents (milligrams), types of laxative, types of opioid, stage of cancer, anti-cancer drug administered within 1 month of evaluation of laxative effect, laxative administration time, and cancer type.

The effect of newly prescribed laxatives was evaluated 3 days after administration. The effect of laxatives was evaluated based on whether the OIC was improved. The OIC was defined based on Rome IV diagnostic criteria [7]. Details of Rome IV diagnostic criteria for the diagnosis of OIC used in this study have been published previously [9–11].

## Statistical Analysis

The analytical procedure employed was logistic regression, with the response =  $Y$  being a binary categorical variable (laxative effective or laxative not effective) and evaluated simultaneously with multiple predictors of OIC =  $X$ . To improve accuracy, predictors that were not essential to explain the response =  $Y$  were excluded.

Independent variables were analysed for multicollinearity (correlation coefficient  $|r| \geq 0.7$ ), since correlations among variables can lead to unreliable and unstable results of regression analyses. Independent variables were extracted based on the strength of the correlation with OIC or clinical significance. First, univariate logistic regression analyses between outcomes and each potential independent variable were performed. Subsequently, a multivariate logistic regression model was constructed by employing the forward-backward stepwise selection procedure with the resulting candidate variables. The model used a variable entry criterion of 0.15 and a variable retention criterion of 0.1. Optimal cut-off thresholds were determined using receiver operating characteristic (ROC) curve analysis.

For all statistical analyses, values of  $P < 0.05$  (two-tailed) were considered significant. All analyses were performed using JMP version 14.3.0 (SAS Institute, Cary, NC).

## Results

All 208 patients were newly prescribed laxatives, but 33 patients were excluded from this study due to insufficient data. Table 1 presents the clinical characteristics of the remaining 175 enrolled patients, potential variables related to OIC, and the results of univariate analyses. The forward stepwise selection procedure identified the following candidate variables: age, BMI, chemotherapy with taxane within 1 month, daily dosage of opioid, use of naldemedine, laxative prescription within 2 days of opioid initiation, and addition or switching due to insufficient prior laxatives.

Table 1  
Patient characteristics, extracted variables, and results of univariate analyses (n = 175)

	<b>Laxative not effective</b> <b>(n = 77)</b>	<b>Laxative effective</b> <b>(n = 98)</b>	<b>P value</b>	<b>Odds ratio</b> <b>(95%CI)</b>
Sex, male, n (%)	50 (64.9)	54 (55.1)	0.189	0.66 (0.36–1.23)
Age (y), median (range)	69 (42–90)	70 (35–89)	0.682	0.99 (0.96–1.03)
Height (cm), median (range)	161.5 (145–176)	159.5 (143–182.6)	0.890	1.00 (0.96–1.04)
Weight (kg), median (range)	54 (32.5–77.5)	51.4 (32.8–84)	0.180	0.98 (0.95–1.01)
BMI (kg/m <sup>2</sup> ), median (range)	21.0 (13.0–28.9)	20.0 (14.2–30.3)	0.171	0.94 (0.86–1.03)
BSA, median (range)	1.56 (1.22–1.86)	1.54 (1.20–2.04)	0.305	0.35 (0.05–2.58)
PS (0/1/2/3/4)	0/16/33/25/3	0/19/37/35/7	0.385	1.17 (0.82–1.67)
Stage of cancer (1/2/3/4)	5/7/9/56	0/7/13/78	0.062	1.48 (0.98–2.22)
Anti-cancer drug administered within 1 month of evaluation				
<i>Taxane, n (%)</i>	8 (10.3)	5 (5.1)	0.194	0.46 (0.15–1.48)

CI, confidence interval; BMI, body mass index; BSA, body surface area; PS, ECOG performance status

\*P<0.05

	<b>Laxative not effective</b> <b>(n = 77)</b>	<b>Laxative effective</b> <b>(n = 98)</b>	<b>P value</b>	<b>Odds ratio</b> <b>(95%CI)</b>
<i>Fluorouracil, n (%)</i>	6 (7.8)	16 (16.3)	0.098	2.31 (0.86–6.22)
<i>Platinum, n (%)</i>	12 (15.6)	20 (20.4)	0.414	1.39 (0.63–3.05)
Type of opioid				
<i>Morphine, n (%)</i>	5 (6.5)	13 (13.3)	0.151	2.20 (0.75–6.47)
<i>Fentanyl, n (%)</i>	3 (3.9)	3 (3.1)	0.763	0.78 (0.15–3.97)
<i>Oxycodone, n (%)</i>	47 (61.0)	61 (62.2)	0.871	1.05 (0.57–1.94)
<i>Tramadol, n (%)</i>	4 (5.2)	5 (5.1)	0.978	0.98 (0.25–3.79)
Daily dose, morphine-equivalents (mg), median (range)	30 (10–144)	30 (7.5–576)	0.473	1.00 (1.00–1.01)
Type of laxative				
<i>Magnesium oxide, n (%)</i>	25 (32.5)	40 (40.8)	0.257	1.43 (0.77–2.68)
<i>Sennoside, n (%)</i>	16 (20.8)	15 (15.3)	0.294	0.98 (0.95–1.02)

CI, confidence interval; BMI, body mass index; BSA, body surface area; PS, ECOG performance status

\*P<0.05

	<b>Laxative not effective</b> <b>(n = 77)</b>	<b>Laxative effective</b> <b>(n = 98)</b>	<b>P value</b>	<b>Odds ratio</b> <b>(95%CI)</b>
<i>Lubiprostone, n (%)</i>	3 (3.9)	4 (4.1)	0.950	1.05 (0.23–4.84)
<i>Naldemedine, n (%)</i>	42 (54.5)	64 (65.3)	0.149	1.57 (0.85–2.89)
Laxative prescription within 2 days of opioid initiation, n (%)	15 (19.5)	16 (16.3)	0.588	0.81 (0.37–1.76)
Addition or switching due to insufficient prior laxative, n (%)	33 (42.9)	35 (35.7)	0.336	0.74 (0.40–1.37)
<b>Cancer type, n (%)</b>				
<i>Colon, n (%)</i>	5 (6.5)	9 (9.2)	0.517	1.46 (0.47–4.54)
<i>Gastric, n (%)</i>	1 (1.3)	9 (9.2)	0.056	7.69 (0.95–62.0)
<i>Pancreatic, n (%)</i>	16 (20.8)	18 (18.4)	0.689	0.86 (0.40–1.82)
<i>Esophageal, n (%)</i>	3 (3.9)	5 (5.1)	0.705	1.33 (0.31–5.73)
<i>Liver, n (%)</i>	3 (3.9)	2 (2.0)	0.472	0.51 (0.08–3.15)

CI, confidence interval; BMI, body mass index; BSA, body surface area; PS, ECOG performance status

\*P<0.05

	<b>Laxative not effective</b> <b>(n = 77)</b>	<b>Laxative effective</b> <b>(n = 98)</b>	<b>P value</b>	<b>Odds ratio</b> <b>(95%CI)</b>
<i>Lung, n (%)</i>	12 (15.6)	17 (17.3)	0.758	1.14 (0.51–2.55)
<i>Breast, n (%)</i>	3 (3.9)	5 (5.1)	0.705	1.33 (0.31–5.73)
<i>Urinary tumor, n (%)</i>	9 (11.7)	5 (5.1)	0.121	0.41 (0.13–1.27)
<i>Ovarian, n (%)</i>	2 (2.6)	4 (4.1)	0.595	1.60 (0.28–8.95)
<i>Uterus, n (%)</i>	1 (1.3)	5 (5.1)	0.203	4.09 (0.47–35.7)
<i>Hematopoietic tumor, n (%)</i>	3 (3.9)	5 (5.1)	0.705	1.33 (0.31–5.73)
<i>Head and neck, n (%)</i>	12 (15.6)	13 (13.3)	0.664	0.83 (0.35–1.94)
<i>Others, n (%)</i>	7 (9.1)	1 (1.0)	0.036*	0.10 (0.01–0.86)

CI, confidence interval; BMI, body mass index; BSA, body surface area; PS, ECOG performance status

\*P<0.05

Multivariate ordered logistic regression analysis was performed using these variables. Significant factors identified included BMI (odds ratio [OR] = 0.141, 95% confidence interval [CI] = 0.027–0.733; P = 0.020), chemotherapy with taxane within 1 month (OR = 0.255, 95% CI = 0.068–0.958; P = 0.043), use of naldemedine (OR = 2.791, 95% CI = 1.220–6.385; P = 0.015) and addition or switching due to insufficient prior laxatives (OR = 0.339, CI = 0.143–0.800; P = 0.014) (Table 2). ROC analysis revealed that poor OIC



control was more likely to occur with BMI  $\geq 21.5$  kg/m<sup>2</sup>, showing 45.3% sensitivity and 71.1% specificity (area under the ROC curve [AUC] = 0.57).

Table 2

Results of multivariate ordered logistic regression analysis for variables extracted by forward selection (n = 175)

Variable	P value	Odds ratio	95%CI	
			Lower endpoint	Upper endpoint
Age	0.149	0.285	0.052	1.569
BMI	0.020*	0.141	0.027	0.733
Taxane	0.043*	0.255	0.068	0.958
Daily dose (mg) converted to morphine	0.935	1.169	0.028	48.5
Naldemedine	0.015*	2.791	1.220	6.385
Laxative prescription within 2 days of opioid initiation	0.671	0.815	0.317	2.098
Addition or switching due to insufficient prior laxative	0.014*	0.339	0.143	0.800
CI, confidence interval; BMI, body mass index				
*P<0.05				

## Discussion

The multivariate ordered logistic regression analysis performed in this study showed that risk factors for OIC included BMI, chemotherapy with a taxane within 1 month, use of naldemedine and addition or switching of laxatives.

BMI was extracted as a significant factor for OIC. Previous studies have reported obesity as a risk factor for constipation [12, 13]. Yurtdaş et al. discussed a connection between obesity and constipation, low physical activity, inadequate dietary fibre intake and poor nutritional habits (fast food, not eating enough fibre and not drinking enough water) are reasons for obesity and constipation [12]. The results of this study were also consistent with the results of previous studies. On the other hand, ROC curve analysis revealed a BMI cut-off of  $\geq 21.5$  kg/m<sup>2</sup> for the group likely to be poorly OIC controlled. The World Health Organization has defined obese or overweight patients as individuals with BMI  $\geq 25$  kg/m<sup>2</sup> [14]. Patients with BMI  $\geq 21.5$  kg/m<sup>2</sup> do not represent an obese population, so this result seems to be due to the fact that the target population for analysis comprised advanced cancer patients with cancer-related pain, mostly with cachexia and not good ECOG-PS. Further verification is needed in this regard among cancer patients with OIC.

The results of this study showed that OIC was poorly controlled when chemotherapy with taxane was given within 1 month. Taxanes are anticancer drugs that have a side effect of constipation due to neuropathy [15]. Taxane-induced neuropathy persists for a long period in clinical practice. If a taxane was administered within 1 month of evaluation of laxative effect, side effects may persist. OIC control may thus be difficult.

The initiation of naldemedine was extracted as a predictor of the effectiveness of OIC control. All were opioid-treated patients in this study, suggesting that naldemedine is most effective for OIC. Naldemedine is a novel PAMORA being developed for the treatment of OIC without affecting central analgesia. Therefore, this mechanism of action suggests that the use of naldemedine will prove effective in avoiding OIC. However, the guidelines for OIC suggest that classic laxatives should be used first, and if the effects are insufficient, use of novel constipation treatments or PAMORA is recommended [16–18]. Further verification of the appropriate timing of naldemedine initiation is needed.

Addition or switching due to insufficient prior laxatives was also extracted as a risk factor for OIC. Poor control of OIC clearly makes sufficient control difficult to obtain, even with the addition of or switching to new laxatives. OIC is less tolerant and requires early control. Clinicians need to make early adjustments to address OIC.

Several limitations to the current study need to be considered. First, the retrospective nature of the study may have decreased the validity of the data obtained. Second, since this study was performed at a single institute, prospective multicentre studies are needed to confirm the results.

In conclusion, high BMI, chemotherapy including a taxane within 1 month of evaluation of laxative effect, no use of naldemedine and addition or switching due to insufficient prior laxatives were identified as risk factors for OIC in advanced cancer patients with cancer pain. However, our findings need to be confirmed in further studies. Nevertheless, these results may assist in developing strategies to improve QOL among patients with OIC.

## **Declarations**

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### **Author contributions**

YK: concept and design, data analysis, data interpretation, manuscript writing; YI, MS, SS & KY: concept and design, data acquisition, data interpretation; MU: concept and design, data interpretation, supervision of the manuscript. All authors read and approved the final manuscript.

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No funding was received for conducting this study.

### **Data availability**

Data not available due to ethical restrictions.

### **Code availability**

Not applicable

### **Ethical approval**

The Medical Ethics Review Committee of Seirei Hamamatsu General Hospital approval no.3310 and Faculty of Pharmacy, Osaka Medical Pharmaceutical University approved this study, approval no.0088. All procedures were performed in accordance with the ethical standards of the Seirei Hamamatsu General Hospital and Osaka Medical Pharmaceutical University of Medicine Institutional Medical Ethics Review Committee and the 1964 Declaration of Helsinki and its later amendments. No prospective studies with human participants or animals were performed by any of the authors for this article.

This study retrospectively analysed 208 cancer patients newly prescribed laxatives for OIC or OIC prevention at Seirei Hamamatsu General Hospital between November 2016 and June 2021. All study protocols were approved by the Medical Ethics Review Committee at Seirei Hamamatsu General Hospital (approval no. 3310) and the Faculty of Pharmacy at Osaka Medical Pharmaceutical University (approval no. 0088).

### **Consent to participate**

Given the retrospective nature of this work, the need to obtain informed consent was waived for the individual participants included in the study, in accordance with the standards of the Seirei Hamamatsu General Hospital and Osaka Medical Pharmaceutical University of Medicine Institutional Medical Ethics Review Committee.

### **Consent for publication**

All authors give their consent for this manuscript to be published in *Supportive Care in Cancer*.

### **Conflict of interest**

None declared.

## **References**

1. Mercadante S (2011) Emerging drugs for cancer-related pain. *Support Care Cancer*. 19:1887-93.

2. Wiffen PJ, Wee B, Derry S, Bell RF, Moore RA (2017) Opioids for cancer pain - an overview of Cochrane reviews. *Cochrane Database Syst Rev.* 7:CD012592.
3. Krashin D, Murinova N, Jumelle P, Ballantyne J (2015) Opioid risk assessment in palliative medicine. *Expert Opin Drug Saf.* 14:1023-33.
4. Sarrió RG, Calsina-Berna A, García AG, Esparza-Miñana JM, Ferrer EF; Working Group ActEIO Project, Porta-Sales J (2021) Delphi consensus on strategies in the management of opioid-induced constipation in cancer patients. *BMC Palliat Care.* 20:1.
5. Mesía R, Virizuela Echaburu JA, Gómez J, Sauri T, Serrano G, Pujol E (2019) Opioid-induced constipation in oncological patients: new strategies of management. *Curr Treat Options Oncol.* 20:91.
6. ALMouaalamy N (2021) Opioid-induced constipation in advanced cancer patients. *Cureus.* 13:e14386.
7. Farmer AD, Drewes AM, Chiarioni G, De Giorgio R, O'Brien T, Morlion B, Tack J (2019) Pathophysiology and management of opioid-induced constipation: European expert consensus statement. *United European Gastroenterol J.* 7:7-20.
8. Argoff CE (2020) Opioid-induced constipation: a review of health-related quality of life, patient burden, practical clinical considerations, and the impact of peripherally acting  $\mu$ -opioid receptor antagonists. *Clin J Pain.* 36:716-722.
9. Palsson OS, Whitehead WE, van Tilburg MA, Chang L, Chey W, Crowell MD, Keefer L, Lembo AJ, Parkman HP, Rao SS, Sperber A, Spiegel B, Tack J, Vanner S, Walker LS, Whorwell P, Yang Y (2016) Rome IV diagnostic questionnaires and tables for investigators and clinicians. *Gastroenterology.* S0016-5085(16)00180-3.
10. Simren M, Palsson OS, Whitehead WE (2017) Update on Rome IV criteria for colorectal disorders: implications for clinical practice. *Curr Gastroenterol Rep.* 19:15.
11. Palsson OS, Whitehead W, Törnblom H, Sperber AD, Simren M (2020) Prevalence of Rome IV functional bowel disorders among adults in the United States, Canada, and the United Kingdom. *Gastroenterology.* 158:1262-1273.e3.
12. Yurtdaş G, Acar-Tek N, Akbulut G, Cemali Ö, Arslan N, Beyaz Coşkun A, Zengin FH (2020) Risk factors for constipation in adults: a cross-sectional study. *J Am Coll Nutr.* 39:713-719.
13. Cattani L, Neefs L, Verbakel JY, Bosteels J, Deprest J (2021) Obstetric risk factors for anorectal dysfunction after delivery: a systematic review and meta-analysis. *Int Urogynecol J.* 32:2325-2336.
14. World Health Organization. Body mass index—BMI. 2021. (<https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi>). Accessed October 17, (2021).
15. Nyrop KA, Deal AM, Shachar SS, Basch E, Reeve BB, Choi SK, Lee JT, Wood WA, Anders CK, Carey LA, Dees EC, Jolly TA, Reeder-Hayes KE, Kimmick GG, Karuturi MS, Reinbolt RE, Specia JC, Muss HB (2019) Patient-reported toxicities during chemotherapy regimens in current clinical practice for early breast cancer. *Oncologist.* 24:762-771.

16. Crockett S, Greer KB, Sultan S (2019) Opioid-induced constipation (OIC) guideline. *Gastroenterology*. 156:228.
17. Garcia JM, Shamliyan TA (2018) Management of opioid-induced constipation in patients with malignancy. *Am J Med*. 131:1041-1051.e3.
18. Müller-Lissner S, Bassotti G, Coffin B, Drewes AM, Breivik H, Eisenberg E, Emmanuel A, Laroche F, Meissner W, Morlion B (2017) Opioid-induced constipation and bowel dysfunction: a clinical guideline. *Pain Med*. 18:1837-1863.