

Twycross Research Prize 2019

An investigation of the sensitivity of the Rome IV criteria for opioid-induced constipation

Declarations:

This research project received an educational grant from Kyowa Kirin. The author has received speaker and advisory board fees from Kyowa Kirin.

Key words: opioid-induced constipation; diagnostic criteria; prevalence

Word count: 2165 (excluding references)

Abstract

**Aim:** The aim of this study was to investigate the prevalence of opioid-induced constipation (OIC) using different diagnostic criteria, and specifically the new Rome IV criteria.

**Methods:** This was a prospective, multi-centre, observational study of 350 patients with cancer who were receiving regular opioid analgesia for cancer pain. Patients were assessed for the presence of OIC using: a) Simple question (“are you constipated?”); b) Camilleri definition; c) EAPC definition (constipation); d) Rome IV criteria; and e) comprehensive Specialist Palliative Care (SPC) clinician assessment (“gold standard”). Patients also completed the Bowel Function Index (to assess the adequacy of treatment), the PAC-QOL (to assess related quality of life), and the MSAS-SF (to assess correlation between constipation and other physical and psychological symptoms).

**Results:** The prevalence of OIC according to the different diagnostic criteria was:

- “Simple” question: 32.8%
- EAPC definition: 27.7%
- Camilleri definition: 59.4%
- Rome IV criteria: 23.7%
- Specialist Palliative Care clinician assessment: 60.8%

Of the 213 patients that were deemed to have OIC by comprehensive SPC clinician assessment, only 79 were Rome IV positive (and 134 were Rome IV negative). Thus, the sensitivity of Rome IV criteria was only 37.4%, (specificity 98%). In contrast, there was a good correlation between the SPC clinician assessment and the Camilleri definition (sensitivity 85.7%; specificity 73.2%). Data on the other PROMS will be presented in the full report.

**Conclusions:** Asking a simple question (“are you constipated”) will miss many patients with OIC. The “gold standard” appears to be a comprehensive SPC clinician assessment, although the Camilleri

definition appears to be a useful screening question for clinical practice. The Rome IV criteria does not appear to be a sensitive method for diagnosing OIC.

## Introduction

Constipation is commonly experienced by patients receiving palliative care and is a cause of significant morbidity in this patient population. It affects 40-90% of patients with advanced cancer (Fallon *et al*, 1999), and is often multi-factorial. In particular, use of opioid analgesics is a common cause of constipation, and OIC affects 40-70% of patients (Cherney *et al*, 2001).

The wide variety in OIC prevalence can be attributed to the different methods of assessments used. Presently, diagnostic criteria for OIC includes both objective and subjective criteria. Patients often attribute subjective criteria such as straining and painful defecation to being “constipated”, whilst measures used in clinical trials attribute more weight to objective criteria such as frequency of bowel movements (Bell *et al*, 2009). Additionally, its prevalence varies in different study populations. Potter *et al* (2003) report that constipation is the third most common symptom in patients receiving palliative care, and unsurprisingly, has the highest prevalence in hospice and hospital in-patients (rather than outpatients).

Constipation may impact quality of life. Patients may experience psychological distress (Dhingra *et al*, 2013), and avoid social activities (Friedrichsen *et al*, 2004) because of constipation. It is also associated with socio-economic burdens including presenteeism and absenteeism (Morlion *et al*, 2015), as well as increased rates of consultations with healthcare providers (Bell *et al*, 2009).

This study had two aims; firstly, to investigate the prevalence of OIC using a range of different diagnostic criteria, and secondly, to determine the sensitivity and specificity of the Rome IV criteria for OIC in a heterogeneous group of patients with cancer pain.

## Methods

This was a prospective, observational, non-commercial study of adult patients with cancer who were receiving regular opioid analgesia for at least one week for cancer pain. Patients were eligible for the study regardless of the stage of their disease (localised, advanced, metastatic) or whether they were receiving anticancer treatments. This was a multi-centre study, conducted across six sites in the United Kingdom (one tertiary cancer centre, and five hospices). Exclusion criteria included patients unable to give written study consent or complete the questionnaire.

Patients completed a written questionnaire, which recorded demographic details, cancer diagnosis, opioid medication (name, formulation, and dose) and concomitant medications. Patients also

recorded their Eastern Oncology Co-operative Group (ECOG) performance status (Oken *et al*, 1982).

Data was collected using a variety of assessment tools:

1. “Simple” question (“are you constipated?”) Options - yes/no/unsure
2. EAPC definition question (Larkin *et al*, 2008) Options – yes/no/unsure
3. Camilleri definition question (Camilleri *et al*, 2014) Options – yes/no/unsure
4. Rome IV criteria for OIC (Lacy *et al*, 2016). A patient-reported tool for diagnosing OIC, based on 7 specific criteria.
5. Bowel Function Index (BFI) (Argoff *et al*, 2015; Rentz *et al*, 2009; Ueberall *et al*, 2011). The BFI is a validated, 3 item, patient-reported tool for assessing the treatment of OIC.
6. Patient Assessment of Constipation – Quality of Life Questionnaire (PAC-QOL) (Marquis *et al*, 2005). The PAC-QOL is a validated, 28-item, patient-reported tool for assessing the impact of constipation over time, with answers rated 0-4.
7. Memorial Symptom Assessment Scale – Short Form (MSAS-SF) (Chang *et al*, 2000). The MSAS-SF is a validated, 32 item questionnaire. The patient answers “yes” or “no” to whether they have had that particular symptom in the last week (and then proceeds to rate the severity of the symptom).
8. Specialist Palliative Care Clinician assessment – completed by a doctor or clinical nurse specialist to determine a) whether the patient has constipation b) whether the patient has OIC c) whether the patient has additional causes for constipation

The assessments were completed in a single visit. The study received Ethics approval, and approval from the relevant Research, Development and Innovation Department.

## Results

### *Patient characteristics*

83 (23.7%) patients were Rome IV positive, and 267 (76.3%) patients were Rome IV negative.

	<b>Rome IV positive n = 83</b>	<b>Rome IV negative n= 267</b>
Age	64 (range 30-87)	64 (range 29-93)
Gender		
female	47 (57%)	124 (46%)
male	36 (43%)	143 (54%)
ECOG		
0	8 (10%)	22 (8%)
1	31 (37%)	105 (39%)
2	26 (31%)	79 (30%)
3	15 (18%)	56 (21%)

4	3 (4%)	5 (2%)
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Table 1: Patient characteristics

<b>Primary cancer diagnosis</b>	<b>n = 350</b>
Gastrointestinal	123 (35.1%)
Urological	58 (16.6%)
Gynaecological	37 (10.6%)
Head and neck	37 (10.6%)
Lung	33 (9.4%)
Breast	29 (8.3%)
Haematological	13 (3.7%)
Skin	10 (2.9%)
Cancer of unknown primary	6 (1.7%)
Other	3 (0.9%)
Neurological	1 (0.2%)

Table 2: Prevalence of participants' primary cancer diagnosis

*Sensitivity and specificity of the Rome IV criteria*

By comparing the positive and negative results from the Rome IV criteria for OIC against the Specialist Palliative Care clinician assessment to identify OIC, the sensitivity of the Rome IV criteria is 37.4%. By comparing the Camilleri definition positive and negative results against the Specialist Palliative Care clinician assessment to identify OIC, the sensitivity of the Camilleri definition is 85.7%.

<b>Assessment tool</b>	<b>Sensitivity %</b>	<b>Specificity %</b>
Rome IV criteria for OIC	37.4	98
Camilleri	85.7	73.2

Table 3: Sensitivity and specificity of the Rome IV criteria for OIC and the Camilleri definition

*Prevalence of constipation according to different assessment tools*

Comparison of the different assessment tools indicated a prevalence of constipation of: 64.2% (Specialist Palliative Care clinician assessment (60.8% prevalence of OIC)); 64% (MSAS-SF); 59.4% (Camilleri definition); 32.8% "simple" question; 27.7% EAPC definition; 23.4% Rome IV criteria.

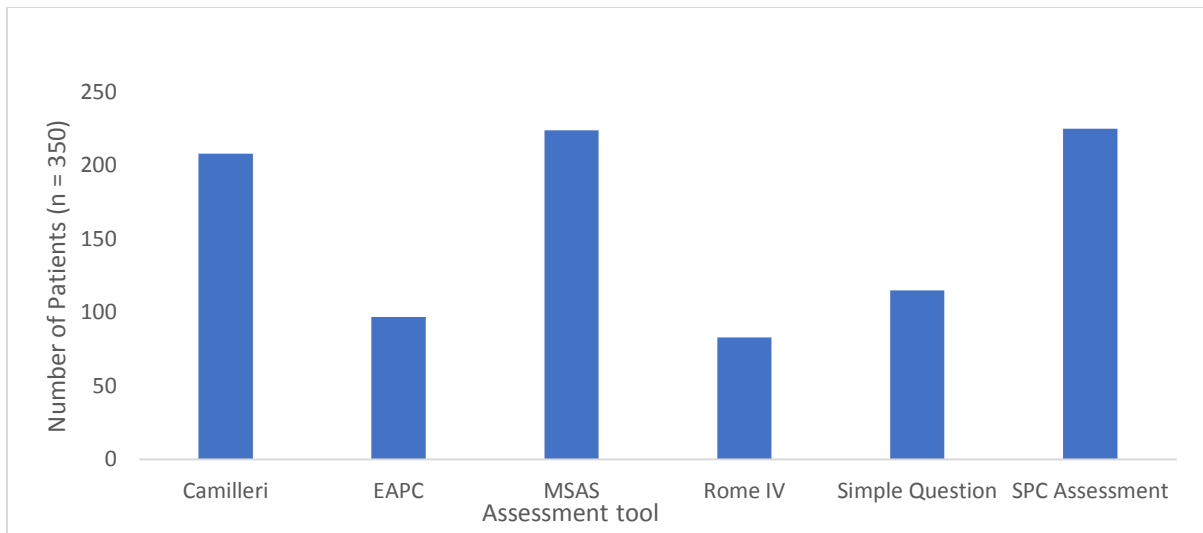


Figure 1: Prevalence of constipation according to different assessment tools

*Correlation with BFI scores*

The mean BFI score for Rome IV positive patients was 58 (range 43-73). The mean BFI score for Rome IV negative patients was 32 (range 10-57).

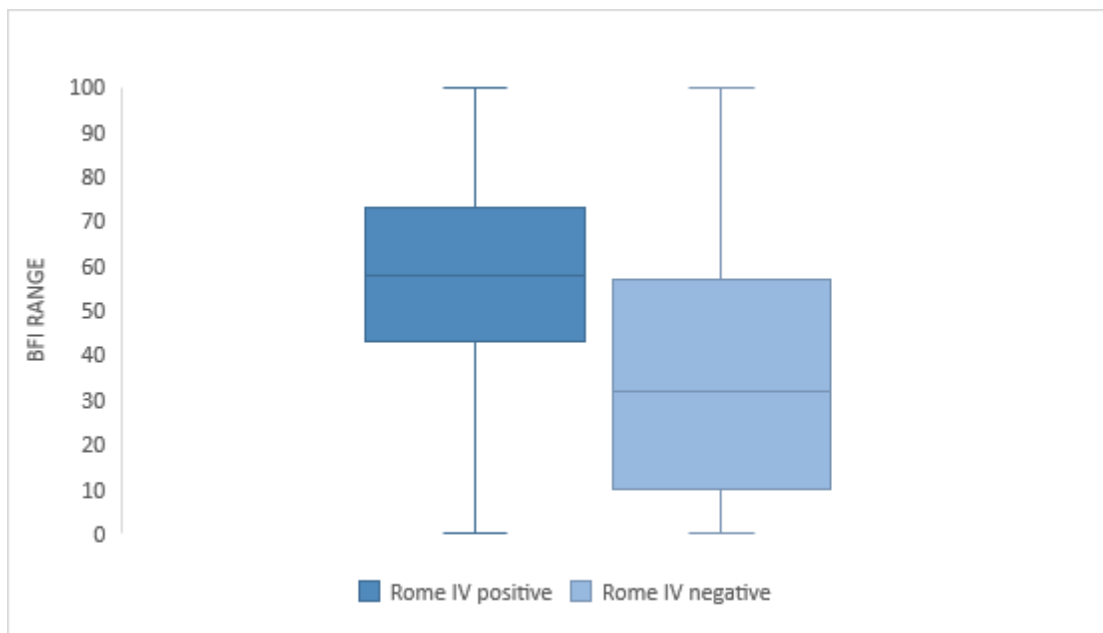


Figure 2: Comparison of BFI scores for Rome IV positive and Rome IV negative patients

*Correlation with symptoms on MSAS-SF*

The mean number of symptoms for Rome IV positive patients was 17 (range 13-22). The mean number of symptoms for Rome IV negative patients was 16 (range 12-20).

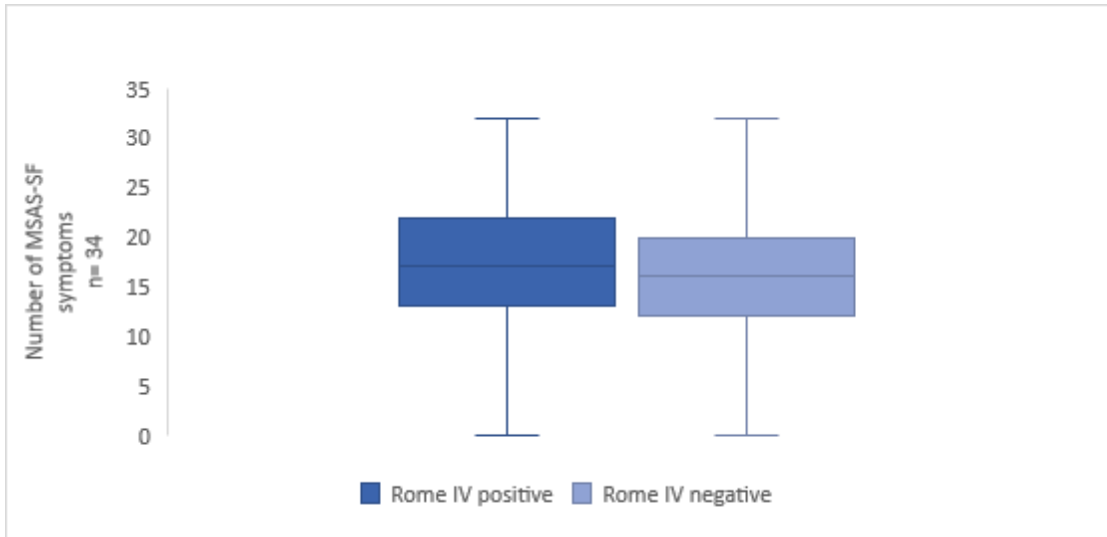


Figure 3: Comparison of MSAS-SF symptoms for Rome IV negative and positive patients

*Correlation with psychological symptoms on PAC-QOL assessment*

The mean number of “mild” symptoms on PAC-QOL assessment (classified as numerical rating 1 or 2) was 12 (range 7-16) and was 6 (range 2-12) for “severe” symptoms (classified as numerical rating 3 or 4) for Rome IV positive patients. The mean number of “mild” symptoms on PAC-QOL assessment was 10 (range 5-15) and was 4 (range 2-7) for “severe” symptoms for Rome IV negative patients.

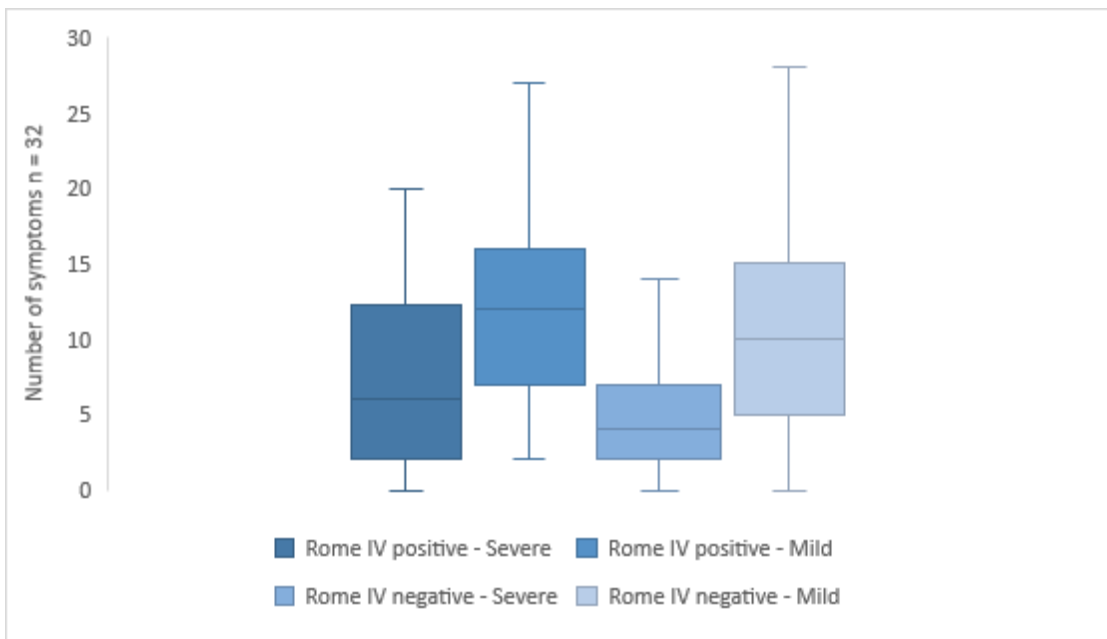


Figure 4: Comparison of PAC-QOL “mild” and “severe” symptoms for Rome IV positive and negative patients.

## Discussion

One of the main findings of this study is the low sensitivity rate for the Rome IV criteria. This indicates that Specialist Palliative Care clinicians are diagnosing more patients with OIC than are being diagnosed by the Rome IV criteria. Interestingly, this is similar to the sensitivity rate of the Rome IV criteria for functional constipation (32.2%; specificity 93.6%. Palsson *et al*, 2016). This is clinically relevant, as it means that patients may be under-diagnosed, leading to inadequate or inappropriate treatment. Conversely, the high specificity rate indicates that the Rome IV criteria accurately detects those patients who truly do not have OIC. This is clinically relevant, as it may direct clinicians to manage constipation more accurately according to aetiology.

These results indicate that there is good correlation between the Camilleri definition and Specialist Palliative Care clinician assessment. This is clinically useful, as it suggests that the Camilleri definition may be utilised as an initial screening tool for the assessment of OIC. A positive Camilleri definition should then lead to a Specialist Palliative Care clinician assessment.

It is interesting that the rate of OIC prevalence was higher on the MSAS-SF questionnaire than the “simple” question, as essentially, they ask the same question. This difference in prevalence may be due to the order of the different assessment tools in the study questionnaire. The “simple” question is the first assessment tool in the questionnaire, and the MSAS-SF is the final assessment tool. Upon completion of the MSAS-SF, participants have worked through seven separate assessments of constipation, some of which ask detailed questions about symptoms associated with constipation (i.e. straining, bloating). Patients, therefore, may have re-considered their response to the binary question “are you constipated?” in light of the influence of the previous assessment tools.

The mean BFI score for Rome IV positive patients was 58. Argoff *et al* (2015) propose that a score equal to or greater than 30 indicates inadequately treated OIC. This suggests that Rome IV positive patients are inadequately treated, which has important clinical implications as this may result in poor symptom management.

There is no meaningful difference between the mean number of symptoms on the MSAS-SF for Rome IV positive and negative patients. Likewise, there was little difference in the mean number of “mild” or “severe” PAC-QOL symptoms when comparing Rome IV positive and negative patients. Both Rome IV positive and negative patients experienced more “mild” than “severe” symptoms. This suggests that psychological symptoms may be due to other factors, rather than constipation alone; however, further analysis is needed to investigate this definitively. Whilst the PAC-QOL is a validated assessment tool, it was not specifically designed for use in patients with cancer pain receiving opioid analgesia. It

is possible, therefore, that some of the questions about specific physical complaints such as bloating and early satiety (questions 1 and 6 respectively) may reflect symptoms of opioid-induced bowel dysfunction due to delayed gastric emptying for example, rather than opioid-induced constipation. Nevertheless, this is clinically important as it emphasises that clinicians need to remain alert to underlying psychological distress in this patient population.

There are both strengths and limitations of this study. One significant strength is the sample size of 350 patients. The heterogeneity of the study population makes the results relevant to all cancer patients, regardless of the stage of cancer treatment. Its relevance, therefore, has implications for both Palliative Care and Oncology specialities. The study was completed across a range of clinical settings, capturing a broad demographic. The questionnaire is comprehensive and uses a range of assessment tools.

Limitations of the study include that the outcome of the Specialist Palliative Care clinician assessment may vary according to professional background (medical or nursing), and years of experience. As this was a multi-site study, there may have been inadvertent variability of practice across sites. The Rome IV criteria has not been validated for use and includes some medical jargon which patients may find difficult to understand, therefore, the results of the Rome IV criteria specifically, may not be reproducible.

In conclusion, the results of this study add new and relevant information for clinical practice. Asking a simple question (“are you constipated?”) is likely to lead to under-diagnosis of constipation. The Camilleri definition appears to be a useful screening tool, which can be easily used in all Palliative Care settings. A comprehensive Specialist Palliative Care clinician assessment should follow a positive Camilleri definition. The low sensitivity rate of the Rome IV criteria indicates that many patients with OIC are not being identified, which may lead to inadequate treatment. Furthermore, the correlation between Rome IV positive patients and a positive BFI score (mean 58) indicates that patients with OIC are not being adequately treated. This study, therefore, highlights the importance of adequate assessment, diagnosis and treatment of OIC, and adds new information regarding the low sensitivity and high specificity rate of the Rome IV criteria.



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