

Original contribution

Chronic pain patients and time to sustained acceptable pain scores after major surgery - A retrospective registry analysis

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HIGHLIGHTS

- The time required for surgical pain to resolve is a clinically meaningful outcome.
- Pain at rest took longer to resolve in patients with chronic pain than in those without baseline pain.
- Chronic pain prolonged movement-evoked pain even more than it prolonged recovery of pain at rest.
- Consequently, the postoperative pain burden was greater in patients with chronic pain than in those without baseline pain.

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ABSTRACT

Study objective: We tested the hypothesis that pre-existing chronic pain is associated with prolonged time to reach sustained acceptable pain scores after major surgery.

Design: Retrospective study using the German Network for Safety in Regional Anaesthesia and Acute Pain Therapy registry.

Setting: Operating rooms and surgical wards.

Patients: 107,412 patients recovering from major surgery who were cared for by an acute pain service. 3.3% of the treatments were in patients who reported chronic pain with functional or psychological impairment.

Interventions and measurement: We compared time to sustained adequacy of postoperative pain control defined by numeric rating scores <4 at rest and with movement in patients with and without chronic pain using an adjusted cox proportional hazard regression model and Kaplan-Meier analysis. The observation period was censored at 10 days and propensity score matching was used as a sensitivity analysis.

Main results: Postoperative pain at rest took significantly longer to resolve in patients with chronic pain than in those without (adjusted hazard ratio 1.42, 95% CI 1.36–1.49, $P < 0.001$). Postoperative pain with movement took even longer to resolve in patients with chronic pain (adjusted HR 1.65, 95%CI 1.56–1.75, $P < 0.001$).

Conclusions: Patients with chronic pain sustain more surgical pain than those without, and the pain takes longer to resolve. Clinicians providing postoperative pain management should consider the special needs of chronic pain patients.

1. Introduction

Adequate management of postoperative pain remains challenging,

and many patients do not receive adequate pain management after surgery [1,2]. Numerous studies report associations between postoperative pain intensity and complications [3,4], prolonged

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hospitalization and pain chronicity [5,6]. Factors that contribute to surgical pain intensity include specifics of the surgical procedure itself [7] and individual patient characteristics such as sex, age, and personality. The evidence on chronic pain as a risk factor for prolonged postoperative pain remains sparse and conflicting. While some studies identified pre-existing chronic pain as an important risk factor for the development of severe acute pain [8–11], a meta-analysis was unable to do so [12].

Chronic pain is common and, depending on the definition used, has a prevalence varying from 27% (pain longer than 3 months) to 3% (pain causing functional and psychological impairment) [13]. Persistent pain is accompanied by altered pain perception, functional limitations, depression, and avoidance behaviors. Patients with chronic pain often take opioids, which are themselves risk factors for severe postoperative pain [8,14]. Preoperative chronic pain is a risk factor for high postoperative pain intensity [8], independent of the time and extent of surgery [9]. Nonetheless, studies of postoperative pain in chronic pain patients are scarce and largely focus on the initial 24 h after surgery. The extent to which chronic pain prolongs the duration of acute postoperative pain remains unclear [15].

Mean values over time do not account for the dynamic and individual nature of pain or variable treatment durations. We therefore selected the time at which postoperative pain was controlled as our primary endpoint. We analyzed the time needed for inpatients with and without pre-existing chronic pain to reach a stable and adequate pain intensity, defined as sustained scores <4 points on an 11-point numerical rating scale (0 = no pain, 10 = worst pain imaginable), using the Network for Safety in Regional Anaesthesia and Acute Pain Therapy registry. Our co-primary hypotheses were that postoperative pain at rest and with movement takes longer to resolve in patients with history of chronic pain than in patients without chronic pain.

2. Methods

2.1. Ethics

Approval for this retrospective cohort study was provided by the Ethics Committee of the Saarland Medical Chamber, Saarbrücken, Germany (Chairperson Prof. Dr. U. Grundmann) on July 17, 2020 (identification no. 153/20). Written consent was waived as the registry data are completely anonymous (regularly proof of protection of data privacy, Saarland commissioner, March 12, 2014). Based on the submitted study protocol, registry data were released on June 04, 2020, by the Scientific Panel of the network (www.net-ra.eu). This article is consistent with the **RE**porting of studies **C**onducted using **O**bservational **R**outinely-collected **D**ata (**RECORD**) guidance [16].

2.2. Registry

The Network for Safety in Regional Anaesthesia and Acute Pain Therapy was founded in 2007 under the auspices of the German Society for Anaesthesiology and Intensive Care Medicine and the Professional Association of German Anaesthesiologists (Nürnberg, Germany). The registry collects perioperative primary data on regional anaesthesia and postoperative acute pain management procedures performed by acute pain services [17]. As previously described, each participating hospital uses its own system for documenting data on the patient, the regional anaesthesia or acute pain therapy procedure setup, and the postoperative rounds of the acute pain service [18,19]. The documentation is subjected to on-site quality control and then transmitted to the registry in anonymized form. The uploaded data is not automatically checked for completeness, as not all fields provided by the registry are required.

2.3. Acute pain service

Acute pain services in Germany are activated when expected pain intensity or the invasiveness of a pain procedure exceeds a level that normal wards can easily handle. Whereas minor surgeries (for example catheter implant, screw removal, hernia repair, tooth extraction) are typically managed by surgeons, major surgeries (for example open thoracotomy, major abdominal surgery, complicated hip fracture, polytrauma) typically involve care by acute pain services. The service usually manages patient-controlled intravenous analgesia and continuous regional anaesthesia catheters in combination with oral medications with the aim of minimizing pain (NRS < 4) and facilitating mobilization and recovery. This procedure results from national [20] and international guidelines [21,22], which support the use of continuous regional analgesic techniques. Inpatients are visited at least daily, and more frequently if needed, until the pain is under control. Surgical pain scores at rest and with movement need to be documented at each visit. Acute pain services should be staffed by physicians or by nurses with additional qualifications in acute pain management and are available round the clock [23].

2.4. Data extraction and cleaning

We extracted data from 2007 to 2019, a period that included 110,989 acute pain management procedures (predominantly continuous regional anaesthesia) performed by acute pain services from 26 hospitals. We limited our analysis to adults (>18 years) from hospitals that submitted at least 100 cases. We excluded procedures with implausible time stamps resulting in negative treatment times (Fig. 1).

Data integrity of the remaining 107,412 cases was evaluated according to specific rules that identified and deleted incorrectly entered data and identified cases with missing information. We deleted implausible data for sex (i.e., male designation excludes obstetrics) and age (119 years maximum according to the registry restriction *year of birth* > 1900). We also deleted implausible data for height, weight and BMI. The permissible range for height was 154 cm for women or 166 cm for men up to 249 cm, and for weight 47 kg for women or 55 kg for men up to 249 kg, both according to the 3. percentile for 18 year old women respectively men and the registry restrictions for maximum height and weight. The permissible range for the BMI was 17.5 kg/m² for women or 17.8 kg/m² for men up to 85 kg/m² according to the previously defined restrictions for height and weight. Subsequently only cases with internally consistent data were used for analysis.

2.5. Definitions

The net-ra registry provides postoperative pain scores at rest and with movement, which are documented at each visit by the acute pain service on an 11-point numerical rating scale (0 = no pain, 10 = worst pain imaginable). Pain scores <4 indicate a tolerable pain threshold [24]; we therefore defined pain as adequately controlled once the NRS was sustained at <4 points. According to the registry specifications, pain at rest is defined as pain in the surgical area without any type of exertion. Pain with movement is defined as pain on muscular exertion in the surgical area and in the area of expected spread of regional anaesthesia. We censored the observation period at 10 days because thereafter pain cannot be attributed to surgery with sufficient certainty. Censored cases were included in the calculations at a duration of 10 days.

The definition of a chronic pain syndrome in the net-ra registry (pain lasting longer than three months and leading to functional and/or psychological impairment) corresponds to the definition of the German Pain Society and the International Association for the Study of Pain. Treating anesthesiologists decide whether patients meet criteria for a chronic pain syndrome based on available information (including medical history, physician's letters, and medication).

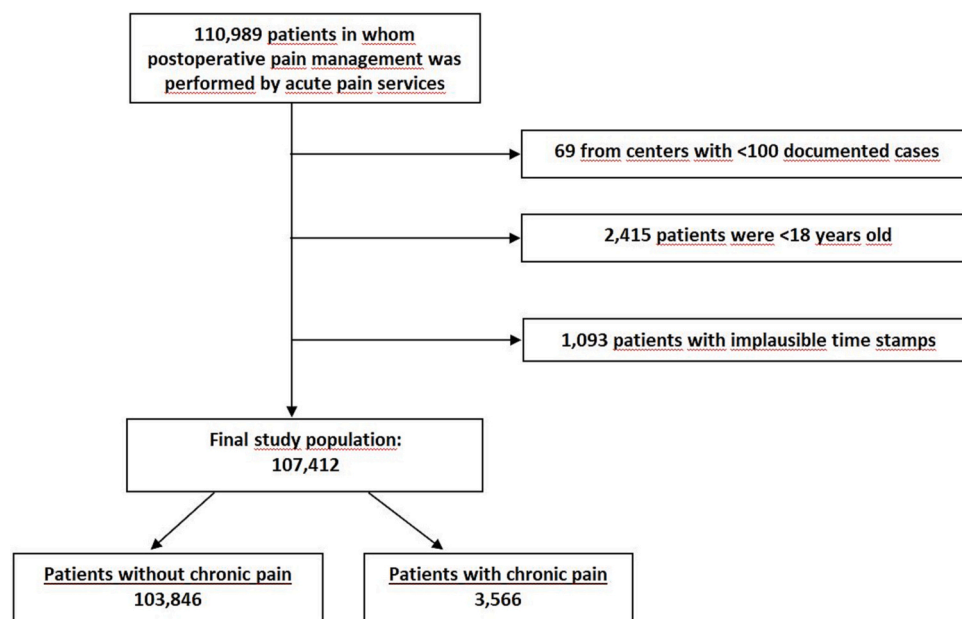


Fig. 1. Flowchart of data selection.

2.6. Statistical analysis

We compared patients with and without chronic preoperative pain. We had two primary outcomes. The first was the time to acceptable pain scores at rest. The second was the time to acceptable pain scores with movement.

Our analyses are largely concordant with the a priori statistical analysis plan that was part of our study protocol submitted to the registry prior to data release. Among the confounding factors that we planned to include, preoperative pain scores and height had too few entries to be used. Because preoperative pain scores in the net-ra registry, unlike postoperative pain scores, are nonspecific and capture any type of pain present at the time of the pre-anaesthesia evaluation, omission of this previously planned confounding factor was not considered critical. The same was true for BMI, which was comparable in each study group. Year of surgery, hospital center, sex, age, American Society of Anesthesiologists (ASA) physical status, preoperative use of opioids or non-opioid analgesics, cancer pain, diabetes, peripheral arterial disease, rheumatism, and alcohol and/or drug abuse were considered confounders as planned.

Kaplan-Meier cumulative incidence curves were constructed to examine the proportion of patients with a sustained adequate pain level NRS < 4 at rest and with movement in both groups during the postoperative course. Curves were compared using the Mantel-Cox log rank test, assuming a statistically significant difference for a P value < 0.05. Multivariable Cox proportional-hazards regression analyses (Wald test with a 5% type-1-error rate) were used to estimate the adjusted hazard ratios and related 95% confidence intervals for an adequate and sustainable postoperative pain relief (NRS < 4) at rest and with movement. The potential confounding factors listed in the previous paragraph were included in our models.

Testing for multicollinearity revealed that the variance inflation factors for independent variables were < 1.75, with exception of the ASA status. Statistical evaluation was performed using IBM SPSS Statistics 26 (IBM, USA). Two-sided P values < 0.05 were considered statistically significant.

In a post hoc sensitivity analysis, propensity scores were estimated via logistic regression using all potential confounders. Matched pairs were created using nearest neighbor 1–1 matching on the propensity score with caliper $0.01 \times \text{SD}(\text{PS})$ without replacement. Using the matched

data sets, the treatment effect for pain at rest and pain with movement was estimated by univariable Cox proportional-hazards regression analysis and doubly robust adjustment [25].

3. Results

Our dataset included 3566 analyzable patients who had a history of chronic preoperative pain and 103,846 who did not. Demographic and morphometric characteristics of both groups are shown in Table 1.

The median time to acceptable pain scores (NRS value sustainable < 4) at rest was 33 h in patients with chronic pain (95% CI 29.7–36.0) and 25 h in patients without (95% CI 24.9–25.1), a difference of about eight hours ($P < 0.001$, Fig. 2). The adjusted hazard ratio (HR) to achieve acceptable pain scores at rest was 1.42 (95% CI 1.36–1.49, $P < 0.001$, >99% power at a 0.05 significance level) for patients without chronic pain (Table 2, Fig. 2).

The median time to acceptable pain scores (NRS value sustainable < 4) with movement was about twice as long as the time for pain at rest in patients without chronic pain (52.2 h, 95% CI 51.5–52.9 versus 25 h, 95% CI 24.9–25.1). In chronic pain patients, time to acceptable pain scores with movement was tripled compared to pain at rest (95.8 h, 95% CI 89.9–101.7 versus 33 h, 95% CI 29.7–36.0). Patients with chronic pain thus took about 44 h longer to reach sustained relief from pain with movement than patients without chronic pain ($P < 0.001$, Fig. 3). After confounder adjustment, the hazard ratio for patients without chronic pain was 1.65 (95% CI 1.56–1.75, $P < 0.001$, >99% power at a 0.05 significance level, Table 2, Fig. 3).

Higher ASA physical status were associated with prolonged pain at rest and with movement (Table 2). Preoperative opioid use, cancer pain, and alcohol and/or drug abuse also prolonged postoperative pain. In contrast, diabetes and rheumatoid arthritis did not appear to contribute.

3.1. Sensitivity analysis

Propensity score matching resulted in 4338 cases for pain at rest and 3970 cases for pain with movement. The adjusted hazard ratio for a sustained and adequate pain relief at rest was 1.45 (95% CI 1.35–1.55, $P < 0.001$) in patients without chronic pain. The adjusted hazard ratio for pain with movement was 1.69 (95% CI 1.56–1.84, $P < 0.001$).

Table 1

Demographic and morphometric data of patients with and without chronic pain.

	Patients with chronic pain n = 3566	Patients without chronic pain n = 103,846
Demographic data		
Female sex	2074 (58%)	54,713 (53%)
Age (years)	61 (15)	58 (17)
BMI (kg·m) ⁻²	28 (7)	28 (6)
ASA physical status		
1	183 (6%)	11,748 (17%)
2	996 (35%)	34,059 (50%)
3	1568 (55%)	22,004 (32%)
≥4	122 (4%)	990 (1%)
Cancer pain	78 (2%)	137 (0.1%)
Diabetes	666 (19%)	12,412 (12%)
Occlusive peripheral arterial disease	190 (5%)	962 (1%)
Rheumatoid arthritis	77 (2%)	326 (0.3%)
Alcohol and/or drug abuse	101 (3%)	900 (1%)
Opioid use >1 month	1218 (34%)	406 (0.4%)
Non opioid use >1 month	421 (12%)	331 (0.3%)
Technical data		
Year of surgery	2014 (3)	2014 (3)
Continuous regional anaesthesia	3168 (89%)	95,734 (92%)
Single shot regional anaesthesia	61 (2%)	3199 (3%)
Patient controlled intravenous anaesthesia	204 (6%)	2390 (2%)
Combinations	133 (4%)	2523 (2%)
General surgery	821 (23%)	26,861 (26%)
Traumatology and Orthopaedics	1520 (43%)	36,585 (35%)
Gynaecology	141 (4%)	9514 (9%)
Urology	81 (2%)	7438 (7%)
Cardiac surgery	650 (0.6%)	12 (0.3%)
Other types of surgery	991 (28%)	22,798 (22%)

Summary statistics is presented as mean ± SD, N (%) as appropriate. BMI, body mass index; ASA, American Society of Anesthesiologists.

Table 2

Results of the multivariable Cox proportional-hazard regression analyses.

	Pain at rest sustainable NRS < 4	p-value	Pain with movement sustainable NRS < 4	p-value
Patients without chronic pain vs patients with chronic pain	1.42 (1.36–1.49)	<0.001	1.65 (1.56–1.75)	<0.001
Female sex	1.03 (1.02–1.05)	<0.001	1.07 (1.05–1.09)	<0.001
Age	0.999 (0.998–0.999)	<0.001	0.997 (0.996–0.997)	<0.001
ASA physical status		<0.001		<0.001
2	0.86 (0.84–0.88)	<0.001	0.84 (0.82–0.87)	<0.001
3	0.73 (0.71–0.75)	<0.001	0.70 (0.68–0.72)	<0.001
≥4	0.55 (0.51–0.59)	<0.001	0.54 (0.50–0.58)	<0.001
Cancer pain	0.74 (0.62–0.88)	<0.001	0.70 (0.55–0.88)	0.003
Diabetes	0.99 (0.96–1.01)	0.270	1.00 (0.98–1.03)	0.847
Occlusive peripheral arterial disease	0.92 (0.86–0.98)	0.010	0.96 (0.89–1.04)	0.337
Rheumatoid arthritis	0.99 (0.88–1.11)	0.806	1.08 (0.93–1.25)	0.318
Alcohol and/or drug abuse	0.88 (0.81–0.95)	<0.001	0.82 (0.75–0.90)	<0.001
Opioid use > 1 month	0.85 (0.79–0.91)	<0.001	0.80 (0.73–0.87)	<0.001
Non opioid use > 1 month	1.12 (1.03–1.23)	0.010	1.10 (0.98–1.25)	0.111
Year of surgery	1.04 (1.04–1.04)	<0.001	1.04 (1.04–1.05)	<0.001

Summary statistics is presented as Hazard ratios and 95% confidence intervals. Predefined confounders are written in italics. ASA, American Society of Anesthesiologists; NRS, 11-point numeric rating scale.

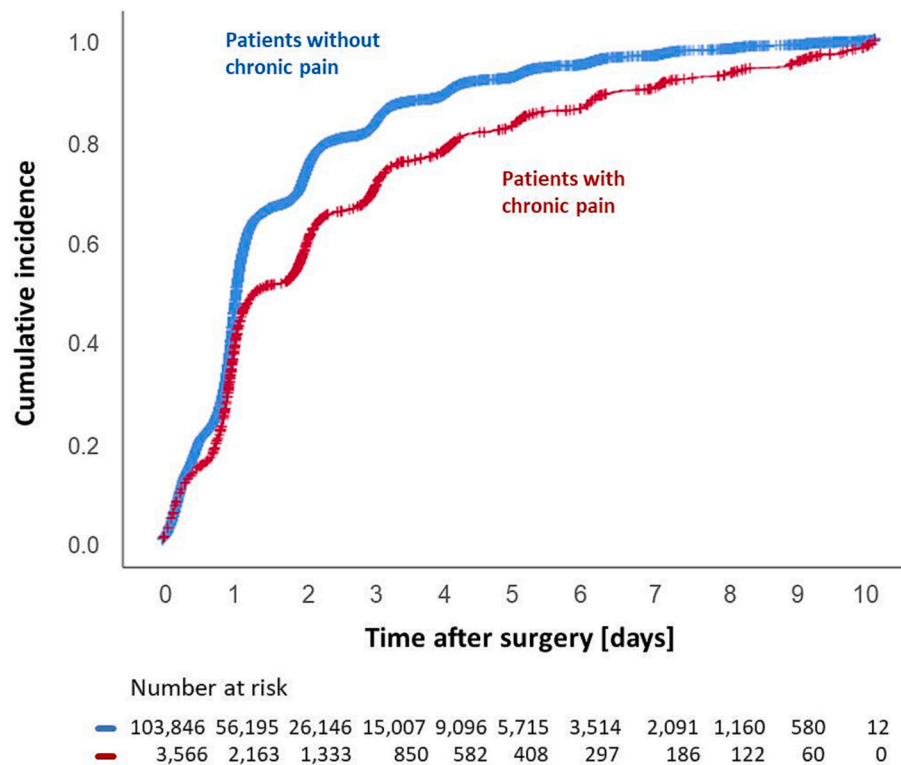


Fig. 2. Kaplan-Meier cumulative incidence curve for time to reach acceptable pain scores at rest (sustained NRS < 4). Vertical lines indicate censored patients. Hazard ratio is 1.42 (1.36–1.49) for patients without chronic pain ($P < 0.001$).

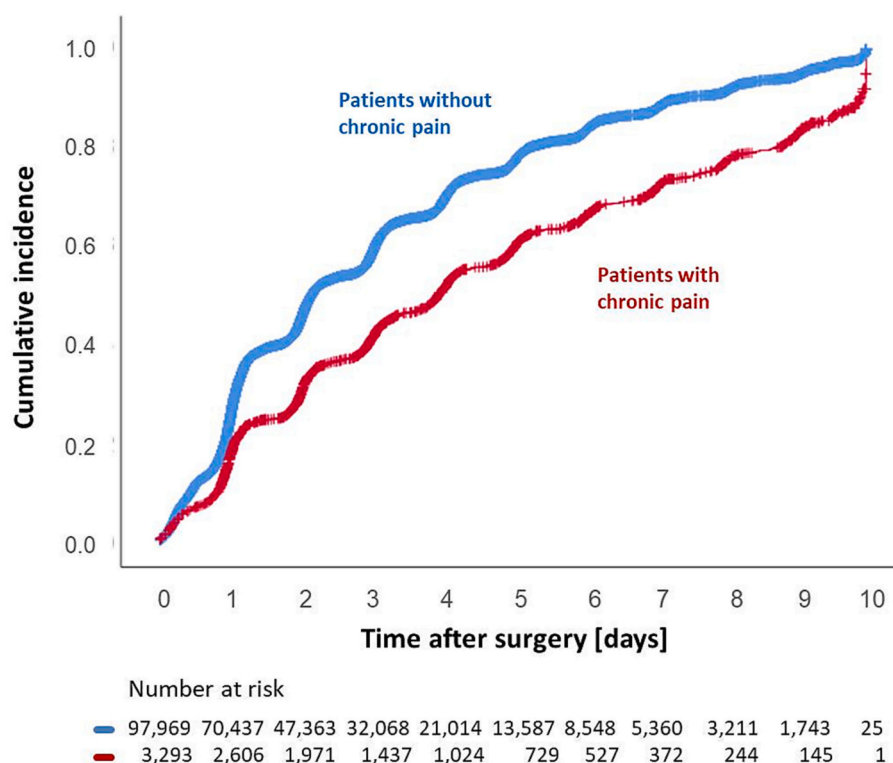


Fig. 3. Kaplan-Meier cumulative incidence curve for time to reach acceptable pain scores with movement (sustained NRS < 4). Vertical lines indicate censored patients. Hazard ratio is 1.65 (1.56–1.75) for patients without chronic pain ($P < 0.001$).

4. Discussion

Our analysis of a large registry with data provided by acute pain services shows that postsurgical pain at rest and with movement takes longer to resolve in patients with history of chronic pain than in those without chronic pain. While prolonged resolution is unsurprising, the magnitude of the effect (42–65% increase in the hazard) is novel, and indicates that the prolongation is of a clinically meaningful magnitude.

As recommended by national and international organizations, patients with major surgery or procedures expected to be painful are usually treated by acute pain services in Germany. These patients are offered continuous regional anaesthesia or patient-controlled intravenous analgesia with round-the-clock care provided by acute pain specialists. This labour-intensive care is reflected in the overall low pain scores of our cohort. For example, mean pain scores \pm SD for maximum pain with movement on the first day after surgery was 3.4 ± 2.2 points for patients without chronic pain and 4.0 ± 2.5 points for patients with chronic pain. Patients without acute pain management report more pain, even after minor surgical procedures [9]. Thus, it is reasonable to assume that the observed differences between patients with and without chronic pain would also be present without involvement of an acute pain service, but possibly over a higher range of pain intensities.

The 3.3% prevalence of chronic pain syndrome in our study cohort is consistent with the previously described prevalence for Germany [13]. As might be expected, concomitant conditions such as diabetes, peripheral arterial disease, rheumatism, and alcohol and/or drug abuse were significantly more common in patients with chronic pain than in patients without. 34% of patients with chronic pain were taking opioids before surgery, in comparison to 0.4% in patients without chronic pain ($P < 0.001$).

Preoperative opioid use is an identified risk factor for severe postoperative pain within the first 24 h [8,26]. Our analysis shows that this risk persists after the first postoperative day, and that the time required for adequate pain relief is prolonged in patients who chronically use

opioids. The proportion of patients taking any opioid medications increased from 0.4% preoperatively to 18% postoperatively in patients without a history of chronic pain. In contrast, opioid used preoperatively (34%) and postoperatively (31%) remained essentially unchanged in patients with a history of chronic preoperative pain. A possible explanation is that clinicians consciously or unconsciously capped opioid administration in patients who used pain medication chronically. Similar undertreatment has been described for patients with alcohol and/or drug abuse [27], who also had prolonged postoperative pain in our analysis.

Large registry studies show that chronic pain before surgery is a risk factor for severe pain within 24 h after surgery [8,9]. Many analyses of postoperative pain consider means or medians at specified times over predefined – and usually short – periods [10,11]. We extend previous work by mapping pain intensity over time in terms of a dichotomous and clinically meaningful outcome, namely sustained adequate analgesia. The importance of this approach is illustrated by the fact that only about 40% of all patients had sustained adequate analgesia at rest within 24 h of surgery, and only about 20% did with movement.

The importance of considering pain over time is also illustrated by the fact that pain scores at rest and with movement were similar over the initial day of surgery in patients with and without chronic pain, but then diverged. Had we only considered the initial 24 postoperative hours, as in many previous studies [8,9,26,28,29], we would have missed clinically meaningful differences between the populations that appeared subsequently. Additionally, our use of time to reach sustained acceptable pain levels considers individual pain trajectories.

Because chronic pain patients suffer longer from surgical pain, they might be at particular risk for pain-related complications including myocardial infarction [3], limited mobilization and consequently the risks of immobilization [30], and surgical complications [4]. An additional potential consequence of severe preoperative pain is neuroplastic changes in the central nervous system which might promote pain chronification [5,31]. This sensitisation might be enhanced by opioid

treatment [32].

Our analysis identified additional risk factors for prolonged postoperative pain. The higher the ASA physical status, the longer the patients suffered from relevant rest and exertion pain in the surgical area. A possible explanation may be that the risk of undertreatment increases with the number of comorbidities. Furthermore, our results for cancer pain are consistent with a previous report of pain after breast cancer surgery [33] where patients reporting preoperative breast pain were at greater risk of experiencing severe postoperative pain.

There are thus many reasons to direct special attention to all patients who have inadequate postoperative analgesia. Patients with chronic pain sustain more postoperative pain than those without, and the pain takes longer to resolve. Clinicians providing postoperative pain management should therefore also consider the special needs of chronic pain patients.

4.1. Limitations

The net-ra registry gathers anonymized primary data from various hospitals. The associated risk of under-reporting and inaccuracy is therefore hard to estimate but may be substantial. However, it seems unlikely that the amount of underreporting and inaccuracy differs as a function of chronic pain status. Preoperative pain scores, although presumably important, could not be included in the multivariate model. The registry only captures patients after major surgery treated by an acute pain service which is not available to all patients. Our results therefore do not directly apply to patients having minor surgery. Furthermore, most patients had continuous regional anaesthesia techniques which may limit generalizability. However, it is unlikely that the described difference in pain control would not be present with standard oral therapy alone. There are always unmeasured confounders which also might have influenced our results. Similarly, postoperative pain scores were recorded for clinical purposes and were thus less consistent than they would have been in a trial.

Disclosures

Daniel Sessler's department conducts research funded by Pacira. Thomas Volk received honoraria for lectures from CSL Behring and Pajunk. Thomas Volk is the current president of the European Society of Regional Anaesthesia and Pain Therapy (ESRA). Christine Kubulus, Silja Mahlstedt and Gudrun Wagenpfeil declare no competing interests. Support for the study was provided solely from institutional/hospital/departmental sources. The Network for Safety in Regional Anaesthesia and Acute Pain Therapy is supported by the Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e.V. and Berufsverband Deutscher Anästhesisten e.V.

CRediT authorship contribution statement

Christine Kubulus: Conceptualization, Methodology, Data curation, Formal analysis, Validation, Visualization, Writing – original draft. **Silja Mahlstedt:** Conceptualization, Methodology, Data curation, Formal analysis, Validation, Visualization. **Gudrun Wagenpfeil:** Methodology, Formal analysis. **Daniel I. Sessler:** Formal analysis, Writing – review & editing. **Thomas Volk:** Conceptualization, Methodology, Writing – review & editing, Supervision, Resources.

Declaration of Competing Interest

None.

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Appendix

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