BJA

British Journal of Anaesthesia, 119 (4): 821–9 (2017)

doi: 10.1093/bja/aex236
Clinical Practice

Prediction of persistent post-surgery pain by preoperative cold pain sensitivity: biomarker development with machine-learning-derived analysis

J. Lötsch[1,2,*], A. Ultsch[3] and E. Kalso[4]

[1]Institute of Clinical Pharmacology, Goethe-University, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany, [2]Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Project Group Translational Medicine and Pharmacology TMP, Theodor-Stern-Kai 7, 60596 Frankfurt am Main, Germany, [3]DataBionics Research Group, University of Marburg, Hans-Meerwein-Straße 6, 35032 Marburg, Germany and [4]Department of Perioperative Medicine, Intensive Care and Pain Medicine, Pain Clinic, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

*Corresponding author. E-mail: j.loetsch@em.uni-frankfurt.de

Abstract

Background. To prevent persistent post-surgery pain, early identification of patients at high risk is a clinical need. Supervised machine-learning techniques were used to test how accurately the patients' performance in a preoperatively performed tonic cold pain test could predict persistent post-surgery pain.

Methods. We analysed 763 patients from a cohort of 900 women who were treated for breast cancer, of whom 61 patients had developed signs of persistent pain during three yr of follow-up. Preoperatively, all patients underwent a cold pain test (immersion of the hand into a water bath at 2–4 °C). The patients rated the pain intensity using a numerical ratings scale (NRS) from 0 to 10. Supervised machine-learning techniques were used to construct a classifier that could predict patients at risk of persistent pain.

Results. Whether or not a patient rated the pain intensity at NRS=10 within less than 45 s during the cold water immersion test provided a negative predictive value of 94.4% to assign a patient to the "persistent pain" group. If NRS=10 was never reached during the cold test, the predictive value for not developing persistent pain was almost 97%. However, a low negative predictive value of 10% implied a high false positive rate.

Conclusions. Results provide a robust exclusion of persistent pain in women with an accuracy of 94.4%. Moreover, results provide further support for the hypothesis that the endogenous pain inhibitory system may play an important role in the process of pain becoming persistent.

Key words: Post surgery pain; cold induced pain; supervised machine-learning; human experimental pain

Persistent pain is a major health care issue, as defined by WHO, affecting about a fifth of the European population, increasing to a third in the over-70-yr olds.[1 2] Chronic pain has a highly complex pathophysiology[3] and is triggered by several different

Editorial decision: May 16, 2017; **Accepted:** June 27, 2017

Editor's key points

- Persistent pain after breast surgery is a major clinical challenge, with limited preventative strategies.
- Identification of individuals at greater risk of persistent pain, before surgery, is important.
- Preoperative testing of conditioned pain modulation (CPM) was combined with three yr pain follow-up.
- Using machine learning, CPM had high negative predictive value for low persistent pain risk.

causes, such as cancer[4] and surgery.[5] The prevalence of persistent pain as an outcome of surgery varies from 10 to 50%.[6 7] This variation is partly as a result of how persistent pain is defined. For persistent pain in breast cancer survivors, the prevalence has been reported to vary between 25–60%, and 34% of the affected patients had symptoms and signs of neuropathic pain.[8] A more recent prospective study, however, reported a prevalence of at least moderate pain after breast cancer surgery of 13.5%.[9] Thus, persistent pain remains a clinical issue in breast cancer survivors and in order to prevent persistent post-surgery pain, early identification of patients at high risk is needed.

Several factors including the type of surgery[10] and psychological factors have been associated with persistent pain after breast cancer surgery.[11–15] A particular line of evidence suggests that heightened baseline pain sensitivity and dysfunction of the endogenous pain-inhibitory system may render individuals at greater risk of experiencing severe acute clinical pain.[16] Hence, assessment of individual responses to experimental pain stimuli, has been proposed as a possible method of identifying patients at high risk of developing persistent pain.[16] In support of this hypothesis, preoperative testing of conditioned pain modulation in 62 patients undergoing thoracotomy identified patients who were or were not likely to develop persistent post-thoracotomy pain.[17] In another small study of 20 patients undergoing abdominal surgery, stronger preoperatively measured conditioned inhibitory pain modulation was associated with less late postoperative pain.[18] Evidence of dysfunctional pain inhibition in fibromyalgia[19] points in the same direction. In this context, tonic cold pain is often chosen as the experimental pain stimulus.[20]

In the present study, we tested how accurately the patients' performance in a preoperatively-performed tonic cold pain test predicted persistent post-surgery pain in a cohort of 900 women, who were followed for three yr after breast cancer surgery.[21 22] We applied contemporary data science methods to derive parameters from the preoperative cold pain sensitivity tests. Using techniques of supervised machine learning,[23 24] parameters obtained from preoperative cold pain sensitivity tests were associated with development of persisting pain during three yr follow-up after breast cancer surgery. This allowed patients developing or not developing persistent pain to be identified with high clinical confidence. The goal of this study was to assess whether parameters derived from a preoperative cold pain test could predict the development of persistent postoperative pain.

Methods

Patients

The study followed the Declaration of Helsinki and was approved by the Coordinating Ethics Committee of the Helsinki University Hospital. Each participating subject provided written informed consent. We enrolled women who had unilateral non-metastasized breast cancer treated at the Helsinki University Hospital between 2006 and 2010, with either breast-conserving surgery or mastectomy with axillary surgery (sentinel biopsy and/or axillary clearance). Exclusion criteria were neoadjuvant therapy (i.e. administration of therapeutic agents such as chemotherapy to shrink the tumour before the main surgical treatment),[25] and immediate breast reconstruction surgery. Of the 1536 consecutive eligible patients, 1149 patients were invited to participate, of whom 126 patients declined and 23 were withdrawn. Of the 1000 remaining patients, a further 100 were excluded from the current analysis because the cold pain test device was not available during their assessment (Fig. 1). The whole study cohort and the protocol have previously been described in detail.[9 22]

Assessments of pain

Preoperative experimental tonic pain test

The study was explained to the patients before enrolment. After written informed consent was obtained, the patients filled in questionnaires and participated in the experimental pain tests for contact heat and cold pain. In the current analysis, we focus only on the cold pain test.

In the tonic cold pain test, the patients immersed the hand contralateral to surgery into a cold water bath with a controlled temperature of 2–4 °C (JULABO USA Inc., Allentown, PA), for the maximum time tolerated by the patient but not longer than 90 s. Time to withdrawal was noted and the intensity of the evoked pain was measured using a Numerical Rating Scale (NRS) of 0-10 at withdrawal and every 15 s during the test.

Postoperative pain scores

The main target parameter of this analysis was the development of pain after breast cancer surgery. Therefore, post-surgical pain was assessed using NRS ranging from 0 to 10 (0=no pain, 1–3=mild pain, 4–6=moderate pain, 7–10=severe pain).[26] Post-surgical pain intensity was recorded at months 1, 6, 12, 24 and 36 after surgery using questionnaires sent to the patients and asking identical assessments of presence and intensity of pain in the areas of previous breast cancer surgery (breast, axilla). In addition, incidents such as surgeries and accidents that could have provided an independent cause for the continuation of pain were inquired about. The pain ratings acquired at six months or later after surgery were the basis for the classification of a patient into the "persistent pain" or the "non-persistent pain" group, described in the data analysis section. Six months was considered to more adequately reflect the present clinical setting[21] than the original definition of persistent post-surgical pain proposing a lower bound of two months,[27] which seems premature for the diagnosis of chronic pain after breast cancer surgery as adjuvant therapies continue longer.

Data analysis

Data were analysed using the R software package (version 3.3.2 for Linux; http://CRAN.R-project.org/)[28] on an Intel Xeon® computer running on Ubuntu Linux 16.04.1. Two missing values in the remaining data set were imputed using a k nearest neighbour algorithm with k=3,[29] applying the weighted average method and Euclidean distance implemented in the "DMwR" R library (https://cran.r-project.org/ package=DMwR).[30] This

provided a data set consisting of a 6 x 900 matrix comprising six pain NRS values of pain intensity from 900 women every 15 s after immersion of the patient's arm into cold water.

Parameters derived from the preoperative cold pain sensitivity test were explored for their predictive performance with respect to persistent pain after the surgery. This task was approached using supervised machine learning[23 24] and feature selection techniques.[31] Supervised machine learning tries to infer a functional connection between the input data and a desired output value (case labels). In the present work, the input data consist of the parameters acquired during the cold pain tolerance test, while the case labels are given by the presence or absence of persistent pain after the surgery. Thus, in supervised machine-learning, the goal is to learn a mapping from inputs x to output y, given a labelled set of input-output pairs $D = \left\{(x_i, y_i)\right\}_{i=1}^{N}$. Here, D denotes the so-called "data space[1]" with a predefined division into an input space X comprising x_i, the features possibly predicting the diagnosis of persistent *vs* non-persistent pain, and the output space Y comprising y_i, the possible diagnoses of persistent/non-persistent pain. Creation of the "data space" required defining the "output", y_i, from the postoperative pain ratings at 12-36 months and creating the "input" or "feature" space, x_i, from parameters derived from the preoperative cold pain test, which will be described as follows.

Firstly, the "output space", y_i, was obtained by classifying the patients into those who developed or did not develop persistent pain, the "persistent pain" and the "non-persistent pain" groups. Specifically, patients with NRS ≤ 3 at month 36 after surgery ($NRS_{month36} \leq 3$) were identified as in principle belonging to the "non-persistent pain" group, while those with NRS>3 at month 36 after surgery ($NRS_{month36} > 3$) belonged in principle to the "persistent pain" group. Further criteria for the "non-persistent pain" group were the presence of no more than mild pain, (i.e. $NRS_{month12..month36} \leq 3$) while the "persistent pain" group was more precisely characterized by always having at least moderate pain without a consistent tendency to ameliorate, (i.e. $NRS_{month36} > 3$ *and* $NRS_{month12..month36} > 0$ *and* $(NRS_{month36} - NRS_{month24}) \geq 0$. In the machine-learning context,[23] this represented a binary classification task. As 137 patients did not meet these criteria, they were excluded and the sample size was reduced to n=763. To account for a response rate <100%, [i.e. for incomplete returns of questionnaires (recovery rate of 86, 82, 81, 81 and 78% in month 1, 6, 12, 24 and 36, respectively)], the classification (group assignment) was firstly performed on the original non-imputed NRS pain rating data. The classifications of the remaining patients were obtained by applying the following rules: If all available ratings were $NRS_{month12..month36} \geq 5$ then the case was subsumed to the group "persistent pain". In contrast, if the available ratings were $NRS_{month6..month36} \leq 3$ and $(NRS_{month24} < NRS_{month6})$, i.e. a decrease over time, then the case was subsumed to the group "non-persistent pain".

Secondly, the "input space", x_i, was created by deriving candidate parameters from the cold pain ratings acquired during the preoperative test. After exploration of the data (Fig. 2), the following five key features of interest were derived. They comprised (i) the time to reach the individual maximum NRS among the six measurements at intervals of 15 s, (ii) the time to reach NRS=10, (iii) the sum of the individual NRS scores, (iv) the maximum NRS rating provided during the test, and (v) whether pain intensity of NRS=10 had been reached or not. "Feature" selection was performed based on differences in these parameters between the pain persistence groups (output space) (persistent or non-persistent pain) which were analyzed using Wilcoxon signed rank tests[32] or χ^2 statistics using an α level set at 0.05.

Thirdly, a functional connection between the input data and a desired output value (case labels) was inferred. The "input space" created as described above, consisted of a 5 x 763 matrix comprising the five parameters, listed as i – v in the paragraph above, derived from the cold pain ratings acquired during the preoperative cold pain test. These five parameters formed the feature vector $X \in N^5$ that was mapped to the "output space" comprising the discrete classes $\in$ Y, (i.e. y_1="persistent pain" and y_2="non-persistent pain"). All possible classifier values were iteratively assessed with respect to test performance measures. The main criteria were $\prod sensitivity, specificity$ and the balanced accuracy of assigning a patient to the correct group. Specifically, test sensitivity and specificity were calculated as *sensitivity [%]=100 · true positives/(true positives + false negatives)* and *specificity [%]=100 · true negatives/(true negatives + false positives)*.[33] The balanced test accuracy proposed to overcome problems in accuracy calculations in imbalanced datasets[34] was calculated as *0.5 · (true positive/all positive + true negative/all negative)* equal to $0.5 \cdot \sum sensitivity, specificity$. For the best rules, classification performance parameters were derived as described above with the addition of the negative and positive predictive values calculated as *NPV [%]=100 · true negative/(true negative + false negative)* and *PPV [%]=100 · true positive/(true positive + false positive)*, respectively.[35]

Results

Cold pain data were available from 900 women (Fig. 2) of whom n=763 were included in the analyses based on the criteria of fulfilling either that of persistent pain during the three yr postoperative follow up (n=61) or that of non-persistent pain (n=702).

Visual inspection of the raw NRS data (acquired at an interval of 15 s at six time points after immersion of subjects' hands in cold water) suggested inter-individual differences in the maximum pain intensity and the velocity at which it was reached (Fig. 2). The five cold sensitivity parameters, (i) time to reach the individual maximum NRS rating, (ii) the time to reach NRS=10, (iii) the sum of the individual NRS scores, (iv) the maximum NRS rating provided during the test and (v) whether or not NRS=10 was reached during the test differed significantly between the groups of persisting *vs* non-persisting pain (Wilcoxon tests: P=0.039, P=0.009, P=0.029 and P=0.009, respectively (Fig. 3), χ^2 test for NRS=10: P=0.015). Specifically, the times to reach the maximum NRS or NRS=10 were significantly shorter in the persistent than in the non-persistent pain group, and the sum total of maximum NRS ratings, was higher in the persistent pain group. More patients belonging to the "persistent pain" group rated their maximum pain as NRS=10.

For the parameters derived from the preoperative cold pain test, rules were identified (Table 1) for each parameter to provide its best classification performance, to correctly identify patients who will experience persistent pain, which was

[1]**Data space** is the space in which the n-dimensional feature vectors can be observed. A particular dimension's data space may be bound to certain ranges. For example, $[0...100]^n$ may be a data space of percentages. Sometimes data space is used synonymously with feature space.

Feature vector x x is an n-dimensional vector of numerical features (parameters) that represent one data object (case). The complete set of features in a data set forms the so-called "**feature space**".

The **output space** Y consists of possible classes, in a medical context diagnoses y_i, presently defined as persistent or non-persistent postoperative pain

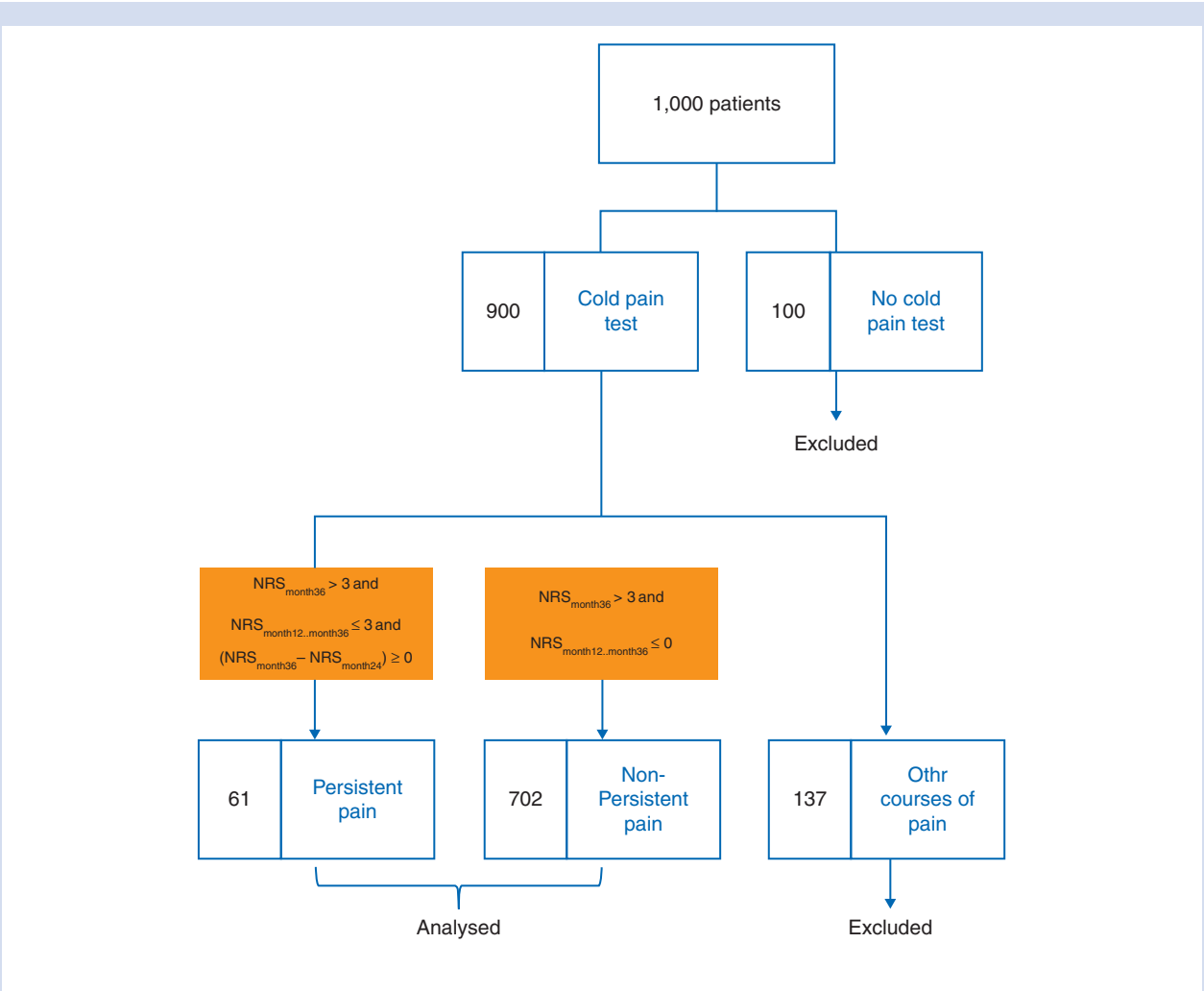

Fig 1 Flow chart showing the classification of the patients based on the three-yr development of pain after breast cancer surgery. A total of 853 women fell into the two main pain persistence groups (output space) of persistent or non-persistent pain, according to the criteria displayed in the grey-shaded frames. This was the main cohort analysed. The remaining 143 women in whom the assignment criteria applied only partly were excluded from the machine-learning classifier development but were used as an exploratory SHORTENED "test" data set. NRS, Numerical rating Scale. Incomplete return rates, (i.e. fraction of pain questionnaires not returned), were dealt with by imputation, as described in Methods.

assessed by calculating test sensitivity and specificity (Fig. 4). As the parameter "maximum NRS" performed best at a value of NRS=10 (see number iv in the above paragraph), the rule derived from it coincided with that of the parameter (v), (i.e. "whether or not NRS=10 was reached"). Judged by the product of sensitivity and specificity as used for classifier building, the parameter $T_{NRS=10}<45$ s (see number ii in the above paragraph) performed best in correctly identifying a patient belonging to the "persistent pain" group (Table 1). In addition, if NRS=10 was never reached during the cold test, the negative predictive value was almost 97%, (i.e. that pain would not be persistent). However, the positive predictive value for persistent pain was low among all parameters tested (Table 1).

Discussion

In a large clinical data set of 763 women treated for breast cancer, an association between the intensity of preoperative experimental cold pain and the risk of developing persistent pain after surgery was established, in agreement with previous small studies.[17 18] The ability of a patient to tolerate experimentally-induced tonic cold pain, predicted how much pain they experienced after surgery at three yr. Thus, women who were less sensitive and better tolerated the pain induced by immersion of their hand in cold water, were also less likely to develop persistent pain after breast cancer surgery than those women in whom the pain quickly rose to the maximum intensity. The diagnosis of persistent pain was conservatively established from a prospective three-year follow-up. The selection of the observation period between six months and three yr after breast cancer surgery and the strict criteria for the diagnosis of persistent pain, resulted in a lower incidence of chronic pain of 8% as compared with the previously reported incidence of at least moderate pain at one yr from the same cohort[9] of 25–60% in a recent publication.[8]

The results of our study indicate that the response to tonic noxious stimulation such as cold may be used as a biomarker of

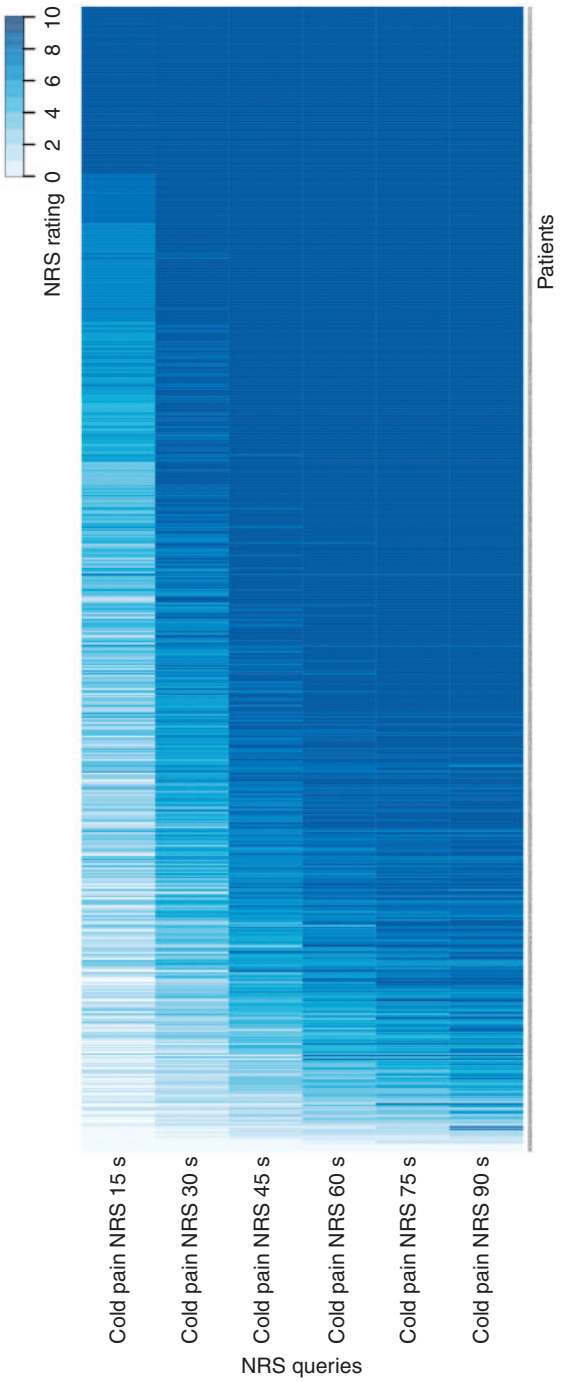

Fig 2 Matrix heat plot of the Numerical Rating Scale (NRS 0-10) pain ratings asked six times from 900 patients at intervals of 15 s after immersion of the hand in cold water (2–4 °C). The NRS rating is given as colour code (from light blue=NRS 0 to dark blue=NRS 10). The plot provides an overview of the pattern of the NRS ratings (rows, *n*=900 patients; columns, ratings given at different time points), arranged by sorting the NRS ratings ("vectors") in descending order of rating intensity to place more similar individual "vectors" close to each other. The figure has been created using the R software package (version 3.3.2 for Linux; http://CRAN. R-project.org/28); specifically, using the "heatmap.2" function of the R library "gplots" (https://cran.r-project.org /package=gplots).

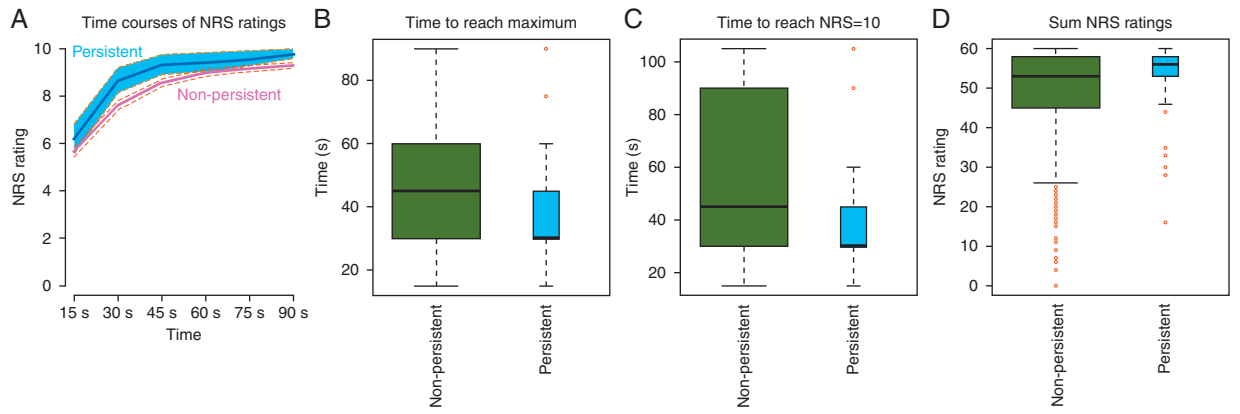

Fig 3 NRS ratings of perceived pain intensity during immersion of the hand in cold water (2–4 °C). (A) Time courses of the NRS ratings, means (solid lines) and 95% confidence intervals (shaded regions), for the pain persistence groups (output space). (B-D) Differences in parameters derived from the NRS ratings, [i.e. (B) time to reach maximum NRS, (C) time to reach NRS=10 and (D) sum of NRS ratings]. The widths of the boxes are proportional to the respective numbers of subjects per group. The minimum, quartiles, median (solid horizontal line within the box), and maximum are used to construct a "box and whisker plot". The figure was created using the R software package (version 3.3.2 for Linux; http://CRAN. R-project.org/28). NRS, Numerical Rating Scale 0-10.

Table 1 Comparative test performance measures for the correct prediction of persisting pain provided by the five candidate parameters ("classifiers") derived from NRS ratings. The classifier rules (first row) have to be applied as "*if the condition is true then an individual belongs to the persistent pain group (output space); else to the non-persistent pain group*". PPV, Positive Predictive Value; NPV, Negative Predictive Value; NRS, Numerical Rating Scale (0–10)

Test performance measure	Time to reach maximum NRS	Time to reach NRS=10	NRS sum	Maximum NRS	NRS=10 reached
Classifier rule for "persistent pain"	$T_{max}<45$ s	$T_{NRS=10}<45$ s	$Sum_{NRS}\geq 50$	$Max_{NRS}=10$	$Max_{NRS}=10$
Sensitivity [%]	60.7	59	77	90.2	
Specificity [%]	58.1	60.5	38.3	24.4	
PPV [%]	11.2	11.5	9.8	9.4	
NPV [%]	94.4	94.4	95.1	96.6	
Balanced accuracy [%]	59.4	59.8	57.7	57.3	

an individual's capacity to tolerate continuous painful input and that this parameter could be a predictor of a low *vs* high risk for the development of persistent pain. This is in line with an earlier report suggesting a predictive value for the response to experimentally-induced cold in a clinical cohort of young men undergoing thoracic surgery for correction of chest malformation.[14] According to the updated definition from the NIH-FDA Joint Biomarker Team[36] (see also http://www.fda.gov/ downloads/NewsEvents/ MeetingsConferences Workshops/ UCM519805.pdf; accessed July 25, 2017), "biomarker" or "biological marker" generally refers to a measurable indicator of some biological state or condition, a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention.[36] This definition is satisfied by sensitivity to tonic experimental cold pain as an indicator of a risk of developing persistent pain after major surgery. Moreover, the mapping of features x_i to output classes (pain groups) y_i as presented in $D = \left\{(x_i, y_i)_{i=1}^{N}\right.$ expresses the biomarker definition in machine-learning or data science terms. Among five options tested (Table 1), using $T_{NRS=10}<45$ s provided the best overall test performance. All of the tested biomarkers showed strength in the negative predictive value of approximately 95% for non-persistence of pain. The classifier or predictor may not be feasible in everyday clinical practice, but could be used in clinical trials aiming at preventing the development of persistent pain. However, the proposed biomarker, and any possible alternatives (Table 1), showed weakness in its positive predictive value of only approximately 10% for persistence of pain. This will be associated with a high number of false positives and therefore, when relying only on a patient's ability to oppress cold pain, multidisciplinary preventative interventions would be applied to a proportion of cases unnecessarily. Indeed, in the present data set, using $T_{NRS=10}<45$ s predicted persistent pain for $n=313$ women, of whom 277 (88%) were false positives. This emphasizes the proposal to use the present test to exclude the development of persistent pain, while the search for a completely satisfactory biomarker of chronic pain will continue.

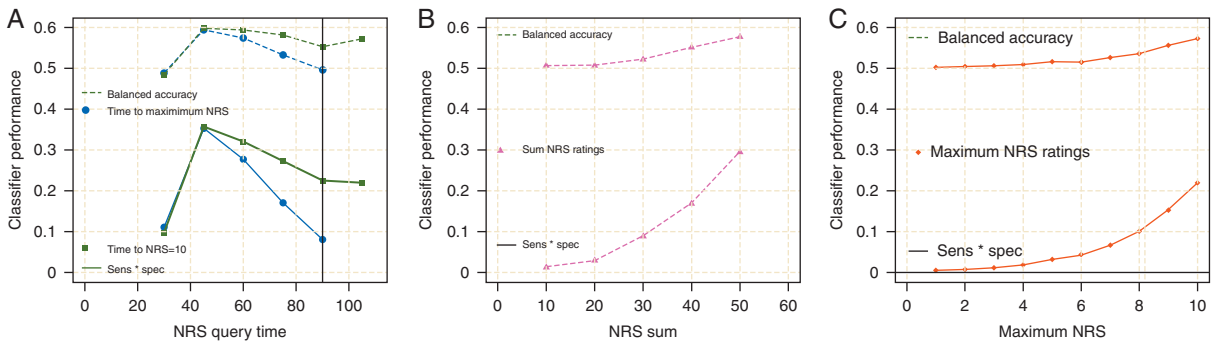

Fig 4 Performance of the classifiers derived from experimentally-induced cold pain for the prediction of persistent pain after breast cancer surgery. The solid lines show the product of sensitivity and specificity (Sens * Spec) for different cut-offs for (i) the time to reach maximum NRS and (ii) the time to reach NRS=10 (A) and (iii) the sum NRS (B), or (iv) the maximum NRS rating during the test (C). The dashed lines show the corresponding balanced accuracies of the obtained classification. The perpendicular black line on the left panel indicates the cut-off of 90 s; when NRS=10 was never reached, the time was arbitrarily set at 90 s. The analysis was done iteratively with increasing x-values and it assessed the performance of the classifier defined as, for example, "*if time to reach NRS_10≥actual test time, an individual belongs to the non-persisting pain group (output space) else to the persisting pain group*". The test performances resulting in each iteration are plotted. The figure was created using the R software package (version 3.3.2 for Linux; http://CRAN.R-project.org/28). NRS, Numerical Rating Scale (0-10).

The search for biomarkers or predictions of persistent pain is an active research topic. A PubMed query on April 12, 2017 for "(predict* or biomarker) AND (chronic or persistent) AND pain AND (breast cancer surgery) NOT review[Publication Type]" produced 44 hits, of which 22 reported clinical trials that assessed predictive factors of persistent pain after breast cancer surgery. A variety of candidate predictors was assessed, including patient characteristic and psychological parameters, characteristics of the cancer, pain present before surgery, and rarely also genetic factors such as variants in cytokine related genes *IL10* or *IL1R2*.[37] A recent meta-analysis including 30 studies with a total of 19,813 participants concluded that development of persistent pain after breast cancer surgery was associated with younger age, radiotherapy, axillary lymph node dissection, greater acute postoperative pain and preoperative pain.[38] However, most studies restricted the analysis to establishing statistical significance of the association between predictive factors and persistent pain without aiming at devolving a diagnostic tool or biomarker. Of note, a preoperative experimental pain test was not among previously analysed potential predictors of persistent pain after breast cancer surgery.

In addition to the possible utility as a test to identify patients in whom the development of persistent pain is unlikely, present results point at an association between the ability to tolerate experimentally-induced tonic cold and a lower risk for persistent pain. This also raises interesting questions regarding the physiology of the cold pressor test and its association with the modulation of responses to noxious input. Descriptions of many chronic pain syndromes note that the disorder (e.g. fibromyalgia, headache, complex regional pain syndrome) is associated with hypersensitivity to pain and with reduced endogenous inhibition of pain, implying that an individual's processing of pain-related information changes with the onset of the syndrome.[16] Similarly, a subject's reduced endogenous inhibition of pain has been proposed to increase the patient's risk of chronic pain.[17 18] The individual differences in the pain modulation system preventing or facilitating pain persistence, however, raise the question of whether inhibitory pathways of pain can be "trained" or modulated by psychological interventions[39] or drugs, before a predictable exposure to a recognized cause of chronic pain such as a surgical intervention.[5] Interestingly, duloxetine, a dual-action antidepressant, normalizes endogenous pain control as measured by conditioned pain modulation, leading to improved analgesia in painful neuropathy.[40]

Studies have shown that more severe acute postoperative pain is associated with chronic post-surgery pain suggesting that the strong intensity of pain facilitates its future persistence.[41] For example, early postoperative pain after lateral thoracotomy significantly predicted long-term pain,[42] similarly found with postoperative pain after cosmetic surgery of the thorax.[41] Again, the intensity of postoperative pain after total hip arthroplasty was associated with pain outcomes for up to six weeks after surgery.[43] Further evidence indicates that patients reporting high levels of pain four days after various types of elective surgery were at risk of increased pain six months after the operation.[44] In addition, the development of chronic pain was predicted by the intensity of early postoperative pain after open groin hernia repair.[45] Moreover, preexistent pain resulted as a risk factor in an analysis of present pain after hernia surgery.[46] As a possible explanation of the association of postoperative pain intensity with long-term pain, it has been suggested that the experience of strong perioperative pain facilitates its future chronification.[41] Considering the present results, another possible explanation is that strong perioperative pain reflects the functional state of a patient's endogenous pain inhibition, with low function associating with a higher risk of pain persistence. However, both processes could participate in pain becoming persistent.

Conclusions

Using a data-driven approach in an analyzed cohort of 763 women operated on for breast cancer, a relationship between responses to tonic noxious cold applied preoperatively and the postoperative development of persistent pain has been shown. The use of machine learning, which is an artificial intelligence

based method suitable to discover patterns in data and to perform classification tasks, such as the assignment to the persistent or non-persistent pain groups, was preferred to classical statistical methods where knowledge, or at least presumptions, about the distributions and/or functional dependencies of the data are necessary. Applying machine-learning techniques, **firstly**, a possible classifier was developed that can be used as a clinical biomarker predicting exclusion of persistent pain in a patient with an accuracy of 94.4% (negative predictive value). This provides a clinically sound basis for releasing a patient early from multidisciplinary therapy approaches[47] as the false negative rate of the test was low. However, it does not provide a similarly robust criterion to select women for enhanced therapies given the high false positive rate of the test. **Secondly**, the association established between the ability to oppress pain to tonic noxious cold and the development of persistent pain after a surgery may hint at a pathophysiological relationship. That is, the results provide support for the concept of chronic pain as an expression of the individual tone of the nocifensive system, rather than a reaction to uncontrolled pain experiences during the surgical intervention: this may be further therapeutically addressed.

Authors' contributions

Study design/planning: E.K.
Study conduct: E.K.
Data analysis: J.L., A.U.
Writing paper: J.L., E.K., A.U.
Revising paper: all authors

Acknowledgements

The authors thank Les Hearn for proofreading the manuscript.

Declaration of interest

None declared.

Funding

The work has been supported by the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 602919 (GLORIA, EK, JL), the Landesoffensive zur Entwicklung wissenschaftlich-ökonomischer Exzellenz (LOEWE, JL), Zentrum: Translational Medicine and Pharmacology, the Academy of Finland (EK), and the Helsinki University Hospital Governmental Research funds (TYH2008225, TYH2010210, EK). The funders had no role in method design, data selection and analysis, decision to publish, or preparation of the manuscript.

References

1. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain* 2006; **10**: 287–333
2. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. *Lancet* 1999; **354**: 1248–52
3. Julius D, Basbaum AI. Molecular mechanisms of nociception. *Nature* 2001; **413**: 203–10
4. Portenoy RK. Cancer pain: pathophysiology and syndromes. *Lancet* 1992; **339**: 1026–31
5. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006; **367**: 1618–25
6. Martinez V, Baudic S, Fletcher D. Chronic postsurgical pain. *Ann Fr Anesth Reanim* 2013; **32**: 422–35
7. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. *Anesthesiology* 2000; **93**: 1123–33
8. Schou BI, Smeby NA, Ottesen S, Warncke T, Schlichting E. Chronic pain in breast cancer survivors: comparison of psychosocial, surgical, and medical characteristics between survivors with and without pain. *J Pain Symptom Manage* 2014; **48**: 852–62
9. Meretoja TJ, Leidenius MH, Tasmuth T, Sipila R, Kalso E. Pain at 12 months after surgery for breast cancer. *JAMA* 2014; **311**: 90–2
10. Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. *Expert Rev Neurother* 2009; **9**: 723–44
11. George SZ, Hirsh AT. Psychologic influence on experimental pain sensitivity and clinical pain intensity for patients with shoulder pain. *J Pain* 2009; **10**: 293–9
12. Hirsh AT, George SZ, Bialosky JE, Robinson ME. Fear of pain, pain catastrophizing, and acute pain perception: relative prediction and timing of assessment. *J Pain* 2008; **9**: 806–12
13. Keogh E, Book K, Thomas J, Giddins G, Eccleston C. Predicting pain and disability in patients with hand fractures: comparing pain anxiety, anxiety sensitivity and pain catastrophizing. *Eur J Pain* 2010; **14**: 446–51
14. Lautenbacher S, Huber C, Schofer D, *et al*. Attentional and emotional mechanisms related to pain as predictors of chronic postoperative pain: a comparison with other psychological and physiological predictors. *Pain* 2010; **151**: 722–31
15. Theunissen M, Peters ML, Bruce J, Gramke HF, Marcus MA. Preoperative anxiety and catastrophizing: a systematic review and meta-analysis of the association with chronic postsurgical pain. *Clin J Pain* 2012; **28**: 819–41
16. Edwards RR. Individual differences in endogenous pain modulation as a risk factor for chronic pain. *Neurology* 2005; **65**: 437–43
17. Yarnitsky D, Crispel Y, Eisenberg E, *et al*. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. *Pain* 2008; **138**: 22–8
18. Wilder-Smith OH, Schreyer T, Scheffer GJ, Arendt-Nielsen L. Patients with chronic pain after abdominal surgery show less preoperative endogenous pain inhibition and more postoperative hyperalgesia: a pilot study. *J Pain Palliat Care Pharmacother* 2010; **24**: 119–28
19. Jensen KB, Kosek E, Petzke F, *et al*. Evidence of dysfunctional pain inhibition in Fibromyalgia reflected in rACC during provoked pain. *Pain* 2009; **144**: 95–100
20. Pud D, Granovsky Y, Yarnitsky D. The methodology of experimentally induced diffuse noxious inhibitory control (DNIC)-like effect in humans. *Pain* 2009; **144**: 16–9
21. Sipilä R, Estlander A-M, Tasmuth T, Kataja M, Kalso E. Development of a screening instrument for risk factors of persistent pain after breast cancer surgery. *Br J Cancer* 2012; **107**: 1459–66
22. Kaunisto MA, Jokela R, Tallgren M, *et al*. Pain in 1,000 women treated for breast cancer: a prospective study of pain sensitivity and postoperative pain. *Anesthesiology* 2013; **119**: 1410–21

23. Murphy KP. *Machine Learning: A Probabilistic Perspective*. Cambridge MA, USA: The MIT Press, 2012
24. Bastanlar Y, Ozuysal M. Introduction to machine learning. *Methods Mol Biol* 2014; **1107**: 105–28
25. Trimble EL, Ungerleider RS, Abrams JA, *et al*. Neoadjuvant therapy in cancer treatment. *Cancer* 1993; **72**: 3515–24
26. Dworkin RH, Turk DC, Farrar JT, *et al*. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005; **113**: 9–19
27. Macrae WA. Chronic pain after surgery. *Br J Anaesth* 2001; **87**: 88–98
28. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria, 2008
29. Altman NS. An introduction to kernel and nearest-neighbor nonparametric regression. *Am Stat* 1992; **46**: 175–85
30. Torgo L. *Data Mining with R: Learning with Case Studies*. Boca Raton, FL, USA: Chapman & Hall/CRC, 2010
31. Guyon I, Elisseeff A. An introduction to variable and feature selection. *J Mach Learn Res* 2003; **3**: 1157–82
32. Wilcoxon F. Individual comparisons by ranking methods. *Biometrics* 1945; **1**: 80–3
33. Altman DG, Bland JM. Diagnostic tests. 1: Sensitivity and specificity. *Br Med J* 1994; **308**: 1552
34. Brodersen KH, Ong CS, Stephan KE, Buhmann JM. The balanced accuracy and its posterior distribution. *2010 20th International Conference on Pattern Recognition (ICPR)*, Istanbul, Turkey, p. 3121–4
35. Altman DG, Bland JM. Diagnostic tests 2: predictive values. *Br Med J* 1994; **309**: 102
36. Group F-NBW. BEST (Biomarkers, EndpointS, and other Tools). 2016. Available from https://www.ncbi.nlm.nih .gov/books/NBK326791/ (accessed 25 July 2017)
37. Stephens K, Cooper BA, West C, *et al*. Associations between cytokine gene variations and severe persistent breast pain in women following breast cancer surgery. *J Pain* 2014; **15**: 169–80
38. Wang L, Guyatt GH, Kennedy SA, *et al*. Predictors of persistent pain after breast cancer surgery: a systematic review and meta-analysis of observational studies. *Cmaj* 2016; **188**: E352–e61
39. Scheel J, Parthum A, Dimova V, *et al*. [Psychological prophylaxis training for coping with postoperative pain. Long-term effects]. *Schmerz* 2014; **28**: 513–9
40. Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. *Pain* 2012; **153**: 1193–8
41. Dimova V, Horn C, Parthum A, *et al*. Does severe acute pain provoke lasting changes in attentional and emotional mechanisms of pain-related processing? A longitudinal study. *Pain* 2013; **154**: 2737–44
42. Katz J, Jackson M, Kavanagh BP, Sandler AN. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. *ClinJPain* 1996; **12**: 50–5
43. Page MG, Katz J, Curtis K, Lutzky-Cohen N, Escobar EM, Clarke HA. Acute pain trajectories and the persistence of post-surgical pain: a longitudinal study after total hip arthroplasty. *J Anesth* 2016; **30**: 568–77
44. Peters ML, Sommer M, de Rijke JM, *et al*. Somatic and psychologic predictors of long-term unfavorable outcome after surgical intervention. *Ann Surg* 2007; **245**: 487–94
45. Callesen T, Bech K, Kehlet H. Prospective study of chronic pain after groin hernia repair. *Br J Surg* 1999; **86**: 1528–31
46. Cox TC, Huntington CR, Blair LJ, *et al*. Predictive modeling for chronic pain after ventral hernia repair. *Am J Surg* 2016; **212**: 501–10
47. Chou R, Gordon DB, de Leon-Casasola OA, *et al*. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain* 2016; **17**: 131–57

Handling editor: Lesley Colvin