

RESEARCH ARTICLE

The association of patients' daily summarized self-rated “real-time” pain scores with physical recovery after major surgery – A repeated measurement design

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Abstract

Aim: To determine the associations of patients' documented self-rated pain with self-rated early postoperative physical recovery.

Design: Observational with repeated measures.

Methods: General and orthopaedic inpatients ($N = 479$) were during the period 2012–2015 screened for pain. Individual daily median pain scores at rest and during activity were based on 4–9 self-ratings on postoperative days 1 and 2, using the Numeric Rating Scale. Nine items reflecting physical recovery from the “Postoperative Recovery Profile” were used in a questionnaire.

Results: Associations between median pain scores on postoperative day 1 and physical recovery (fatigue, sleeping difficulties, bladder function, mobilization, muscle weakness and personal hygiene) the same day were found. Additionally, associations were found between median pain scores on day 1 and physical recovery (fatigue, sleeping difficulties, mobilization and muscle weakness) on day 2.

KEYWORDS

numeric rating scale, nurse, nursing, pain, pain assessment, postoperative care, recovery, repeated measures

1 | INTRODUCTION

Using patient-reported outcome measures is a standardized method for the monitoring of patients' experiences of their health (Van Der Wees et al., 2014). The value in monitoring patients' self-rated pain intensity during the first days after major surgery is well described in postoperative care (CPMS, 2015; Gordon et al., 2016; Meissner et al., 2015). This is due to the increasing attention to the relationship between severe pain and risk for developing short- and long-term health-related consequences (Sinatra, 2010) as well as the relationship between pain and physical recovery (Gan, 2017). The goal of fast track surgery programmes, which are quickly developing in general and orthopaedic surgery, is to shorten recovery time. However,

there are no general patient-reported outcome measures monitoring early physical recovery after surgery.

1.1 | Background

Postoperative health-related consequences are associated with the ability to recover, which means to “return to preoperative levels of independence/dependence in activities of daily living” (Allvin, Ehnfors, Rawal, & Idvall, 2008). Postoperative recovery involves nociceptive, emotional, functional and cognitive perspectives (Bowyer & Royse, 2016). Many factors contribute to patient recovery, such as psychological issues (Everhart, Best, & Flanigan, 2015; Flanigan, Everhart, & Glassman, 2015), preoperative health conditions, type

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of surgery and postoperative pain management (Ahmed, Lim, Khan, McNaught, & Macfie, 2010). Most instruments covering patients' advances in postoperative recovery have historically been developed for research or quality improvement in clinical contexts (Strickland, Hamilton, Jenkinson, Murray, & Pandit, 2016). Many of them are extensive, including up to 40 items (Strickland et al., 2016). In the first days after surgery, physical recovery, for which pain has the greatest significance, is described as the first priority by patients (Allvin, Ehnfors, Rawal, Svensson, & Idvall, 2009; Mata et al., 2017). The most common recovery assessment instruments therefore include this dimension (Myles, Weitkamp, Jones, Melick, & Hensen, 2000; Royse et al., 2010), which is also the case in recommendations for clinical postoperative evaluations after major surgery (Gordon et al., 2010; Rothaug et al., 2013).

Many patients experience high pain intensity in the first postoperative days after major and minor surgery (Gerbershagen et al., 2013). Therefore, in postoperative care it is globally recommended to monitor pain intensity at rest and during activity until the pain has resolved (Gordon et al., 2016; SFAI, 2011). The Numeric Rating Scale (NRS) is the recommended scale for measuring pain intensity across different cultural and surgical contexts and is described as functional also in the elderly population (Hjermstad et al., 2011). However, in postoperative care a structured use of the NRS or another equivalent one-dimensional scale has still not been identified in retrospective reviews about documentation of pain (Heikkila, Peltonen, & Salanterä, 2016). One reason for this may be the identified difficulties (i.e., mismatching scores with pain-related behaviours) in interpretation of NRS scores (Eriksson, Wikström, Årestedt, Fridlund, & Broström, 2014; Wikström, Eriksson, Fridlund, Årestedt, & Broström, 2015). Despite these difficulties, patients and healthcare professionals perceive the NRS to be a useful instrument, in communication both between healthcare professionals and patients and between healthcare professionals. Frequently monitored pain scores are also helpful in understanding development of pain over time (Eriksson et al., 2014; Wikström et al., 2015).

In the clinical context, "real-time" recovery data are considered preferable to use as it can be used directly in clinical decisions (Bowyer & Royse, 2016). However, the spread of programmes for enhanced recovery in general and orthopaedic surgery has resulted in a high workload and limited time for healthcare professionals to collect extensive patient data. This causes difficulties in introducing existing recovery assessment instruments. On the other hand, the absence of patient-reported recovery measures may make it impossible to provide adequate individual interventions (Bowyer & Royse, 2016). Moreover, the absence of patient-reported measures may also risk neglecting the philosophy of person-centred care where patients' statements are fundamental in care decisions (Wallström & Ekman, 2018). Therefore, there is a clinical need to find a simple strategy for measuring patients' possibility for physical postoperative recovery that is useful when decisions about care are taken. Significant associations between postoperative patients' experiences of pain, retrospectively expressed with the NRS, and the prediction of early physical recovery have been shown (Eriksson, Wikström, Fridlund,

Årestedt, & Broström, 2017). Furthermore, the validity of a daily summary of patients' self-reported "real-time" pain scores obtained using the NRS has been determined (Wikström et al., 2017). These results indicate that the idea of using patients self-rated pain intensity to understand patients' ability for physical recovery during the first days after surgery is possible. However, to our knowledge, the idea of using "real-time" pain scores to reflect patients' potential for physical recovery has not previously been studied.

2 | THE STUDY

2.1 | Aim

The aim of the study was to determine the associations of patients self-rated "real-time" pain scores with self-rated early postoperative physical recovery.

2.2 | Design

An observational explorative study design with repeated measures was used.

2.3 | Sample and setting

A convenience sample of 582 patients who were scheduled for major orthopaedic or general surgery were from October 2012 until January 2015 asked to participate in the study, and of these, 541 agreed to participate. The inclusion was made 1–2 weeks before surgery. The study was conducted at six care units in three county hospitals in Sweden, where each hospital had 300–400 beds. A standardized pain regimen at the three hospitals included paracetamol and opioids. Epidurals were used at abdominal and urology surgery. Non-steroid anti-inflammatory drugs were used when considered needed. Inclusion criteria were as follows: scheduled for major general or orthopaedic surgery with an expected length of stay of ≥ 2 days, age ≥ 18 years and ability to understand and read the Swedish language. Exclusion criteria were as follows: pre- or postoperative cognitive impairment, or postoperative intensive care. The number of patients who completed the data collection up to postoperative day 2 was 479 and 441 up to postoperative day 3. The main reason for the dropout on day 2 was postoperative discharge.

2.4 | Instruments

Patients' preoperative and postoperative pain intensity at rest and during activity was measured with the one-dimensional NRS. The NRS has been shown to have good validity and reliability in several settings when measuring pain (Hjermstad et al., 2011). The NRS with the end-points of no pain and worst possible pain was used. Data on pain intensity were documented in "real-time." Each patient's "real-time" pain scores at rest and during activity were daily summarized in individually median scores for postoperative day 1 and with the same procedure for day 2. Median pain values were compiled from

TABLE 1 Socio-demographic and clinical data for patients undergoing orthopaedic and general surgery (N = 479)

Variables	N (%)
Age, mean (range)	65 (22–93)
Men, N (%)	268 (56)
ASA level \geq III, N (%)	60 (13)
Orthopaedic surgery, N (%)	289 (60)
Daily intake of analgesia preoperatively	
Non-opioids, N (%)	136 (29)
Opioids, N (%)	66 (14)
Type of surgery, N (%)	
Urology	91 (19)
Lower abdominal	89 (19)
Vascular	6 (1.3)
Other general surgery	2 (0.4)
Joint replacement	225 (47)
Neck and back	49 (10)
Other orthopaedic	15 (3)
Postoperative analgesia day 1, N (%)	
Paracetamol	464 (98)
NSAID	59 (13)
Opioids	362 (78)
Epidural	120 (26)

at least four documented “real-time” NRS scores, which is necessary to achieve a valid median score (Wikström et al., 2017). For each patient, one median score for pain intensity at rest and one during activity were calculated.

Physical recovery was measured using a questionnaire with nine questions covering three of five dimensions of the Postoperative Recovery Profile (PRP) instrument (Allvin et al., 2009). The PRP was developed in a Swedish context, has been proved to be valid and reliable (Allvin et al., 2009) and has been used in several studies (Forsberg, Vikman, Walivaara, & Engstrom, 2015; Jakobsson, Idvall, & Wann-Hansson, 2014; Le, Khankhanian, Joshi, Maa, & Crevensten, 2014). The PRP questionnaire consisted in its entirety of five dimensions: physical symptoms, physical function, psychological items, social items and activity. In accordance with the study aim, the three dimensions of physical recovery were used, that is physical symptoms, physical function and activity. Physical symptoms consisted of five items (pain, nausea, fatigue, appetite changes and sleeping difficulties), physical function consisted of four items (gastrointestinal function, bladder function, mobilization and muscle weakness), and activity was one item (personal hygiene). Since pain was measured in “real time” with the NRS, pain was excluded from the PRP questionnaire. The impact on each recovery item was assessed with four options: none, mild, moderate and severe. These answer options were dichotomized into none/mild and moderate/severe when analysing the association between pain intensity and the recovery items. The content validity after exclusion of items from the PRP was based on patients' ranking of the importance of recovery items

before postoperative discharge from hospital (Allvin et al., 2011). In line with the original version of the PRP (Allvin et al., 2009), each recovery item was analysed individually and no sum score of the recovery items was made. The external validity was strengthened by the fact that data were retrieved from six wards at three hospitals.

2.5 | Data collection

Patients were enrolled from October 2012–January 2015. Those patients who at the enrolment call prior to surgery consented to participate answered a first questionnaire containing socio-demographic questions as well as questions about preoperative pain intensity (NRS) and physical status according to PRP aspects of physical recovery. The second and third questionnaires were completed retrospectively on postoperative days 2 and 3. These questionnaires contained the same PRP items as were used in the preoperative questionnaire. Every fourth hour on postoperative days 1 and 2, the patients were asked by the nurses in charge to self-rate their pain intensity at rest and during activity with the verbally communicated NRS. The nurses were also instructed to ask patients to rate their pain when breakthrough pain occurred. The scores were documented in a protocol designed for the study. Designated research nurses at each of the six included care units collected clinical data from medical records, such as type of surgery, the American Society of Anesthesiologists (ASA) Physical Status classification (ASA level) and analgesia given postoperatively on day 1.

2.6 | Ethical considerations

The study was conducted in accordance with the ethical principles of the Helsinki Declaration (WMA, 2013). Patients eligible for the study were asked for their participation regardless of sex, socioeconomic status or ethnicity. Participation was voluntary and did not affect care. Dropout from the study did not need to be specified. The Regional Ethical Review Board of Linköping gave ethical approval on 12 March 2012 (M249-08).

2.7 | Data analysis

Descriptive statistics (mean, range, medians and percentages) were used to present socio-demographic and clinical data. Each patient's “real-time” NRS scores were summarized daily into individual median scores on postoperative days 1 and 2, respectively. The calculated median scores were categorized into three groups (0–3, 4–6 and 7–10) to illustrate none to mild, moderate and severe pain, respectively, as done in previous research (Couceiro, Valenca, Lima, Menezes, & Raposo, 2009; Eriksson et al., 2017; Forsberg et al., 2015). The individual median values for pain intensity at rest and during activity were the above groups used in the logistic analysis (95% confidence interval) of associations between pain intensity and impact on early physical recovery. Pain intensity (i.e., median scores) from day 1 was used as a predictor variable for early physical recovery on postoperative day 2. A significance level below 5% was

Number of real-time pain ratings	Day 1		Day 2	
	Rest, N (%)	Activity, N (%)	Rest, N (%)	Activity, N (%)
0–3	85 (18)	119 (24)	163 (34)	246 (51)
4	139 (29)	150 (31)	129 (27)	119 (25)
5	116 (24)	101 (21)	80 (17)	73 (15)
6	96 (20)	67 (14)	38 (8)	34 (7)
7	35 (7)	33 (7)	6 (1.3)	7 (1)
8	7 (2)	7 (2)	1 (0.02)	1 (0.02)
9	1 (2)	2 (0.4)	1 (0.02)	1 (0.02)

TABLE 2 Frequency of patients' self-rated real-time pain

TABLE 3 Pain intensity (NRS) collected in real-time

Pain intensity	N	Prehospital pain	Pain day 1	Pain day 2
At rest, md (q1–q3)	474	2 (0–5)	2 (0–4)	1 (1–3)
During activity, md (q1–q3)	469	6 (1–8)	4 (2–5)	2 (4–5)

considered as statistically significant. Odds ratio was calculated on the full range of NRS scores.

3 | RESULTS

3.1 | Socio-demographic and clinical characteristics

The sample consisted of (479) patients, representing major general (40%) and orthopaedic surgery (60%). The mean age of the sample was 65 years with a range from 22–93 years, and 56% were men. Patients with an ASA level of \geq III (13%) and preoperative ongoing opioid treatment (14%) were included. Preoperatively, the proportion of patients with average pain intensity \geq 4 at rest was 39% and during activity 63%. Most patients (87%) were treated with opioids postoperatively and 26% received an epidural, Table 1.

3.2 | Patients' pain experiences measured with the NRS

On postoperative day 1, the proportion of patients who had \geq 4 documented "real-time" NRS scores at rest was 82% and 75%, during activity. On day 2, the proportions were 53% and 49%, respectively (Table 2). The proportion of patients who on day 1 had obtained a median score at rest of 0–3 was 73%, 4–6: 24% and 7–10: 3%, and during activity, the responding proportions were 40%, 39% and 21%. On day 2, the proportion of patients who obtained a median pain score at rest of 0–3 was 86%, 4–6: 13% and 7–10: 1%, while during activity the responding proportions were 46%, 44% and 10%, respectively. Median pain (calculated from individual daily median scores) on day 1 for the whole sample was two at rest and four during activity (Table 3).

3.3 | Association between median NRS scores on day 1 and physical recovery on day 1

The response rate of the questionnaire on postoperative day 2 was 89%, regarding physical recovery on day 1. The analyses showed that patients' median pain intensity at rest significantly reflected five of nine recovery items on day 1. Statistically significant associations ($p < .001$) were found for the following items: fatigue, sleeping difficulties, mobilization, muscle weakness and personal hygiene. Pain intensity during activity was significantly associated with the same items of recovery as at rest, fatigue ($p = .090$), sleeping difficulties ($p < .001$), mobilization ($p < .001$), muscle weakness ($p = .010$) and personal hygiene ($p = .007$) and, additionally, bladder function ($p = .010$). As for the significant items, an increased odds ratio was seen for impact on physical recovery with increased pain both at rest (Figure 1a) and during activity (Figure 1b).

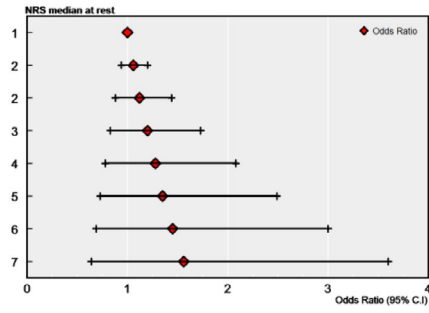
3.4 | Association between median NRS scores on day 1 and physical recovery on day 2

The response rate of the questionnaire on postoperative day 3 was 82%, regarding physical recovery on day 2. The pain intensity on day 1 at rest (individual median value) was significantly associated with three of nine recovery items on day 2. These were as follows: nausea (NRS 4–6; $p = .150$, NRS 7–10; $p = .026$), sleeping difficulties ($p = .001$); and mobilization ($p < .003$). The median scores of pain intensity during activity on day 1 were significantly associated with four of nine recovery items on day 2. Associations were found between pain intensity and the items: fatigue ($p < .015$), gastrointestinal function ($p = .018$), mobilization ($p < .001$) and muscle weakness ($p < .006$). As for the significant items, an increased odds ratio was seen for impact on physical recovery on day 2 with increased pain both at rest (Figure 2a) and during activity on day 2 (Figure 2b) apart from the item nausea.

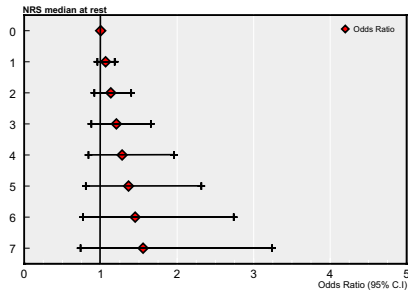
4 | DISCUSSION

The aim of this study was to determine associations between patients' individual daily median score at rest and during activity and

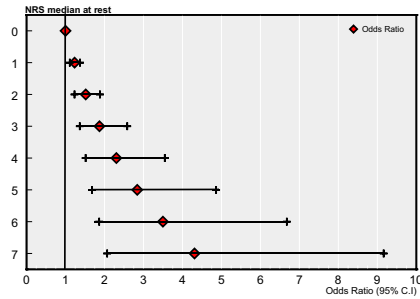
(a) Nausea



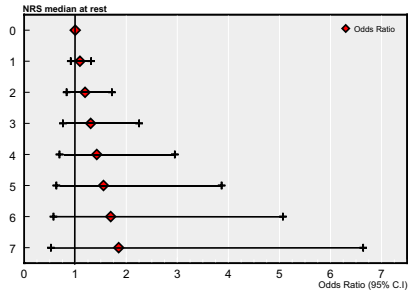
Gastrointestinal function



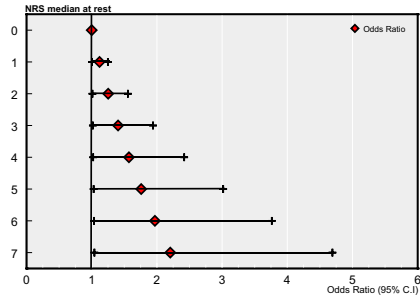
Fatigue



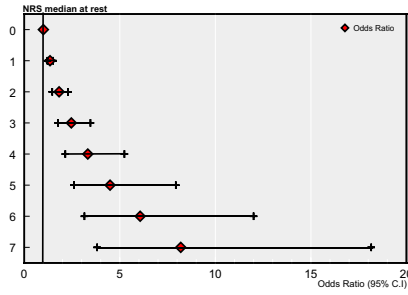
Bladder function



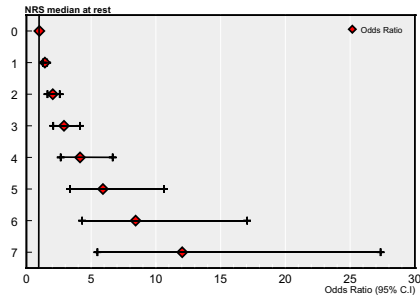
Appetite changes



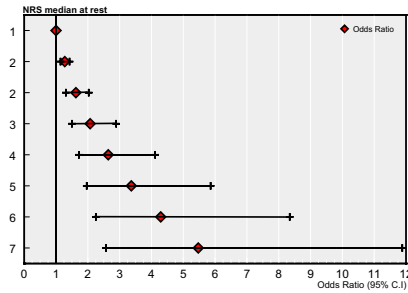
Mobilization



Sleeping difficulties



Muscle weakness



Personal hygiene

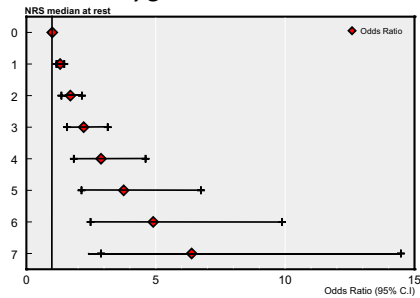
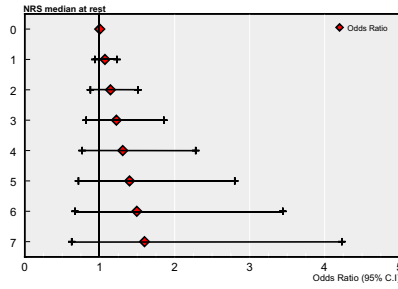
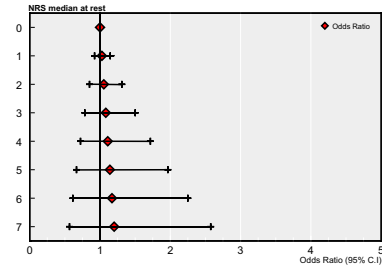


FIGURE 1 (a) The association between median NRS scores at rest day 1 and physical recovery on day 1. Items in italic style are significant. (b) The association between median NRS scores during activity day 1 and physical recovery on day 1. Items in italic style are significant

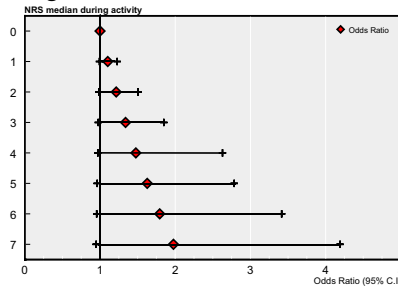
(b) Nausea



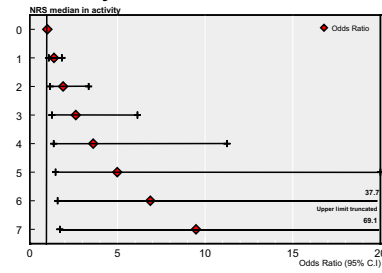
Gastrointestinal function



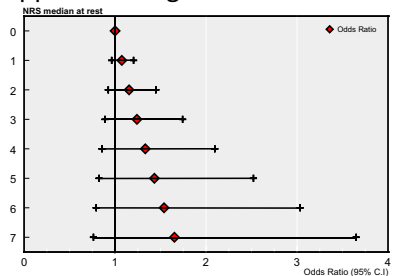
Fatigue



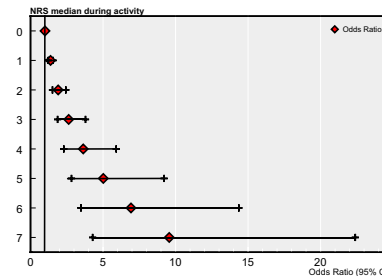
Bladder function



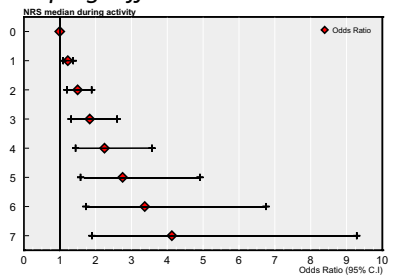
Appetite changes



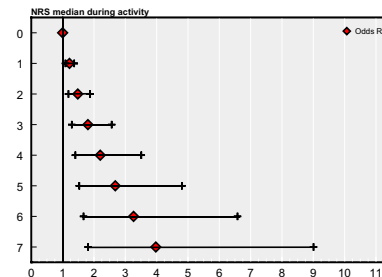
Mobilization



Sleeping difficulties



Muscle weakness



Personal hygiene

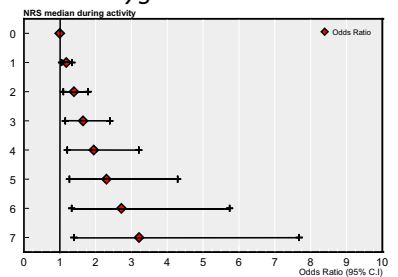
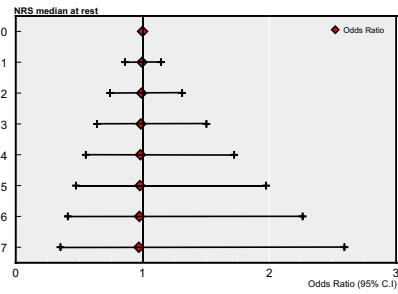
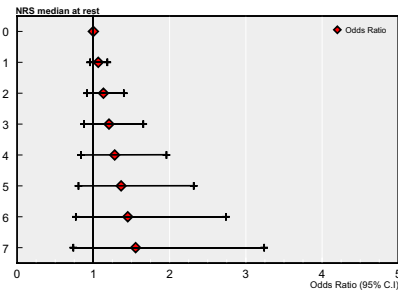


FIGURE 1 (Continued)

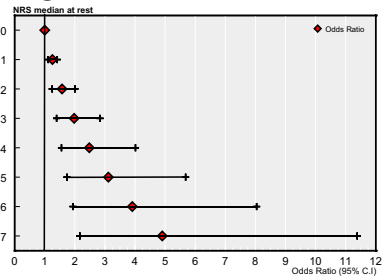
(a) Nausea



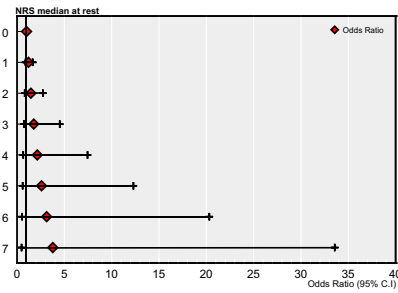
Gastrointestinal function



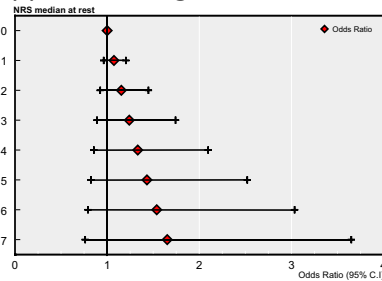
Fatigue



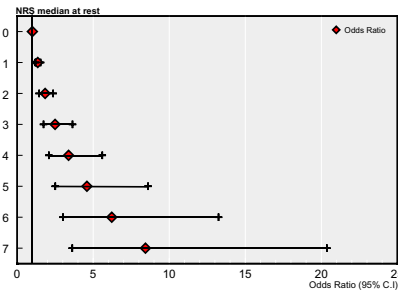
Bladder function



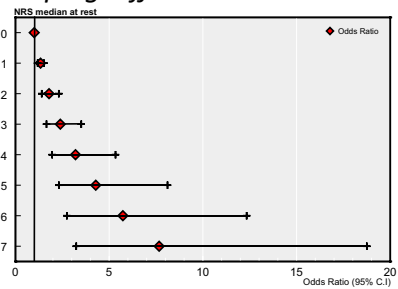
Appetite changes



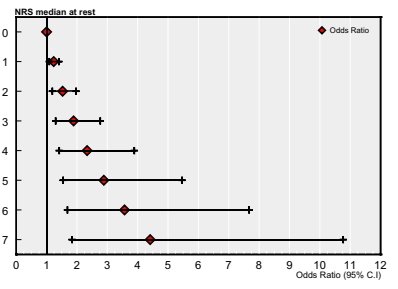
Mobilization



Sleeping difficulties



Muscle weakness



Personal hygiene

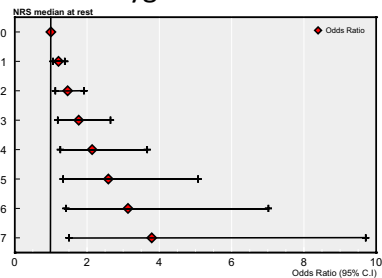


FIGURE 2 (a) The associations between median NRS scores at rest day 1 and physical recovery on day 2. Items in italic style are significant. (b) The associations between median NRS scores during activity day 1 and physical recovery on day 2. Items in italic style are significant

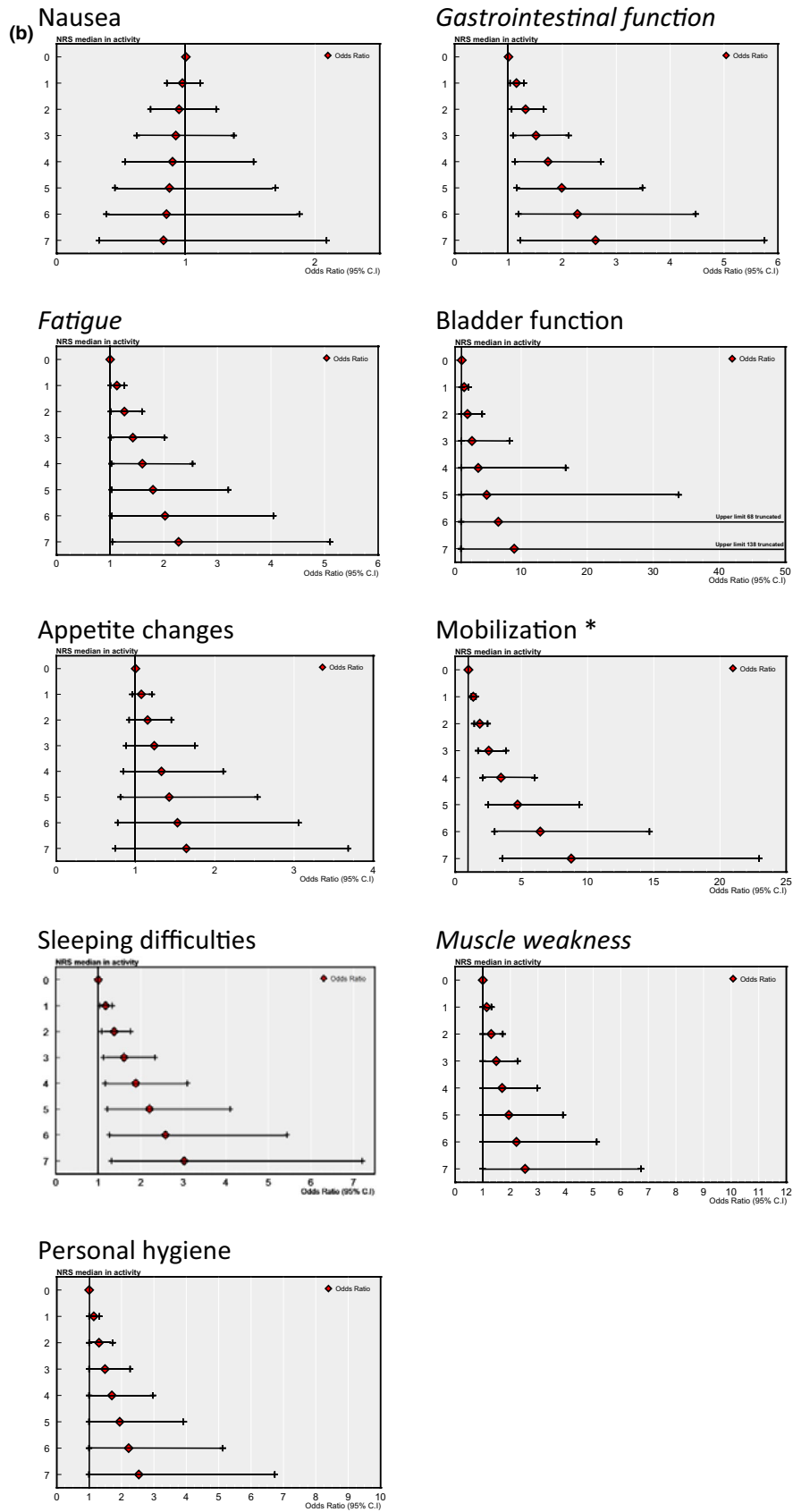


FIGURE 2 (Continued)

postoperative physical recovery after major surgery. The main results showed clinically significant associations between postoperative self-reported pain intensity and several aspects of physical recovery on postoperative day 1. Similar significances were shown in associations between postoperative pain intensity on day 1 and physical recovery on day 2, which indicate that patients' individually calculated daily median pain at rest and during activity can be used to identify patients at risk for delayed physical recovery.

The main results confirm previous research using patients retrospectively stated average pain intensity when associations with physical recovery were analysed in the same manner as in this study (Eriksson et al., 2017). However, there were fewer significantly associated recovery items when using median pain scores in comparison with using patients' retrospective stated average scores. In the light of these results, daily collection of patients' retrospectively retrieved average pain scores from the day before seems to be the most methodologically appropriate technique for collection of data in postoperative care. On the other hand, the collection of "real-time" self-rated pain scores is most important when understanding how to manage patients' pain, such as on those occasions when breakthrough pain is present and persistent and the pain management being administered needs to be frequently reassessed (Gordon et al., 2008; Wikström, Eriksson, Årestedt, Fridlund, & Broström, 2014). Our data collection revealed that patients' NRS scores during breakthrough pain and reassessments were rarely documented, while the adherence to given time frames of 4 hr was more accurate. Similar results were found by Carr et al. (2014) who therefore suggested more frequent assessments of patients with high scores of pain intensity. The same approach is applied when vital signs with the early warning scores are monitored; that is, higher scores lead to more frequent measurements (Hollis et al., 2016). However, in contrast to actions taken following high early warning scores, decisions about intervals between pain assessments should involve the patient as pain is an individual experience.

When using patients' documented pain ratings (i.e., daily summarized into an individual median score) as an indirect measure to reflect and predict early physical recovery, pain assessments must be performed regularly and must be of high quality. This conclusion can be made by comparing the results when using patients' statements of retrospective pain scores (Eriksson et al., 2017). Previous analyses showed quality to be associated with the number of documented NRS scores and healthcare professionals' performance when obtaining patients' pain scores. A higher risk of obtaining a lower median than patients reported retrospectively was revealed and resulted in fewer patients in severe pain (medians of NRS 7–10) than was retrospectively stated (Wikström et al., 2017). When patients are assessed with an open question that can be answered with a yes or no and with the answer no monitor NRS 0, the risk of obtaining a false low "real-time" score may occur. This problem can be ruled out by always asking patients to use the full range of the NRS. Furthermore, a culture of considering patients' statements in symptom assessments and a calculation function

in journal tables designed for the monitoring of patients' symptom assessments would facilitate implementation of daily median scores from patients' "real-time" scoring on several occasions per day.

As stated before, the quality of daily average measures of pain intensities and associations with physical recovery are found to be higher when patients are asked for a retrospective score covering the day before. However, little is known about patients' memory capacity in the first days after surgery. Hovasapian and Levine (2016) showed in an experimental study design that memory of pain was almost unchanged up to 3 days after exposure to pain. However, in the postoperative context there are patients who become tired and cognitively affected due to a decline in health status and the effects of perioperative anaesthesia and analgesia. Tiredness has been shown to impact on memory capacity (Khoshnejad, Fortin, Rohani, Duncan, & Rainville, 2014), and patients' postoperative altered cognitive functions have gained increased attention in recent research (Bowyer & Royse, 2016). In this sample, the participants possessed the capability to complete the questionnaire. However, the fact that some patients, especially the elderly, might suffer from temporary postoperative decline in cognitive functions must be taken into consideration if collected retrospective average scores are asked for. There will be an obvious risk of collecting false retrospective pain scores from these patients. A small group of patients may not be able to recall any pain from the day before.

The idea of monitoring patients' postoperative recovery by using patients' pain scores is to simplify something that is complex and multifaceted. With limited resources in health care, there is a need to balance workload (e.g., collection of data) with other care duties to maintain the quality of care (Magalhaes et al., 2017). Furthermore, experiences from different contexts show that most patients, including the elderly and patients with a diminished cognitive ability, can score their symptoms with the NRS in "real-time" (Hjerstad et al., 2011; van Dijk, Kappen, Wijck, Kalkman, & Schuurmans, 2012;). Since information about patients' pain intensity ideally should be collected regularly in accordance with postoperative guidelines (Gordon et al., 2016; SFAI, 2011) and the philosophy of person-centred care (McCance, McCormack, & Dewing, 2011; Wallström & Ekman, 2018), pain scores that have already been collected could serve as a basis for discussions about a patient's possibility to recover.

Pain is a highly subjective experience which means that the threshold for impact on recovery varies among patients (Eriksson et al., 2014; van Dijk et al., 2014). Additionally, the absence of postoperative pain does not guarantee that there are no other aspects impeding recovery such as common side effects from analgesia, for example nausea, dizziness and tiredness or complications. Neither psychological nor social aspects can be ignored. Consequently, a dialogue aiming to understand how pain affects physical recovery, including psychosocial considerations, is needed. The use of patients' self-reported pain together with these considerations would enable healthcare professionals to act to promote recovery

using a structured approach, thereby enabling continuity of care. Additionally, patients' stated pain scores could be used as simple and less time-consuming measures in clinical evaluations of postoperative care regimes. Heikkilä et al. (2016) reported that the quality of pain documentation is not of an acceptable standard. Our results can provide approaches to improve documentation of pain which facilitate understanding of patients' pain over time and their prognosis for recovery. As nausea is another major side effect of surgery and use of common postoperative analgesia such as opioids (Gan, Habib, Miller, White, & Apfelbaum, 2014), corresponding studies have been performed considering impacts from nausea on postoperative recovery (Eriksson, Årestedt, Broström, Wikström, 2019, Wikström, Nilsson, Broström, Eriksson, 2019).

4.1 | Limitations

The use of the items from the PRP instrument involving only physical aspects may be considered as a limitation. However, in the analyses, no sum score was compiled; instead, every item was separated and individually analysed when exploring the association with pain intensity.

The low number of documented pain ratings for a large group of patients is considered as a limitation. Another limitation was the fact that the reference variable (patients with a calculated median score of 0–3) in the logistic regression analysis was large, 73% at rest and 40% during activity. Additionally, there were few patients who had a calculated median score of NRS 7–10. These could be reasons that there were fewer than expected significant associations between NRS 7–10 and impact on the studied recovery items. Future studies may discover whether stronger associations between physical recovery and pain can be reached with a greater number of "high quality" median scores, that is when patients in pain are more frequently assessed.

5 | CONCLUSIONS

With the knowledge of the importance of high-quality pain assessments, the conclusion is that daily median pain scores can be used when assessing patients' possibilities for physical recovery in the first days after major surgery. Documented daily median pain scores at rest and during activity can indicate the need for evaluating the impact on physical recovery in discussion with the patients. However, to reveal what aspect of recovery might be affected is fundamental as recovery is multifaceted and the perception of pain scores varies between individuals. The knowledge of associations between pain and physical recovery on the following day can potentially be a motivator to pay closer attention to patients in pain and prioritize pain management.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

LW and KE: Draft, analysis and preparation of the manuscript. MN: Analysis and preparation of the manuscript.

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