CLUSTERS OF ACUTE POSTSURGICAL PAIN PATIENTS:
ARE THERE HIGH-RISK PATIENTS AND HOW TO IDENTIFY THEM?
A STUDY IN THE INTERNATIONAL PAIN OUT REGISTRY

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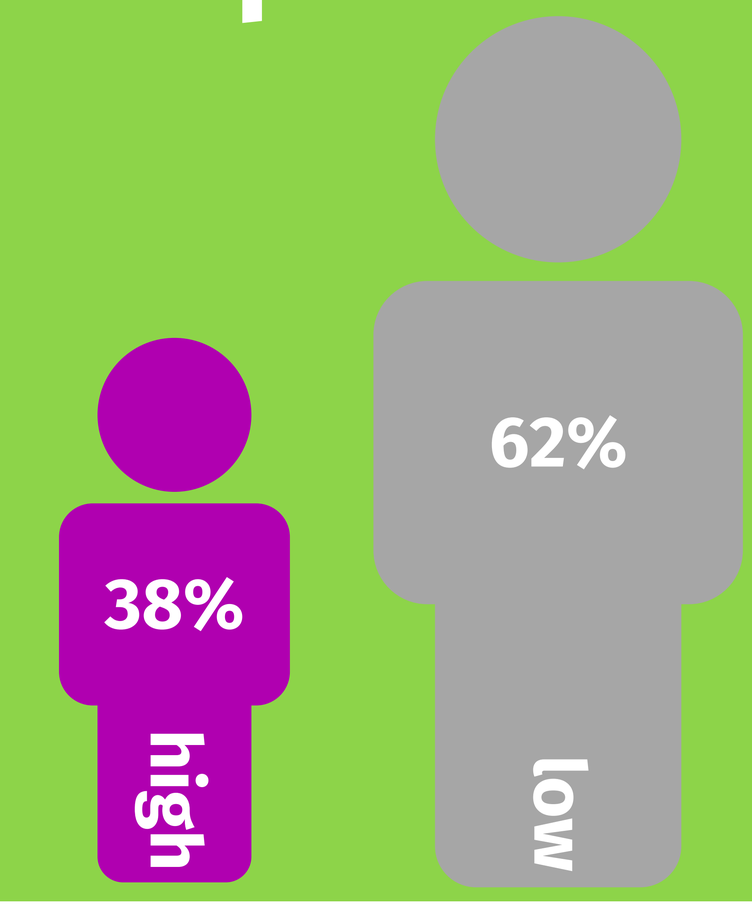
In 10,000 patients from Europe, Mexico and China we found a cluster of patients with a high burden of pain on the first postoperative day.



Compared to the second cluster these patients show worse results in multiple pain-related outcomes and have a higher risk for chronic postsurgical pain.

They can be characterized and identified with a multidimensional pain composite score.

Background and aims

Postoperative pain is still common and undertreated at a global level[1]. Despite a large spectrum of multimodal treatment strategies[2], international efforts for quality improvements[3] and specific guidelines, e.g. for elective caesarean section[4], acute pain after surgery still seems to be poorly controlled. A wide range of studies within the last 20 years demonstrated high numbers of patients reporting moderate to severe levels of pain. This holds for large registry studies in Germany[5 6], other European countries[7 8], the US[9] and review data in nearly 20,000 patients[10]. Most studies demonstrate huge variability in patient reported outcomes (PROs) and treatment related variables (e.g. opioid administration on the normal ward) on the patient and the institutional level. There is also increasing evidence that specific patient sub-groups exist in the early phase after surgery, which were mainly identified by cluster analysis [11-14]. To the best of our knowledge, all previous studies in the acute postoperative setting focused on pain intensity ratings when obtaining patient clusters.The primary aim of this study was to identify and characterize relevant patient clusters on the first postoperative day (POD1) taking into account PROs from multiple domains, i.e. pain intensity, interference with pain, emotional impairment and side effects. The secondary aim was to obtain a continuous multidimensional pain-related outcome, which is suitable to distinguish between patient clusters, is of prognostic relevance for chronic postsurgical pain (CPSP) and can serve as continuous multidimensional outcome in future studies.

Methods and Results

Workflow

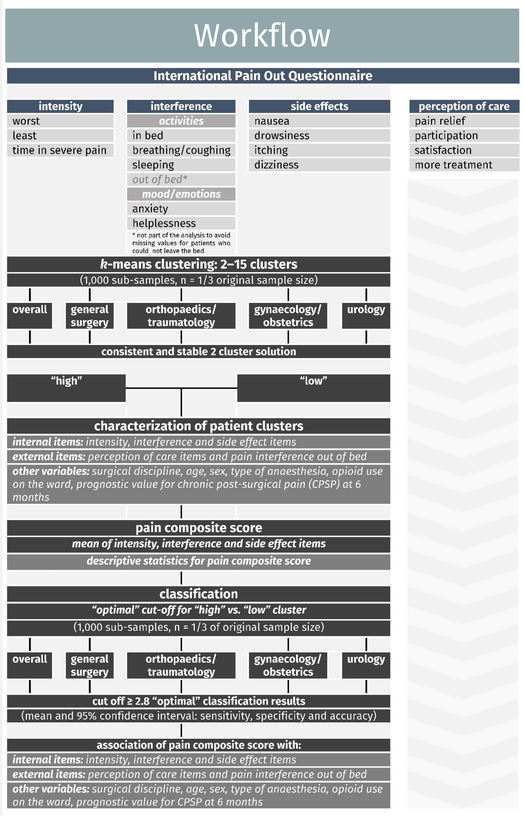


Figure 1. Summary of the workflow. In total 9,765 patients from 105 wards in 64 hospitals from 10 countries were included in the analysis (2016-2019). Most patients underwent general surgery (n = 4,221, 43.2%), followed by orthopaedic/trauma surgery (n = 3,778, 38.7%), gynaecologic/obstetric surgery (n = 1,222, 12.5%) and urologic surgery (n = 544, 5.6%).

Cluster characterization

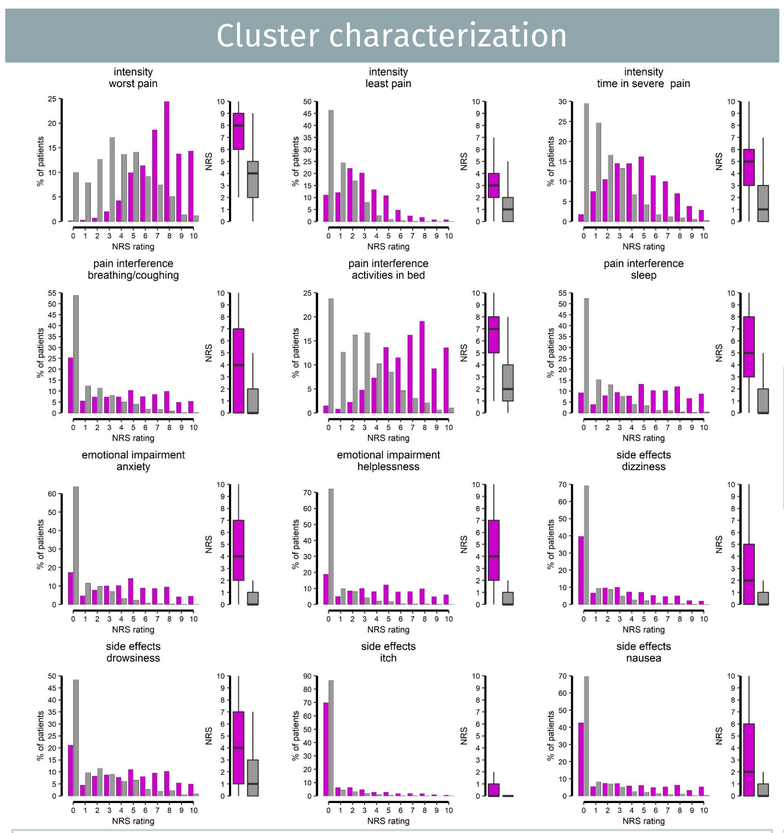


Figure 2. Distribution of patient reported outcome ratings used for *k*-means clustering. A highly stable 2 cluster solution was identified within various sub-samples across and within the surgical disciplines. Results are shown separately for patients within the high (38%, C_{high}: magenta) *vs.* low (62%, C_{low}: grey) pain intensity/interference/side effects cluster. Group differences in all PROs were clinically and statistically significant. E.g. the median ratings for worst pain intensity for C_{high} and C_{low} were 8 and 4, respectively. Patients in C_{high} spent in median 50% of the time in severe pain compared to 10% of the patients in C_{low}. Interference with pain, emotional impairment and side effects were also higher in C_{high}.

Validation

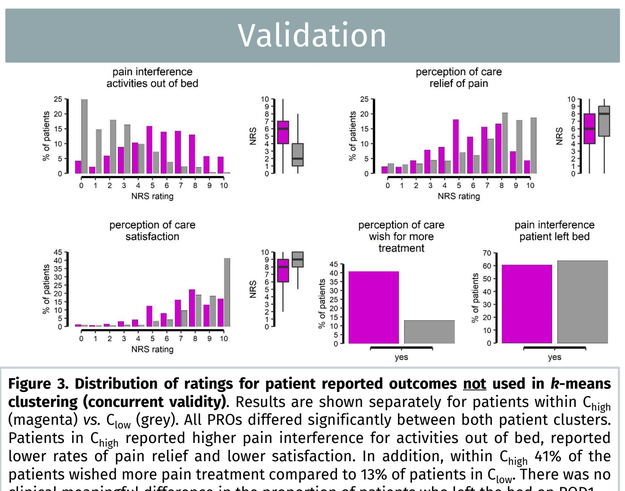


Figure 3. Distribution of ratings for patient reported outcomes <u>not</u> used in *k*-means clustering (concurrent validity). Results are shown separately for patients within C_{high} (magenta) *vs.* C_{low} (grey). All PROs differed significantly between both patient clusters. Patients in C_{high} reported higher pain interference for activities out of bed, reported lower rates of pain relief and lower satisfaction. In addition, within C_{high} 41% of the patients wished more pain treatment compared to 13% of patients in C_{low}. There was no clinical meaningful difference in the proportion of patients who left the bed on POD1.

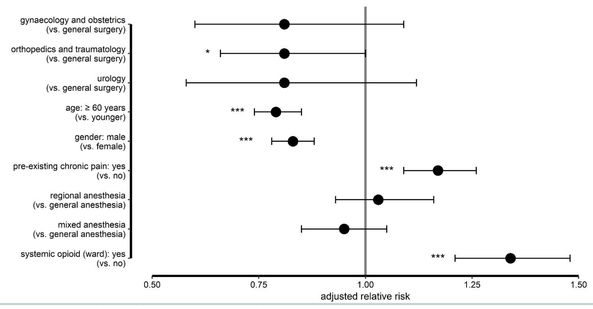


Figure 4. Results of the multivariable regression model (n = 9,494 patients with complete data) with cluster membership as dependent variable. Variables commonly associated with PROs on POD1 were chosen as independent variables (**concurrent validity**). Adjusted relative risks (points) and corresponding 95% confidence intervals (capped lines) are shown (***: p values <0.001). Women, younger patients, patients with pre-existing pain and patients with opioid administration on the normal ward were more frequently represented in C_{high}.

Pain Composite Score

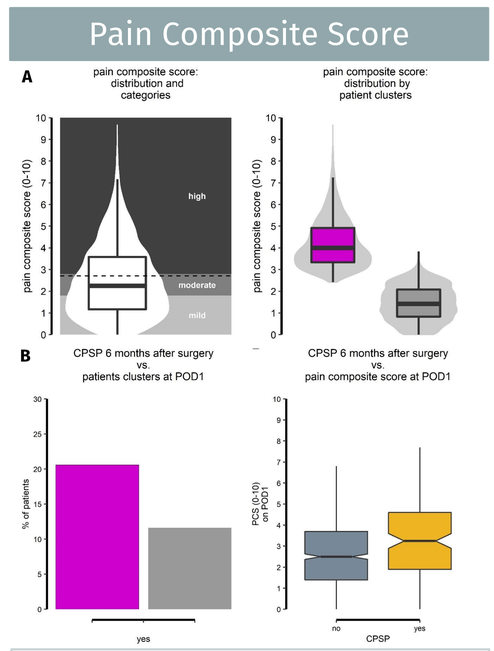


Figure 3. Distribution of the pain composite score (PCS). The PCS as the mean of all items shown in **Figure 2** revealed good to excellent Cronbach's α coefficients (0.84 to 0.87) for the total sample and within the surgical disciplines. **(A)** PCS values between 0–1.8 might be considered as none/mild, values, ≥ 1.9 as moderate and values ≥ 2.9 as severe (ABC-analysis). The dashed line indicates the cut off (≥ 2.8) found in analysis for optimal classification of patient cluster membership. This cut off resulted in high sensitivity (0.98) and specificity (0.95).
(B) In the re-analysis of the **EUCPSP-study**[15] (n = 932) we also found a 2 cluster solution at POD1 (C_{High}: 47% and C_{Low}: 53%). Within C_{high} 21% (n = 91) of the patients *vs.* 11.6% (n = 57) in the C_{low} reported at least moderate CPSP 6 months after surgery (RR= 1.81, X^2-test p < 0.001). In addition, we found significant differences between PCS at POD1 in patients with 3.3 (Q_{1-3}: 1.9–4.6) *vs.* without 2.5 (Q_{1-3}: 1.4–3.7) CPSP 6 months after surgery (Mann-Whitney-U test p = 0.001). Multivariable models showed similar results.

Conclusion

Using a data driven approach, we found two highly stable patient clusters regarding multidimensional pain-related PROs on POD1 in two large multinational samples. The first cluster (38% C_{high}) was characterized by worse outcomes for pain intensity, pain interference, emotional impairment and side effects as well as perception of care (e.g. satisfaction with pain treatment) compared to patients from the second cluster C_{low}. Notably, patients in C_{high} (*vs.* C_{low}) at POD 1 had a higher risk for of chronic postsurgical pain 6 months after surgery (RR= 1.81, p<0.001). Based on the items used for cluster analysis, a multidimensional Pain Composite Score was obtained. It is suitable to distinguish between patient clusters, is of prognostic relevance for chronic postsurgical pain (CPSP) and can serve as continuous multidimensional outcome in future studies.

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