

Original Article

Factors associated with laxative therapy escalation for opioid-induced constipation in advanced lung cancer

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Abstract: Objectives: To determine the incidence of opioid-induced constipation (OIC) and identify factors associated with laxative escalation in patients with advanced lung cancer treated with strong opioids. Methods: This single-center retrospective cohort study included 100 patients with stage IIIB-IV lung cancer and moderate-to-severe cancer pain who initiated scheduled strong-opioid therapy between 2023 and 2025. OIC was defined as fewer than three spontaneous bowel movements per week or a Bowel Function Index score > 28.8 after opioid initiation, provided that neither criterion was present at baseline. Laxative escalation was defined as addition of a laxative from another class, switching to another laxative class, increasing the current dose by $\geq 50\%$, or starting a peripherally acting μ -opioid receptor antagonist. The maximum morphine equivalent daily dose (MEDD) was defined as the highest MEDD recorded during the 4-week follow-up period. Factors associated with laxative escalation were identified using univariable and multivariable logistic regression analyses. Results: OIC occurred in 72 patients (72.0%), of whom 38 (52.8%) required laxative escalation. Ten of the 38 patients (26.3%) underwent escalation during days 1-6 after laxative initiation. A maximum MEDD ≥ 90 mg/day during the 4-week observation period (adjusted odds ratio [OR] 3.42, 95% confidence interval [CI] 1.28-9.13; $P = 0.014$), Eastern Cooperative Oncology Group performance status ≥ 3 (adjusted OR 3.18, 95% CI 1.15-8.82; $P = 0.026$), taxane-containing chemotherapy (adjusted OR 2.87, 95% CI 1.04-7.92; $P = 0.042$), and absence of prophylactic laxatives (adjusted OR 2.64, 95% CI 1.01-6.91; $P = 0.048$) were independently associated with laxative escalation. Conclusions: OIC was frequent in patients with advanced lung cancer receiving strong opioids, and often required escalation of laxative therapy. A maximum MEDD ≥ 90 mg/day during the 4-week observation period, poor performance status, taxane-containing chemotherapy, and absence of prophylactic laxatives were associated with escalation.

Keywords: Opioid-induced constipation, advanced lung cancer, laxative therapy escalation, associated factors, peripherally acting μ -opioid receptor antagonist (PAMORA)

Introduction

Approximately 2.5 million new cases of lung cancer and 1.8 million lung cancer-related deaths were reported worldwide in 2022 [1]. Pain is a common symptom in cancer patients, especially in the advanced stage. A meta-analysis reported that 44.5% of cancer patients experienced pain, including 30.6% who experienced moderate-to-severe pain [2]. Opioids are commonly used to manage moderate-or-severe cancer pain [3]. However, opioids can cause gastrointestinal adverse effects, among which constipation is particularly common, which may persist during continued treatment. Opioid-

induced constipation (OIC) not only affects bowel movement frequency and the process of defecation but may also reduce patients' adherence to analgesic treatment. According to the Rome IV criteria, OIC is defined as new-onset or worsening constipation associated with the initiation, modification, or dose escalation of opioid therapy [4]. Patients generally develop limited tolerance to opioid-related bowel dysfunction; and consequently, symptoms often persist during continued opioid exposure [5].

The reported prevalence of OIC varies across studies. A real-world study involving 1,000 patients found that 59% had clinician-diag-

nosed OIC [6]. Reviews of patients with advanced cancer have reported OIC prevalence rates ranging from 50% to more than 80% [7]. In a survey of 597 patients receiving opioid therapy, the prevalence of OIC was 66%; patients with cancer-related pain reported a greater symptom burden and higher levels of dissatisfaction [8]. More recent European real-world data also suggest that OIC may remain inadequately assessed and treated despite its substantial symptom burden [9].

Patients with OIC often have multiple coexisting factors that may affect bowel function, including opioid exposure, reduced mobility, decreased food and fluid intake, concomitant use of other constipating drugs, metabolic disorders, abdominal tumors, peritoneal disease, and poor general condition. When these factors coexist with bowel changes after opioid initiation, and clinicians adjust the type or dose of laxative according to nonstandardized criteria, the observed treatment response may reflect several concurrent processes rather than the independent effect of a single medication.

Severe constipation may cause fecal impaction, and intestinal obstruction or perforation may occur in some patients [7]. Guidelines from the European Society for Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC) recommend assessing bowel function when opioid therapy is initiated, implementing prophylactic bowel management, and performing regular reassessments [10, 11]. Osmotic and stimulant laxatives are commonly used as first-line treatments, and a second class of laxative may be added if necessary. However, conventional laxatives do not control symptoms in all patients [13, 14]. When conventional laxatives provide an inadequate response and mechanical bowel obstruction has been excluded, a peripherally acting μ -opioid receptor antagonist (PAMORA) may be considered [10-12].

Previous studies have investigated factors associated with OIC, early laxative response, and response to naldemedine [15, 16]. However, data on laxative therapy escalation in patients with advanced lung cancer remain limited. Therefore, this study aimed to determine the incidence of OIC, describe patterns of laxative use and escalation, and evaluate factors associated with laxative therapy escalation.

Patients and methods

Study population

This single-center retrospective observational cohort study screened consecutive patients who underwent opioid treatment for cancer pain management between January 1, 2023, and December 31, 2025.

Inclusion criteria: 1) Age ≥ 18 years; 2) Histologically or cytologically confirmed non-small cell lung cancer or small cell lung cancer; 3) Clinical stage IIIB, IIIC, or IV disease according to the 8th edition of the American Joint Committee on Cancer staging system; 4) Cancer-related pain with a Numerical Rating Scale (NRS) score ≥ 4 on two consecutive assessments within 48 h before opioid initiation; 5) Initiation of regularly scheduled treatment with morphine, oxycodone, fentanyl, or hydromorphone between January 1, 2023, and December 31, 2025; 6) Availability of at least 4 weeks of follow-up data after opioid initiation.

Exclusion criteria: 1) Pre-existing chronic constipation meeting the Rome IV criteria before opioid initiation; 2) Previous colostomy, ileostomy, or another bowel-diversion procedure; 3) Mechanical bowel obstruction at the time of opioid initiation; 4) Primary gastrointestinal cancer or peritoneal carcinomatosis with documented obstructive bowel involvement; 5) Regular use of strong opioids during the preceding 30 days; 6) Fewer than 4 weeks of recorded bowel-function follow-up.

A total of 147 potentially eligible patients were screened. Of these, 15 patients had pre-existing chronic constipation, 8 had a colostomy or another bowel-diversion procedure, 7 had mechanical bowel obstruction at opioid initiation, 5 had gastrointestinal malignancy with bowel obstruction, 6 had recent strong-opioid use, and 6 had insufficient follow-up data. Finally, 100 patients were included in this study. The study protocol was approved by the Ethics Committee of the First Hospital of Putian City (Approval No.: 2026-063). The requirement for individual informed consent was waived because the study used existing de-identified data. The study was conducted in accordance with the Declaration of Helsinki and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Data collection and variable definitions

Clinical data were obtained from the hospital's electronic medical records. All data were extracted independently by two investigators and entered into a standardized data-collection form. A senior investigator reviewed and resolved any discrepancies.

Baseline variables included age, sex, body mass index (BMI), smoking status, diabetes mellitus, hypertension, Eastern Cooperative Oncology Group performance status (ECOG PS), serum albumin level, and pain NRS score. Measurements obtained at opioid initiation were used whenever available. If a laboratory measurement was unavailable on that date, the most recent value obtained within the preceding 7 days was used.

Tumor-related variables included histologic type, clinical stage, and metastatic sites, including bone, brain, liver, abdominal, and peritoneal metastases. Anticancer treatment variables included platinum-based chemotherapy, taxane-containing chemotherapy, immune checkpoint inhibitor treatment, and targeted treatment with a tyrosine kinase inhibitor. The initial strong opioid was recorded as sustained-release morphine, controlled-release oxycodone, transdermal fentanyl, or hydromorphone. The initial dose, dose changes, and treatment duration were recorded.

Detailed pharmacologic information for the primary agents evaluated in this study was extracted from the hospital's electronic pharmacy system. The specific agents included controlled-release oxycodone (OxyContin; Mundipharma, Cambridge, UK; specification: 10 mg/tablet), sustained-release morphine (Morphine Sulfate ER; Southwest Pharmaceutical Co., Ltd., Chongqing, China; specification: 30 mg/tablet), transdermal fentanyl (Durogesic; Janssen Pharmaceutica, Beerse, Belgium; specification: 4.2 mg/patch), and the PAMORA agent naldemedine (Symproic; Shionogi & Co., Ltd., Osaka, Japan; specification: 0.2 mg/tablet). Given the retrospective nature of this study spanning a three-year period (2023-2025), multiple batches of these medications were dispensed over time; all agents were standardized commercial products dispensed through the hospital's central pharmacy. For other conventional laxatives and concomitant medica-

tions, standard hospital formulary stocks were utilized.

Opioid doses were converted to morphine equivalent daily dose (MEDD) using a prespecified conversion table. The initial MEDD and the highest MEDD recorded at any time during the 4-week observation period were used for analysis. The approximate equianalgesic doses were as follows: oral morphine 30 mg, oral oxycodone 20 mg, transdermal fentanyl 12.5 micrograms/h, and oral hydromorphone 6 mg [17]. This conversion table was used for analytical purposes and was not intended to serve as a direct prescribing guide.

Concomitant constipating medications included 5-hydroxytryptamine-3 (5-HT₃) receptor antagonists, anticholinergic drugs, calcium channel blockers, and iron supplements.

Bowel-function data were recorded before and after opioid initiation. Bowel function was evaluated using the Bristol Stool Form Scale (BSFS) and the Bowel Function Index (BFI). The BSFS is a seven-point scale used to classify stool consistency and appearance. The BFI was measured at baseline and at weeks 1, 2, and 4. It is a patient-reported instrument comprising three items: ease of defecation, feeling of incomplete evacuation, and the patient's self-assessment of constipation. Each item is scored from 0 to 100, with higher scores indicating more severe constipation. A total score > 28.8 is considered indicative of impaired bowel function, and a change of ≥ 12 points is defined as clinically meaningful [18, 19].

Follow-up data included weekly SBM frequency, Bristol Stool Form Scale score, BFI score, OIC onset, laxative class, laxative drug and dose, date of laxative initiation, dose escalation, additions or switching of laxatives, and PAMORA use.

Definition of OIC and laxative therapy escalation

The Rome IV criteria require new-onset or worsening constipation after opioid initiation, a change in opioid therapy, or dose escalation, with at least two specified symptoms occurring during more than 25% of bowel movements, infrequent loose stools without laxative use, and no qualifying symptoms before treatment

[4]. However, complete data on the frequency and duration of all Rome IV symptoms were not available in every follow-up record; therefore, this study used a pragmatic definition. OIC was defined as an SBM frequency of fewer than three per week or a BFI score > 28.8 at any time during the 4 weeks after opioid initiation, provided that neither condition was present at baseline.

Laxative therapy escalation was defined as a qualifying treatment change prompted by an inadequate response to the initial regimen. Qualifying events included the addition of a laxative from another pharmacologic class, replacement of the initial laxative with an agent from another class, an increase of $\geq 50\%$ in the dose of the current laxative, or initiation of naldemedine or methylnaltrexone. If a patient subsequently underwent more than one treatment change, the escalation type was classified according to the first qualifying escalation event only.

Formal response assessment was performed between days 7 and 14 after laxative initiation when the initial regimen remained unchanged. An adequate response was defined as both at least three SBMs per week without marked straining and a BFI score ≤ 28.8 . The 7-14-day interval was not a mandatory waiting period. If persistent or worsening constipation prompted a clinician-documented qualifying escalation before day 7, the patient was classified as having early treatment failure on the date of the first qualifying escalation. Patients who achieved an adequate response without a qualifying treatment change were assigned to the non-escalation group. Patients with at least one qualifying treatment change were assigned to the escalation group.

Outcome measures

The primary outcome was the identification of factors independently associated with laxative therapy escalation among patients who developed OIC. Secondary outcomes included the incidence of OIC, time from opioid initiation to OIC onset, initial laxative use, escalation patterns, time from initiation of laxative treatment to escalation, changes in BFI score, weekly SBM frequency, and adequate bowel function at week 4 (defined as both at least three SBMs

per week and a BFI score ≤ 28.8). Pain NRS scores were recorded at baseline and at week 4. Patient satisfaction with pain treatment was also recorded.

Statistical analysis

Statistical analyses were performed using SPSS 26.0 and R 4.2.1. The Shapiro-Wilk test was used to assess the distribution of continuous variables. Normally distributed continuous variables were presented as the mean $\pm$ standard deviation (SD) and were compared using the independent-samples *t* tests. Non-normally distributed continuous variables were reported as median and interquartile range (IQR) and were compared using Mann-Whitney *U* tests. Categorical variables are reported as number and percentage and were compared using Pearson chi-square test when the expected cell counts were adequate, or Fisher exact test otherwise.

Each candidate variable was first evaluated using univariable logistic regression. Variables with $P < 0.10$ in the univariable analyses, together with variables selected a priori based on published evidence, were entered into a forward stepwise multivariable logistic regression model. The entry and removal thresholds were set at $P = 0.05$ and $P = 0.10$, respectively. Adjusted associations were estimated in the same model among the 72 patients who developed OIC and were reported as odds ratios (ORs) with 95% confidence intervals (CIs). All tests were two-sided, and a $P < 0.05$ was considered significant.

Results

Baseline demographics and clinical characteristics

Among the included 100 patients, 67 were male. The median age was 63 years (IQR: 55-71), and the median BMI was 21.8 kg/m² (IQR: 19.5-24.2). 38 patients were current smokers, 29 were former smokers, and 33 had never smoked. Histologically, 52 patients had adenocarcinoma, 28 had squamous cell carcinoma, 13 had small cell lung cancer, and 7 had other histological types. Regarding disease stage, 82 had stage IV disease and 18 had stage IIIB or IIIC disease. Bone, brain, liver, and

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Table 1. Baseline demographic and clinical characteristics of the study cohort (N = 100)

Variable	N or Median	% or IQR
Age (years), median (IQR)	63	55-71
Sex: Male	67	67.0%
Sex: Female	33	33.0%
BMI (kg/m ²), median (IQR)	21.8	19.5-24.2
Smoking: Current	38	38.0%
Smoking: Former	29	29.0%
Smoking: Never	33	33.0%
Histology: Adenocarcinoma	52	52.0%
Histology: Squamous cell	28	28.0%
Histology: SCLC	13	13.0%
Histology: Other	7	7.0%
Stage IIIB/IIIC	18	18.0%
Stage IV	82	82.0%
Bone metastases	48	48.0%
Brain metastases	23	23.0%
Liver metastases	19	19.0%
Abdominal/peritoneal metastases	27	27.0%
ECOG PS 1	22	22.0%
ECOG PS 2	43	43.0%
ECOG PS 3	28	28.0%
ECOG PS 4	7	7.0%
Serum albumin (g/L), median (IQR)	33.5	29.8-36.7
Diabetes mellitus	14	14.0%
Hypertension	31	31.0%
Baseline NRS, median (IQR)	6	5-7
Baseline SBM data available	100	100.0%
Baseline BFI data available	100	100.0%

Notes: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; NRS, Numerical Rating Scale; SCLC, small cell lung cancer; SBM, spontaneous bowel movement; BFI, Bowel Function Index; IQR, interquartile range.

abdominal or peritoneal metastases were present in 48, 23, 19, and 27 patients, respectively. ECOG PS was 1 in 22 patients, 2 in 43, 3 in 28, and 4 in 7 patients. The median serum albumin level was 33.5 g/L (IQR: 29.8-36.7). The detailed data are presented in **Table 1**.

Opioid therapy and concomitant medications

As shown in **Table 2**, controlled-release oxycodone was used as the initial opioid in 41 patients, sustained-release morphine in 30, transdermal fentanyl in 21, and hydromorphone in 8 patients. The median initial MEDD was 60 mg/day (IQR: 30-90), and the median maximum MEDD during the 4-week observation period was 90 mg/day (IQR: 60-140).

Forty-three patients reached a four-week maximum MEDD of ≥ 90 mg/day. The median opioid-treatment duration during the available follow-up period was 35 days (IQR: 28-56).

Sixty-one patients received active systemic anticancer treatment. Of these, 34 received platinum-based chemotherapy, 22 received taxane-containing chemotherapy, 18 received immune checkpoint inhibitor therapy, and 15 received targeted treatment. These treatment categories were not mutually exclusive. Concomitant medications included 5-HT₃ receptor antagonist in 45 patients, anticholinergic drugs in 12, calcium channel blockers in 15, and iron supplements in 8 patients.

Incidence and characteristics of OIC

OIC occurred in 72 of 100 patients (72.0%). The median time from opioid initiation to OIC onset was 5 days (IQR: 3-9). Among patients with OIC, the median SBM frequency decreased from 5 per week at baseline (IQR: 4-7) to 2 per week at diagnosis (IQR: 1-3).

The median BFI score at diagnosis was 58.3 (IQR: 42.0-72.5). All 72 patients received laxative treatment.

Forty-one patients received an osmotic laxative as first-line treatment (56.9%), 22 received a stimulant laxative (30.6%), and 9 received a combination of osmotic and stimulant laxatives (12.5%). Thirty-nine patients received prophylactic laxatives at opioid treatment initiation, and 23 developed OIC (59.0%; 23/39). Among 61 patients who did not receive prophylactic laxatives, 49 experienced OIC (80.3%; 49/61). The difference in OIC prevalence between the prophylactic and non-prophylactic groups was significant (Pearson $\chi^2 = 5.381$, $P = 0.020$), as shown in **Table 3**.

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Table 2. Opioid therapy and concomitant medications (N = 100)

Variable	N or Median	% or IQR
Initial opioid: Oxycodone CR	41	41.0%
Initial opioid: Morphine SR	30	30.0%
Initial opioid: Fentanyl TTS	21	21.0%
Initial opioid: Hydromorphone	8	8.0%
Initial MEDD (mg/day), median (IQR)	60	30-90
4-week maximum MEDD (mg/day), median (IQR)	90	60-140
4-week maximum MEDD $\geq$ 90 mg/day	43	43.0%
Duration of opioid therapy (days)	35	28-56
Platinum-based chemotherapy	34	34.0%
Taxane-containing regimens	22	22.0%
Immune checkpoint inhibitors	18	18.0%
Targeted therapy (TKI)	15	15.0%
5-HT3 antagonists	45	45.0%
Anticholinergic agents	12	12.0%
Calcium channel blockers	15	15.0%
Iron supplements	8	8.0%
Prophylactic laxative at opioid start	39	39.0%

Notes: CR, controlled-release; SR, sustained-release; TTS, transdermal therapeutic system; MEDD, morphine equivalent daily dose; TKI, tyrosine kinase inhibitor; 5-HT3, 5-hydroxytryptamine-3; IQR, interquartile range. Anticancer-treatment categories were not mutually exclusive.

Table 3. Incidence and characteristics of opioid-induced constipation (OIC) (N = 100)

Variable	Value	%
OIC incidence	72/100	72.0%
Time to OIC onset (days), median (IQR)	5	3-9
Baseline SBM/week, median (IQR)	5	4-7
SBM/week at OIC diagnosis, median (IQR)	2	1-3
BFI at OIC diagnosis, median (IQR)	58.3	42.0-72.5
First-line laxative: Osmotic agents	41/72	56.9%
First-line laxative: Stimulant agents	22/72	30.6%
First-line laxative: Combination	9/72	12.5%
OIC in prophylactic laxative group	23/39	59.0%
OIC in non-prophylactic group	49/61	80.3%
Prophylactic vs. non-prophylactic comparison	$\chi^2 = 5.381$	P = 0.020

Notes: OIC, opioid-induced constipation; SBM, spontaneous bowel movement; BFI, Bowel Function Index; IQR, interquartile range. The prophylactic-laxative comparison used the Pearson chi-square test.

Laxative therapy escalation patterns

Among the 72 patients with OIC, 38 required laxative therapy escalation (52.8%), whereas 34 patients achieved adequate bowel function with first-line treatment (47.2%). The median time from laxative treatment initiation to escalation was 8 days (IQR: 5-14). Ten of the 38

patients who underwent escalation (26.3%) experienced their first qualifying escalation event within days 1-6 after laxative initiation (**Table 4**). At the first qualifying escalation event, a second laxative class was added in 44.7% of patients, a PAMORA was initiated in 31.6%, the laxative class was switched in 15.8%, and the dose of the existing laxative was increased by $\geq$ 50% in 7.9%. Twelve patients received a PAMORA, including naldemedine in 9 patients and methylnaltrexone in 3 patients. At week 4, adequate bowel function, defined as both SBM $\geq$ 3/week and a BFI score $\leq$ 28.8, was achieved in 23 of 38 patients (60.5%) in the escalation group and 29 of 34 patients (85.3%) in the non-escalation group (Pearson $\chi^2 = 5.487$, P = 0.019) (**Table 4**).

Escalation and non-escalation groups

ECOG PS χ^2 3 was observed in 50.0% of patients in the escalation group and 20.6% of those in the non-escalation group (P = 0.009). A maximum MEDD of $\geq$ 90 mg/day during the 4-week observation period was observed in 63.2% in the escalation and 32.4% in the non-escalation groups (P = 0.009). Taxane-containing chemotherapy was administered in 34.2% and 11.8% of patients, respectively (P = 0.025). Abdominal or peritoneal metastases were present in 39.5% and 17.6%, respectively (P = 0.042). Prophylactic laxatives had been used in 21.1% and 44.1% of patients, respectively (P = 0.036).

The median age was 64 years (IQR: 56-72) in the escalation group and 62 years (IQR: 54-70) in the non-escalation group (Mann-Whitney U = 589, P = 0.524). The median BMI was 21.5 kg/

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Table 4. Patterns of laxative therapy escalation among patients with opioid-induced constipation (OIC) (N = 72)

Variable	N	%
Escalation required	38/72	52.8%
Non-escalation (adequate on first-line)	34/72	47.2%
Time to escalation (days), median (IQR)	8	5-14
First qualifying escalation on days 1-6	10/38	26.3%
First escalation: Added 2nd laxative class	17/38	44.7%
First escalation: PAMORA initiated	12/38	31.6%
First escalation: Switched laxative	6/38	15.8%
First escalation: Dose increase $\geq$ 50%	3/38	7.9%
PAMORA: Naldemedine	9/12	75.0%
PAMORA: Methylnaltrexone	3/12	25.0%
Adequate bowel function at week 4 (SBM $\geq$ 3/week and BFI $\leq$ 28.8): Escalation group	23/38	60.5%
Adequate bowel function at week 4 (SBM $\geq$ 3/week and BFI $\leq$ 28.8): Non-escalation group	29/34	85.3%
Week-4 composite adequate bowel function comparison	$\chi^2 = 5.487$ P = 0.019	

Notes: OIC, opioid-induced constipation; PAMORA, peripherally acting mu-opioid receptor antagonist; IQR, interquartile range. Escalation type represents the first qualifying escalation event for each patient; later additional treatment changes were not used to reclassify the patient. Adequate bowel function at week 4 was defined as both SBM $\geq$ 3/week and BFI $\leq$ 28.8.

m² (IQR: 19.2-23.8) and 22.3 kg/m² (IQR: 19.8-24.6), respectively (Mann-Whitney U = 557, P = 0.318). Age and BMI were evaluated in univariable logistic regression after categorization but were not retained in the multivariable model. Sex, histologic type, disease stage, and initial opioid type did not differ significantly between the groups.

Median BFI score at week 2 was 62.7 (IQR: 48.3-75.0) in the escalation group and 35.2 (IQR: 24.0-45.8) in the non-escalation group (P < 0.001). At week 4, the corresponding values were 41.3 (IQR: 28.5-55.0) and 22.8 (IQR: 15.3-30.2), respectively (P < 0.001). The median SBM frequency at week 2 was 2.0 (IQR: 1.0-2.5) and 4.0 (IQR: 3.0-5.0) per week in the escalation and non-escalation group, respectively (P < 0.001). The details are shown in **Table 5**.

Logistic regression analysis of factors associated with treatment escalation

In the univariate logistic regression analysis (**Table 6**), ECOG PS $\geq$ 3 (OR = 3.86, 95% CI: 1.36-10.98, P = 0.011), a maximum MEDD of $\geq$ 90 mg/day during the 4-week observation period (OR = 3.57, 95% CI: 1.36-9.37, P = 0.010), taxane-containing chemotherapy (OR = 3.88, 95% CI: 1.13-13.28, P = 0.031), absence of prophylactic laxative treatment (OR = 2.96, 95% CI: 1.05-8.32, P = 0.039), and abdominal

or peritoneal metastases (OR = 3.04, 95% CI: 1.02-9.07, P = 0.046) were all associated with laxative therapy escalation. However, the use of a 5-HT₃ receptor antagonist, diabetes mellitus, and serum albumin < 30 g/L were not significantly associated with treatment escalation.

In the multivariable model (**Table 6**), four variables remained statistically significant: maximum MEDD $\geq$ 90 mg/day during the 4-week observation period (adjusted OR = 3.42, 95% CI: 1.28-9.13, P = 0.014), ECOG PS $\geq$ 3 (adjusted OR = 3.18, 95% CI: 1.15-8.82, P = 0.026), taxane-containing chemotherapy (adjusted OR = 2.87, 95% CI: 1.04-7.92, P = 0.042), and absence of prophylactic laxative treatment (adjusted OR = 2.64, 95% CI: 1.01-6.91, P = 0.048). However, abdominal or peritoneal metastases did not demonstrate significance after adjustment (adjusted OR = 2.53, 95% CI: 0.97-6.60, P = 0.058). All variance inflation factors were below 2.5, indicating relatively low degree of linear correlation among the independent variables.

Comparison of BFI and bowel function during follow-up between the escalation and non-escalation groups

The baseline median BFI score was 15.3 (IQR: 8.2-21.5) among patients who subsequently required escalation and 14.8 (IQR: 7.5-20.3) in

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Table 5. Comparison of variables between escalation and non-escalation groups (N = 72)

Variable	Escalation (n = 38)	Non-escalation (n = 34)	Test statistic/P
Age (years), median (IQR)	64 (56-72)	62 (54-70)	Mann-Whitney U = 589; P = 0.524
BMI (kg/m ²), median (IQR)	21.5 (19.2-23.8)	22.3 (19.8-24.6)	Mann-Whitney U = 557; P = 0.318
Male sex, n (%)	26 (68.4%)	22 (64.7%)	$\chi^2 = 0.111$; P = 0.738
ECOG PS ≥ 3 , n (%)	19 (50.0%)	7 (20.6%)	$\chi^2 = 6.728$; P = 0.009
Stage IV, n (%)	33 (86.8%)	27 (79.4%)	$\chi^2 = 0.713$; P = 0.398
Adenocarcinoma, n (%)	20 (52.6%)	18 (52.9%)	$\chi^2 = 0.001$; P = 0.979
Bone metastases, n (%)	20 (52.6%)	16 (47.1%)	$\chi^2 = 0.223$; P = 0.637
Abdominal/peritoneal metastases, n (%)	15 (39.5%)	6 (17.6%)	$\chi^2 = 4.138$; P = 0.042
Liver metastases, n (%)	9 (23.7%)	5 (14.7%)	$\chi^2 = 0.923$; P = 0.337
4-week max MEDD ≥ 90 mg/day, n (%)	24 (63.2%)	11 (32.4%)	$\chi^2 = 6.817$; P = 0.009
Oxycodone CR, n (%)	16 (42.1%)	15 (44.1%)	$\chi^2 = 0.030$; P = 0.863
Fentanyl TTS, n (%)	9 (23.7%)	7 (20.6%)	$\chi^2 = 0.100$; P = 0.752
Taxane chemotherapy, n (%)	13 (34.2%)	4 (11.8%)	$\chi^2 = 5.012$; P = 0.025
5-HT3 antagonist use, n (%)	20 (52.6%)	14 (41.2%)	$\chi^2 = 0.945$; P = 0.331
Prophylactic laxative, n (%)	8 (21.1%)	15 (44.1%)	$\chi^2 = 4.391$; P = 0.036
BFI at week 2, median (IQR)	62.7 (48.3-75.0)	35.2 (24.0-45.8)	P < 0.001
BFI at week 4, median (IQR)	41.3 (28.5-55.0)	22.8 (15.3-30.2)	P < 0.001
SBM/week at week 2, median (IQR)	2.0 (1.0-2.5)	4.0 (3.0-5.0)	P < 0.001
NRS at week 4, median (IQR)	4 (3-5)	3 (2-4)	P = 0.087

Notes: ECOG PS, Eastern Cooperative Oncology Group performance status; MEDD, morphine equivalent daily dose; CR, controlled-release; TTS, transdermal therapeutic system; 5-HT3, 5-hydroxytryptamine-3; BFI, Bowel Function Index; SBM, spontaneous bowel movement; NRS, Numerical Rating Scale; IQR, interquartile range. Categorical comparisons used Pearson chi-square tests; continuous variables were compared with Mann-Whitney U tests. Age and BMI continuous comparisons are descriptive.

Table 6. Univariable and multivariable logistic regression analysis of factors associated with laxative therapy escalation

Variable	Crude OR	95% CI	P	Adjusted OR	95% CI	P
Age ≥ 65 years	1.35	0.53-3.43	0.527	-	-	-
Male sex	1.18	0.45-3.11	0.741	-	-	-
BMI ≥ 24 kg/m ²	0.81	0.29-2.23	0.681	-	-	-
ECOG PS ≥ 3	3.86	1.36-10.98	0.011	3.18	1.15-8.82	0.026
4-week max MEDD ≥ 90 mg/day	3.57	1.36-9.37	0.010	3.42	1.28-9.13	0.014
Taxane chemotherapy	3.88	1.13-13.28	0.031	2.87	1.04-7.92	0.042
No prophylactic laxative	2.96	1.05-8.32	0.039	2.64	1.01-6.91	0.048
Abdominal/peritoneal mets	3.04	1.02-9.07	0.046	2.53	0.97-6.60	0.058
5-HT3 antagonist use	1.58	0.62-4.03	0.330	-	-	-
Serum albumin < 30 g/L	2.14	0.78-5.85	0.139	-	-	-
Diabetes mellitus	1.92	0.56-6.58	0.297	-	-	-
Fentanyl (vs. others)	1.20	0.40-3.59	0.749	-	-	-
Liver metastases	1.80	0.55-5.92	0.331	-	-	-
Stage IV (vs. IIIB/C)	1.69	0.48-5.96	0.414	-	-	-

Notes: OR, odds ratio; CI, confidence interval; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; MEDD, morphine equivalent daily dose; 5-HT3, 5-hydroxytryptamine-3.

patients who did not (P = 0.812), and this score increased after opioid initiation. At week 1, the median BFI score was 55.2 (IQR: 42.8-68.3) in

the escalation group and 40.8 (IQR: 30.5-52.7) in the non-escalation group (P = 0.003). At week 2, the corresponding values were 62.7

Table 7. Comparison of longitudinal bowel function index (BFI) scores, spontaneous bowel movement (SBM) frequency, and week-4 adequate bowel function between groups

Outcome Measure	Escalation (n = 38)	Non-escalation (n = 34)	Statistical result
BFI baseline, median (IQR)	15.3 (8.2-21.5)	14.8 (7.5-20.3)	P = 0.812
BFI week 1, median (IQR)	55.2 (42.8-68.3)	40.8 (30.5-52.7)	P = 0.003
BFI week 2, median (IQR)	62.7 (48.3-75.0)	35.2 (24.0-45.8)	P < 0.001
BFI week 4, median (IQR)	41.3 (28.5-55.0)	22.8 (15.3-30.2)	P < 0.001
SBM/week baseline, median (IQR)	5.0 (4.0-7.0)	5.0 (4.0-6.0)	P = 0.735
SBM/week 1, median (IQR)	2.0 (1.0-3.0)	3.0 (2.0-4.0)	P = 0.006
SBM/week 2, median (IQR)	2.0 (1.0-2.5)	4.0 (3.0-5.0)	P < 0.001
SBM/week 4, median (IQR)	3.0 (2.0-4.0)	5.0 (4.0-6.0)	P < 0.001
Adequate bowel function at week 4 (SBM ≥ 3/week and BFI ≤ 28.8), n (%)	23 (60.5%)	29 (85.3%)	$\chi^2 = 5.487$; P = 0.019
NRS baseline, median (IQR)	6 (5-7)	6 (5-7)	P = 0.923
NRS week 4, median (IQR)	4 (3-5)	3 (2-4)	P = 0.087

Notes: BFI, Bowel Function Index; SBM, spontaneous bowel movement; NRS, Numerical Rating Scale; IQR, interquartile range. Continuous outcomes were compared with Mann-Whitney U tests; the week-4 composite adequate-bowel-function outcome was compared with the Pearson chi-square test.

(IQR: 48.3-75.0) and 35.2 (IQR: 24.0-45.8), respectively (P < 0.001). At week 4, they were 41.3 (IQR: 28.5-55.0) and 22.8 (IQR: 15.3-30.2), respectively (P < 0.001).

The median SBM frequency at week 4 was 3.0 (IQR: 2.0-4.0) per week in the escalation group and 5.0 (IQR: 4.0-6.0) per week in the non-escalation group (P < 0.001). Among the 38 patients who underwent escalation, the median BFI score decreased from 62.7 at week 2 to 41.3 at week 4, representing a reduction exceeding the 12-point threshold. At week 4, 60.5% of the patients (23/38) in the escalation group met the composite criterion for adequate bowel function (SBM ≥ 3/week and BFI ≤ 28.8), significantly lower than the 85.3% (29/34) in the non-escalation group (Pearson $\chi^2 = 5.487$, P = 0.019) (Table 7).

Discussion

In this retrospective cohort of patients with advanced lung cancer receiving strong opioids for moderate-to-severe pain, OIC occurred in 72.0% of patients, higher than the 59% prevalence of clinician-diagnosed OIC reported in a 1,000-patient cancer cohort [6], but OIC remained within the range reported in reviews of patients with advanced cancer [7]. The median duration from opioid initiation to OIC onset was 5 days, indicating that bowel dysfunction often developed early during opioid treatment. More than half of the patients who developed OIC subsequently required a qualifying escalation of laxative therapy.

The relatively high incidence observed in this study may be related to the exclusive inclusion of patients with advanced lung cancer who received strong opioids for moderate-to-severe pain. In addition, OIC was defined pragmatically as fewer than three SBMs per week or BFI > 28.8. Complete documentation of every Rome IV symptom and duration criterion was not available in all medical records. Therefore, the incidence reported here should be interpreted as the incidence of pragmatically defined OIC rather than strict Rome IV-defined OIC. Recent European evidence has similarly suggested that OIC remains inadequately assessed and controlled in routine cancer care [8].

A maximum MEDD of ≥ 90 mg/day during the 4-week observation period had the largest adjusted OR among the associated factors retained in the multivariate model. Opioids reduce propulsive intestinal motility, increase intestinal fluid absorption, and increase sphincter tone through peripheral μ -opioid receptors [5, 12], making a dose-related effect biologically plausible. However, a study in Japanese patients with cancer-related pain found a numerical increase in OIC with higher opioid dose but no statistically significant association between opioid dose and OIC or BFI score [20]. In the present study, the maximum MEDD was defined as the highest dose recorded at any time during the 4-week observation period. It may therefore have been reached after OIC had worsened or after laxative therapy had already been escalated. Accordingly, the temporal relationship between maximum

MEDD and escalation was not established, and reverse causation and time-related bias were possible. The cutoff of 90 mg/day should therefore be interpreted as a cohort-specific associated factor rather than a causal dose threshold. Future studies should evaluate MEDD immediately before OIC diagnosis or laxative escalation, or use time-updated exposure models.

An ECOG PS of ≥ 3 was also associated with laxative escalation. Patients with poor performance status may have reduced mobility, decreased oral intake, dehydration, poor nutritional status, more advanced disease, and a greater medication burden. Because these factors were not fully measured, and ECOG PS may represent several overlapping clinical conditions, the observed association cannot distinguish a direct effect of performance status from the effects of disease burden or unrecorded supportive-care variables.

Taxane-containing chemotherapy was another factor associated with laxative escalation. Taxanes can cause peripheral neurotoxicity, and autonomic involvement may impair gastrointestinal motility. However, direct evidence connecting taxane-related autonomic neuropathy with OIC remains limited [15, 21]. A retrospective study of 175 patients with advanced cancer reported an association between recent taxane treatment and an inadequate early response to laxatives [15]. The present study showed a similar association, although both studies were observational and cannot establish causality.

In addition, the absence of prophylactic laxative treatment was associated with laxative escalation. Among patients who received prophylactic laxatives, 59.0% (23/39) developed OIC, compared to 80.3% (49/61) in those who did not receive prophylactic laxatives. However, prophylaxis was prescribed as part of routine care rather than assigned randomly. Drug class, drug dose, adherence, intake, mobility, and clinician preference were not standardized or fully controlled. Therefore, this association should not be interpreted as definitive evidence of a preventive drug effect. ESMO and MASCC recommend initiating bowel management when regular opioid therapy begins [10, 11]. Nevertheless, published preventive evidence remains mixed. One quasi-experimental study

reported lower constipation severity with early prophylactic laxative use [14], whereas a 2025 propensity score-matched study found no significant reduction in OIC incidence [22].

Abdominal or peritoneal metastases were significantly associated with escalation in univariable analysis but did not reach significance after adjustment ($P = 0.058$). Although patients with mechanical bowel obstruction at opioid initiation were excluded, partial bowel compression, altered motility, abdominal pain, reduced oral intake, and unrecognized disease progression may still have affected bowel function. These factors were not assessed separately and may have contributed to residual confounding.

The addition of a second laxative class was the most frequent first qualifying escalation method, accounting for 44.7% of escalations in the current study. PAMORAs were used as the first qualifying escalation in 31.6% of patients, with naldemedine used more frequently than methylnaltrexone. A multicenter randomized trial found that prophylactic naldemedine reduced OIC in patients with cancer who initiated strong opioids [23]. A systematic review also reported beneficial effects of naldemedine and methylnaltrexone, despite the absence of direct comparisons between these agents and heterogeneous study methods [13].

The current study was not designed to compare the effectiveness of different escalation strategies. Treatment allocation was not random, and the number of patients receiving each strategy was small. Nevertheless, BFI scores remained higher in the escalation group at weeks 1, 2, and 4. Among patients who underwent escalation, the median BFI score decreased from 62.7 at week 2 to 41.3 at week 4, exceeding the 12-point threshold. However, attaining adequate bowel function at week 4 was less frequent in the escalation group than in the non-escalation group (60.5% vs 85.3%; $P = 0.019$). This difference should be interpreted cautiously because patients in the escalation group had more severe constipation before escalation. Regression to the mean, clinician selection, treatment timing, adherence, and differences among laxative regimens were not controlled. Therefore, the lower rate of achieving adequate bowel function in the escalation group does not indicate that escalation was ineffective.

Ten of the 38 patients who underwent escalation experienced their first qualifying escalation during days 1-6 after laxative initiation. This reflects clinician-directed early treatment modification in response to persistent or worsening symptoms and should not be interpreted as a mandatory requirement to wait until day 7.

The study also had several limitations. First, its retrospective, single-center design and relatively small sample size limited the generalizability and statistical power of the findings. This study included 100 patients, of whom 72 patients developed OIC and 38 underwent laxative therapy escalation; consequently, the confidence intervals were relatively wide and the multivariable model may have been vulnerable to overfitting. Second, although baseline SBM and BFI were complete for all patients, other Rome IV symptom-frequency and duration criteria were not consistently documented in the routine medical records; therefore, the OIC incidence may differ under strict Rome IV assessment. Third, only patients with advanced lung cancer were included. The findings should therefore not be generalized to other cancer populations without independent validation. In addition, bowel outcomes were followed for only 4 weeks, precluding assessment of longer-term treatment response or recurrent OIC. Fourth, diet, fluid intake, physical activity, and other potentially relevant factors were not recorded in a standardized form and escalation decisions were made by treating clinicians without a uniform escalation algorithm. Residual confounding may therefore have persisted despite multivariable adjustment. Finally, maximum MEDD was defined as the highest dose recorded throughout the 4-week observation period rather than the dose documented strictly before OIC diagnosis or laxative escalation, resulting in potential reverse causation and time-related bias. Accordingly, the identified associations should not be interpreted as temporally established predictors or causal relationships.

Conclusions

Opioid-induced constipation (OIC) developed in 72 of 100 patients, and 38 of these patients required laxative therapy escalation. A maximum MEDD of ≥ 90 mg/day during the 4-week observation period, ECOG PS ≥ 3 , taxane-containing chemotherapy, and absence of prophylactic

laxative treatment were independently associated with laxative escalation. Abdominal or peritoneal metastases were not statistically significant after adjustment. Given the observational design, these findings indicate associations rather than causal relationships.

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Disclosure of conflict of interest

None.

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