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Predicting Post-operative Pain in Lung Cancer Patients using Pre-operative Peak Alpha Frequency

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Editor. Thoracotomy incisions used to gain access to the thoracic organs in the chest, lead to chronic pain in an estimated 25-60% of cases[1] . Considerable nerve damage is common in thoracotomy, as rib re-tractors used in this operation block conduction of intercostal nerves near to the incision by 50-100%[2]. Video assisted thoracoscopic surgery (VATS), an alternative to conventional thoracotomy, involves less nerve damage due to smaller incisions and no rib re-traction; hence, VATS is associated with increased tolerability for patients and better patient outcomes[3]. However, even with VATS, many patients still suffer from moderate to severe post-operative pain[3] .

A patient's sensitivity to acute post-operative pain is amongst the most significant risk factors for the development of chronic post-surgical pain[4, 5]. However, the extent of neuropathic pain experienced after surgery is highly variable between individuals, even when the underlying nerve injury is assessed as identical[6].

There are currently no reliable methods available to accurately predict sensitivity to acute post-operative pain or the likelihood of it developing into chronic pain[7], thus hindering development of early intervention and prevention strategies. One candidate biomarker for predicting pain sensitivity is peak alpha frequency (PAF). PAF is the frequency with the greatest power in the 8-14 Hz bandwidth, measured using electroencephalography (EEG); PAF is a stable heritable trait within individuals[8] .

PAF in healthy participants, prior to the induction of a prolonged (but temporary) painful experience, is negatively related to their pain ratings[9, 10]. In 2018, Furman and colleagues found a relationship between PAF and experimental pain sensitivity[9]. In 2020, Furman and colleagues replicated and extended this finding, showing that PAF was reliable and could predict pain sensitivity to multiple pain models even months later[10]. These findings suggest that an individual's PAF could serve as a reliable biomarker for their pain ratings, and therefore be a powerful clinical tool.

In this pilot study, we directly investigated, for the first time, if PAF can be used as a clinical tool to stratify pain-sensitive patients. Specifically, we investigated whether pre-operative PAF, measured using cEEGrids (TMSi, Oldenzaal, Netherlands, https://ceegrid.com), correlated with post-operative pain severity in 16 patients (6 female, mean age = 67.5 [4.35] years, range: 59-73 years) undergoing surgery for lung cancer. Written consent, PAF, and baseline pain were collected up to 4 weeks prior to surgery (mean = 8.6 [6.4] days) during standard pre-operative assessments. Within 72 hours after surgery, patients were asked to report their present, average, and worst pain in the last 24 hours (see Supplementary Material A for detailed methods).

The use of EEG in a clinical setting was not novel. However, conventional full-cap EEG has several disadvantages: setup is time-consuming and patients are required to wash their hair, inconveniencing patients and clinical staff. To circumvent these issues we used cEEGrids, newly developed around the ear electrodes. Assessment of PAF using cEEGrids was fast, comfortable for patients, and technically feasible (Supplementary Material B).

We found that pre-operative PAF was negatively correlated with present (n=16), average and worst (n=14) post-operative pain (all ps<0.02; see Supplementary Material C). Post-operative complications prevented assessment of average and worst post-operative pain for two patients. Post-operative pain was not associated with pre-operative pain (Supplementary Material D), operation type (13 VATS, 3 thoracotomy), analgesic type (10 paravertebral catheter, 5 patient controlled analgesia [PCA], 1 epidural), age, or sex (Supplementary Material E).

For classification, we used the receiver operative characteristic (ROC) curve to assess the sensitivity and specificity of pre-operative PAF in identifying patients reporting severe 'worst' post-operative pain (Figure 1A). The area under the curve (AUC) was 0.939 (SE = 0.077, $p<0.001$, 95% CI: 0.80-1.07). Remarkably, PAF of less than 9 Hz offered a sensitivity (i.e. ability to correctly identify a patient reporting severe pain) of 1.0 and a specificity (i.e. ability to correctly identify a patient not reporting severe pain) of 0.86.

When classifying individuals reporting severe 'average' post-operative pain (Figure 1B), the AUC was 0.923 (SE = 0.074, $p<0.001$, 95% CI: 0.778-1.07). PAF of less than 9 Hz offered a sensitivity of 1.0 and a specificity of 0.5. When classifying patients experiencing severe 'present' pain, sensitivity was 0.65 and specificity was 0.54.

Strikingly, we found that a median split of worst post-operative pain ratings revealed significant differences in PAF across patients (Figure 1C). A Mann-Whitney U test showed that pre-operative PAF was significantly faster ($W = 74$, $p=0.004$) for those with lower worst post-operative pain (median = 9.25 Hz, range: 8.65-9.41 Hz) compared to those with higher worst post-operative pain (median = 8.62 Hz, range: 7.81-8.82 Hz).

These results suggest that PAF could be a useful clinical tool for identifying patients likely to experience severe acute pain after thoracic surgery. Follow up data was also collected for some participants at 6 weeks as well as ~15 months post-operatively (see Supplementary Material F).

While our work still remains to be replicated in a larger population of patients, if PAF is indeed found to be a sensitive and specific biomarker of pain sensitivity, it would allow surgeons and anaesthetists to pre-operatively identify patients at risk of severe acute post-operative pain. This identification would enable provision of targeted interventions with pre-emptive analgesic strategies for chronic post-operative pain (e.g. small incision, regional analgesic blockade, or neuropathic pain medications).

This study also has implications for treatment of pain-sensitive individuals undergoing other types of surgeries (e.g. cardiac) or interventions (e.g. chemotherapy). Establishing biomarkers to predict development of acute and chronic post-operative pain could move the focus away from pain treatment and towards pain prevention; pre-operative PAF is a prime candidate that warrants further investigation.

Acknowledgments

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Figure

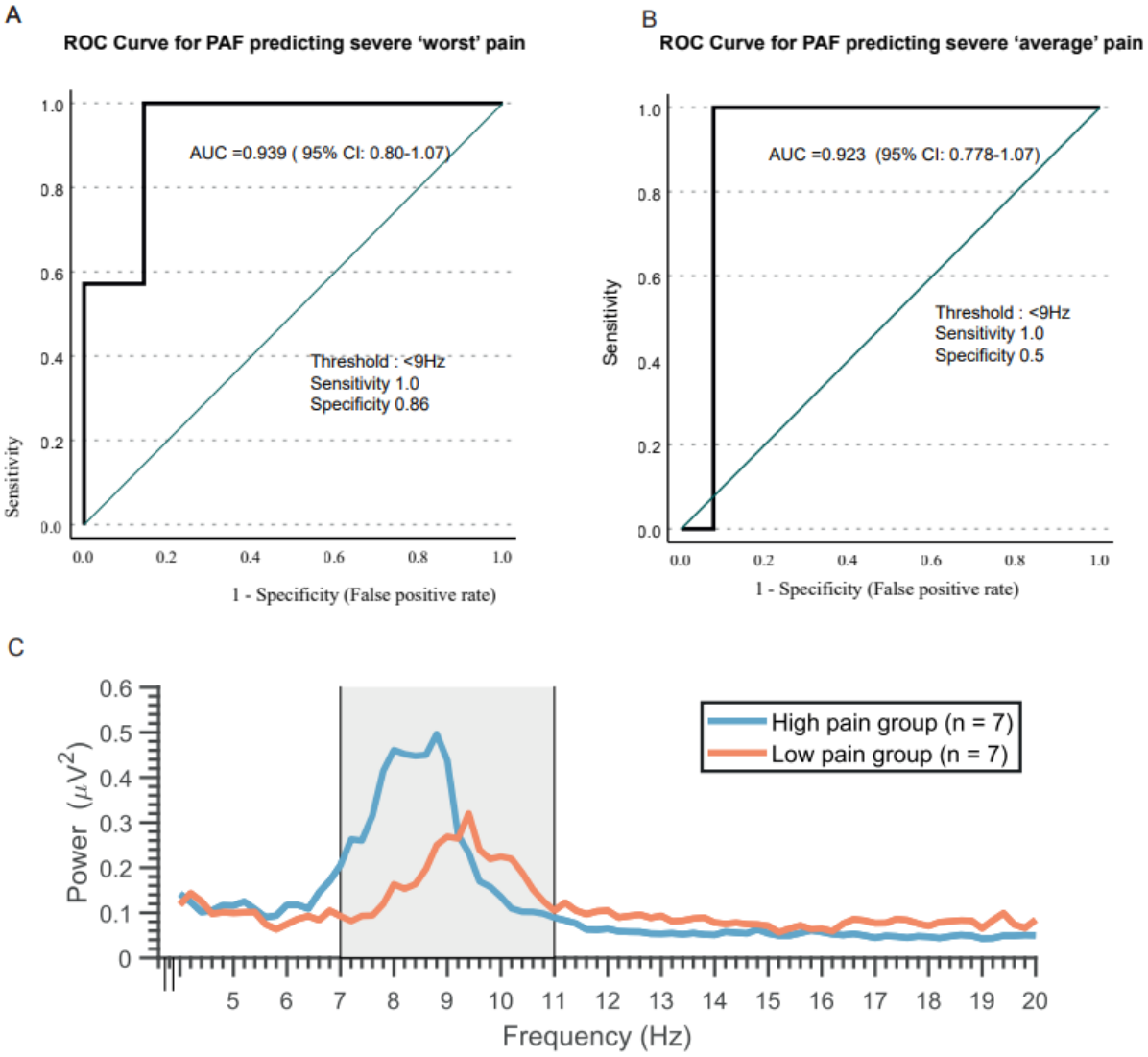

Figure 1. The receiver operating characteristic curve of pre-operative peak alpha frequency (PAF) in (A) classifying severe (>7/10) post-operative pain, and (B) classifying individuals reporting severe "average pain experienced in the last 24 hours" (C) The frequency spectrum of patients (n=14) median split according to their worst post-operative pain, demonstrating that the high pain group had slower PAF.

Supplementary Material A

Detailed methods

Patients

Data were collected as part of a larger prospective research project examining the effects of a rehabilitation programme on postoperative complications in patients undergoing surgery for lung cancer (ROC). The ROC project was approved by the NHS ethics committee on 27th July 2010 (Reference: 10/H1208/41). The addition of the EEG sub-study discussed in the present report was approved on 18th February 2019. Eligibility criteria from the ROC study were used. Patients needed to be: 1) undergoing curative lung resections for lung cancer; 2) equal to or older than 18 years; and 3) able to give written informed consent. Exclusion criteria consisted of: 1) patients not consented to the ROC study; and 2) patients with closed head injury, epilepsy, or previous neurosurgery. Those with current chronic pain conditions (e.g., arthritis, back pain, or cancer pain) were still asked to participate. Such conditions were noted and taken into consideration during analysis.

Twenty patients were recruited from March to June 2019 at the preoperative clinic in Birmingham Heartlands Hospital approximately one week before surgery. The purpose and procedure of both ROC and its EEG sub-study was explained and any questions were answered before informed consent was obtained. We excluded one participant from the analysis since they did not report any degree of pain post-operatively, which would be extremely unlikely. Pre-operative EEG recordings could not be obtained for two patients due to technical issues, and an additional patient was later withdrawn from the ROC study. Therefore, the investigated data set comprised 16 patients (5 females, mean age = 67.5 +/-[4.35], age range = 59-73). All patients in the EEG sub-study were in the non-intervention ROC group, so did not receive pre- or post-operative rehabilitation classes.

Pre-operative EEG data and pain reports were collected within 1-4 weeks prior to the operation, while the post-operative pain-reports were collected within 72 hours after the operation.

Pain assessment.

The pain experienced by the patients was assessed pre- and post-operatively by asking the patients to rate their 1) present pain, as well as 2) the worst pain they had experienced in the last 24 hours, and 3) the average pain experienced in the last 24 hours on a numeric rating scale (NRS: 0 = "no pain", 10 = "worst pain imaginable"). In line with previous investigations, we categorized pain ratings of 4 as the lower limit of 'moderate' pain and ratings of 7 or more as 'severe' pain [1-4].

EEG

The patients' EEG was recorded using two cEEGrids (TMSi, Oldenzaal, Netherlands, http: //ceegrid.com) positioned around the patients' ears. For the cEEGrid setup, the hair around the ear was pinned back with hair grips and the skin was cleaned with alcohol wipes and abrasive gel. Electrolyte gel (sonogel®) was then applied to the cEEGrid electrodes before being placed

around the ear. Exact cEEGrid positioning varied slightly between patients, as placement angle was adjusted to fit individual ear anatomy [5]. EEG signal was continuously recorded with a 0.3-150 Hz band-pass filter and a digital sampling rate of 500 Hz. The EEG signal was amplified and digitized using an eegoTM sports DC amplifier linked to eegoTM software (ANTneuro, Hengelo, the Netherlands). In line with our previous work [6], the electrode directly over the left mastoid (L6) served as the reference electrode, while the electrode over the right mastoid (R5) served as the ground. The data was re-referenced offline to a linked-mastoid reference.

Procedure

Patient recruitment and data collection took place at the Heartlands Hospital, part of University Hospitals Birmingham NHS Foundation Trust (https://www.uhb.nhs.uk/). Following routine pre-operative assessments that occur 1-4 weeks prior to a scheduled operation, eligible patients were briefed on the purpose and procedure of the ROC study as well as the EEG sub-study. Research nurses and the author (S.K.M.) answered any questions the patients had. Patients signed written consent forms and gave pain ratings before the cEEGrids were set up (see EEG section above). The patients were then asked to close their eyes and relax for five minutes, during which their resting state EEG recordings were taken using a tablet. Within 72 hours after their operations, the patients were asked to give post-operative pain ratings.

EEG pre-processing

The pre-processing of the EEG data was completed with custom code in MATLAB R2018a (The MathWorks, Inc.) using EEGLAB 14.1.2b [49], adopting a similar approach to Furman et al.[7] with adjustments for using cEEGrid-EEG rather than cap-EEG. An additional band-pass filter (2-40 Hz) was applied and channels with high-impedance (over 50kΩ) and excessive artefacts were removed. Data were then epoched into 5 second bins (i.e. epochs), and visually inspected to remove epochs with artefacts, defined as EEG characteristics that differ from signals generated by brain activity (e.g. muscle or eye movements).

Independent component analysis (ICA) was applied in order to identify and remove electrocardiogram (ECG) features that are often reflected as an independent component in a subset of people. How strongly the heart-electrical activity volume conducts to the head may influence whether ECG can be seen in EEG recordings, and previous research suggests that ICA identifies the ECG from approximately 50-60% of cEEGrid recordings [5, 8].

Frequency decomposition was completed using FieldTrip [9] and a Hanning taper was applied to reduce edge artefacts [7, 10, 11] The power spectral density in 0.2 Hz bins from 2-40 Hz was derived for each 5 second epoch.

Estimation of PAF

The PAF of a patient was estimated using the cEEGrid location that had the largest signal to noise ratio (SNR) of alpha activity. SNR was defined as the ratio of the relevant signal (i.e. alpha signal, 7-14 Hz) divided by the noise level (i.e. frequencies above and below the alpha range). In each patient the PAF for each 5 second epoch at the electrode with the best SNR channel was estimated using a center of gravity (CoG) method we used in our previous investigations [7, 11].

We defined CoG as follows:

$$CoG = \frac{\sum_{i=1}^{n} f_i * a_i}{\sum_{i=1}^{n} a_i}$$

where f_i is the *i*th frequency bin including and above 7 Hz, n is the number of frequency bins between 7 and 11 Hz, and a_i the spectral amplitude for f_i.

Statistical analysis

Firstly, Shapiro-Wilk tests found that, except for average post-operative pain ($w = 0.92$, $p = 0.21$), self-reported pain measures were not normally distributed ($w = 0.51$-0.84, $p < .05$). Therefore, non-parametric statistical analysis was used to test the relationship between variables for the majority of analyses. The relationship between pre- and post-operative pain was investigated. Due to changes in distribution shape and violations of normality, paired sign tests were used to compare the differences in patients' self-reported pain pre- and post-operatively. Spearman's rank coefficients were calculated to examine the degree of correlation between these variables.

The relationships between pre-operative PAF as an independent variable, and post-operative pain intensity (i.e. present, average, and worst acute pain in the previous 24 hours) as dependent variables was investigated using three approaches: 1) Classification, 2) group comparisons following median splits of post-operative pain intensity, 3) correlations.

For classification, we used the receiver operative characteristic (ROC) curve[12] to assess the sensitivity and specificity of PAF in identifying patients who report a severe degree of post-operative pain. The ROC curve was estimated by varying the threshold of alpha frequency (7-11 Hz) and then calculating the sensitivity (true positive rate) and specificity (true negative rate). The ROC curve is a plot of sensitivity on the y axis against 1−specificity on the x axis for varying values of alpha frequency. Sensitivity refers to the true positive rate (i.e. ability to correctly identify a patient reporting severe pain) and specificity refers to true negative rate (i.e. ability to correctly identify a patient not reporting severe pain). The area under the ROC curve (AUC) is able to provide an overall summary of the diagnostic accuracy of PAF in predicting pain sensitivity, with AUC of 0.5 corresponding to chance and 1.0 corresponding to perfect accuracy. We conducted our ROC analysis in SPSS 27.01.01 with the distribution assumption being nonparametric.

The group comparisons were based on median splits of the data for each post-operative pain measure (current, average, and worst pain) to create low and high pain sensitivity groups. Differences in the median PAF values for these groups were compared using Mann-Whitney U tests. Significance level was set at 0.05. Finally, with regards to correlations, we employed Spearman's rank order coefficients as these tests are more robust to violations of normality.

The potential influence of several confounding factors were investigated using R (v.3.4.1). Pearsons and Spearmans correlations were used to investigate whether age correlated with pre-operative PAF, or post-operative pain, respectively. Mann-Whitney U tests assessed whether there were differences in post-operative pain due to sex or operation type. And a Kruskal-Wallis test assessed whether there were differences in post-operative pain due to analgesic type.

Supplementary Material B

cEEGrid feasibility

Intra-operative EEG is used most often to assess the depth of anaesthesia in order to assist the titration of anaesthesia. The current EEG alogrithms (e.g Patients State Index [13]) used for intra-operative EEG make no claims about risk stratifying patients for post-operative pain. Our approach on the other hand was to collect patients EEG pre-operatively, days before the surgery, to identify patients at risk of higher pain post-operatively using peak alpha frequency (PAF). We should note that one does need to use cEEGrids to detect PAF, the algorithms to estimate it are not proprietary, and any clinical-grade EEG setup can be used to do this, including intra-op EEG monitors. However, we should note that the estimation of PAF should be done before any anaesthesia is given, to avoid the confounding impact of the anaesthetic agents on the EEG.

Assessment of neural activity in clinical patients using cEEGrids was fast, comfortable for patients, and technically feasible. Pre-operative assessments (including pain questioning, cEEGrid setup, recording, and cEEGrid removal), could be completed within 30 minutes of obtaining patient consent. Minor discomfort was reported when it was difficult to fit the cEEGrids to a patient due to them having larger ears. Therefore, production of different sized cEEGrids would be useful to ensure maximal signal quality and comfort for all patients in future.

Supplementary Material C

Additional results

The median split of present post-operative pain scores revealed significant differences in PAF across patients

We performed a Mann-Whitney U test to investigate the null hypothesis that the PAF in the group of patients reporting the lowest 50% of present pain levels and those reporting the highest 50% of pain levels are from continuous distributions with equal medians. We observed that patients in the lower 50th percentile of present post-operative pain levels having a significantly higher PAF (median = 9.22 Hz, range: 8.65-9.41 Hz), than the upper 50th percentile (median = 8.72 Hz, range: 7.8-9.18 Hz). The same test applied to the lower (median = 9.25 range: 8.47-9.41) and upper (median = 8.76 Hz, range: 7.8-9.04 Hz) 50th average post-operative pain scores did not pass the threshold for significance (W=67, p<0.07).

Worst Operative Pain scores correlated were negatively correlated with pre-operative PAF

We investigated if PAF was correlated with the intensity of pain scores reported by the patients. Here we found that the patients worst post-operative pain scores were negatively correlated with their pre-operative PAF (Figure S2. left panel, r = -0.67, p<0.01). The same relationship was observed for average (Figure S2. middle panel, r = -0.60, p<0.02) and present post-operative pain (Figure S2. right panel, r = -0.55, p<0.05).

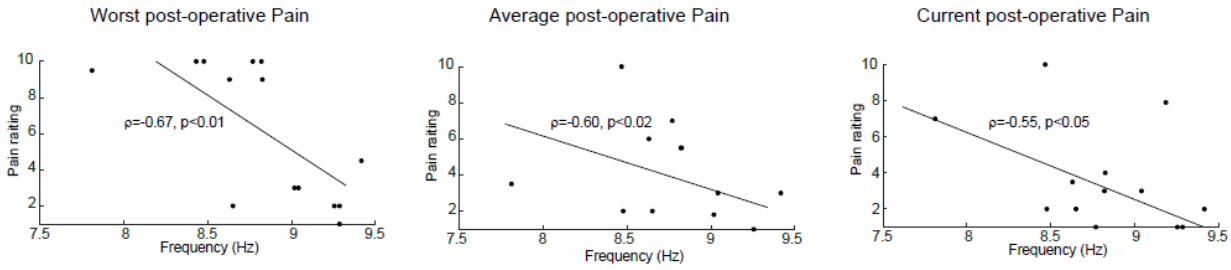

Figure S2. Individual pre-operative peak alpha frequency (PAF) plotted against worst, average, and current post-operative pain intensity in the previous 24 hours. A strong negative correlation was found between PAF and the post-operative pain scores; the lower an individual's PAF, the higher their post-operative pain.

Pain characteristics and relation to PAF

Although the exact mechanisms underlying PAF and pain sensitivity are unclear, the involvement of thalamocortical pathways in pain perception may aid explanations of why pre-operative PAF correlates with severity of maximal pain felt post-operatively. Thalamocortical pathways are thought to play a major role in both physical and emotional aspects of pain perception [14, 15].Given that alpha oscillations are thought to be in-part paced by the thalamus [16, 17], we speculate that PAF may reflect the gating of sensory pain information processing rates between the thalamus and cortex. Specifically, we hypothesize that the frequency of the alpha rhythm reflects the balance between the ascending nociceptive and descending antinociceptive pathways [18]. A low PAF could indicate that greater ascending nociceptive input is reaching the brain relative to descending antinociceptive signals. This

proposition could be empirically supported through studies utilising simultaneous measurements EEG and fMRI could be informative

We should note that the PAF of the patients in this study (mean age 68 years) was overall slower than the young healthy participants (mean age 28 years) in our preceding two studies ([7, 19]. This is consistent with the observation that PAF slows down (by approximately 0.5-1 Hz) as adults reach the age of 70 [20, 21]

While we believe our results are encouraging, there are some caveats to consider. The mechanisms underlying the relationship between PAF and pain are still unclear. Moreover, there are studies using different pain-induction protocols than ours that have even reported the opposite relationship to ours (i.e. PAF being positively correlated with pain intensity) [22, 23] Clearly, more research needs to be done in this domain and a large scale validation of PAF as a biomarker is ongoing ([24])

Supplementary Material D

Pain characteristics

Ten of the patients (62.5%) reported that they currently had no pain during the pre-operative EEG session (Figure S1). The median self-reported pre-operative pain was 0/10 for present, average, and worst pain in the last 24 hours. This produced significant positive skews in distributions. Post-operatively, the median ratings across patients were 2.5, 3, and 6.75/10 for present, average and worst pain in the last 24 hours, respectively.

An exact sign test was used to compare the differences in pain pre- and post-operatively. There was a statistically significant median increase in pain reported post-operatively compared to pre-operatively for current (median increase = 1, S = 11, p=0.0032), average (median increase = 2, S = 11, p=0.0032), and worst (median increase = 2, S = 13, p=00.00092) pain. This demonstrates that the operation caused significant increases in pain.

Five of the patients reporting some pre-operative pain described mild aches and pains, while one patient with osteoarthritis reported current, average, and worst pain in the last 24 hours as 7, 8, and 9.5/10, respectively. This patient and the staff were aware that it might be difficult to control their post-operative pain, as they already took morphine and gabapentin daily. Indeed, this patient, reported present, average, and worst pain post-operatively as 10/10.

However, presence of pre-operative aches and pains did not necessarily indicate that those patients would have high pain post-operatively; only one of the five patients who reported mild pre-operative pain reported severe worst post-operative pain.

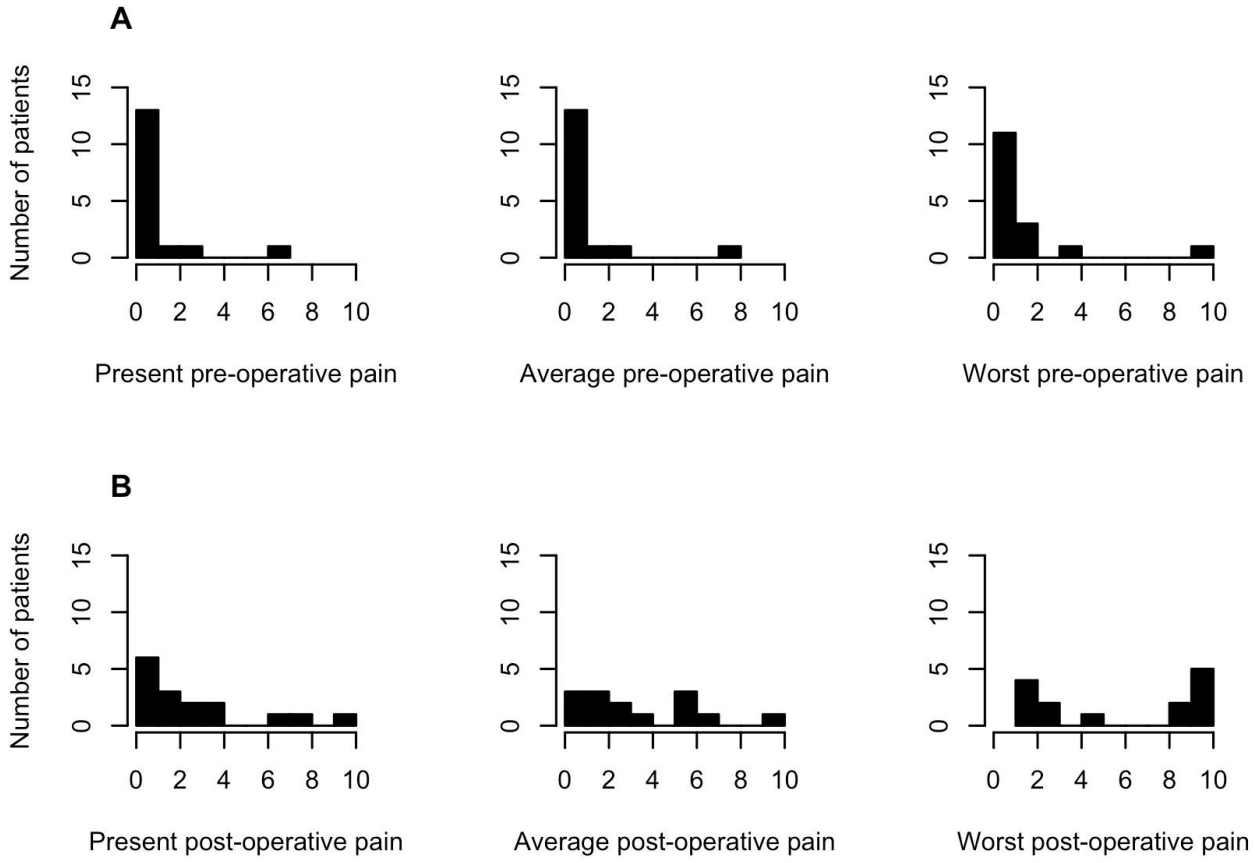

Figure S1. Frequency of self-reported pain intensity pre- (A) and post-operatively (B), on a verbal numeric rating scale (0 = "no pain", 10 = "worst pain imaginable"). Average and worst pain referred to the previous 24 hours. N=16 for all plots except average and worst pain post-operatively (n=14), where post-operative complications prevented collection of these pain assessment for two patients.

Supplementary Material E

Patient characteristics

Several other potentially influencing factors aside from PAF, such as age, sex, operation type, and intra-operative analgesia type, were assessed to investigate whether they were associated with post-operative pain ratings. In addition, Table S.1 displays patient characteristics, comorbidities, and medications, according to low or high worst post-operative pain. We acknowledge these were small numbers for statical analysis. Larger sample sizes are required to investigate the potential impact of these factors further in future.

Regarding patient age and sex, age was not significantly associated with pre-operative PAF, using a Pearsons correlation test ($r = 0.16$, $p=0.56$). Patient age was also not significantly associated with pre- or post-operative pain, using Spearmans correlation tests ($rs = -0.39$-0.1, all $ps>0.14$). Using a Mann-Whitney U test, no significant differences were found in present, average, or worst post-operative pain ratings due to patient sex ($W = 21.5$-35.5, all $ps>0.584$). There was also no significant difference in PAF between males and females ($W = 26$, $p=0.71$).

Regarding operation and anal gesia type, thirteen patients (81.25%) had VATS as the method of incision, meaning that only three patients received a thoracotomy. Ten patients (62.5%) received a paravertebral catheter as analgesia, five received patient controlled analgesia (PCA), and one received an epidural. Using a Mann-Whitney U test, no significant differences were found in current, average, or worst post-operative pain ratings due to the type of operation ($W = 11$-18, all $ps>0.44$). Using a Kruskal-Wallis test, no significant differences were found in current, average, or worst post-operative pain intensity scores due to the type of analgesic used ($\chi2= 0.82$-1.87, all $ps >0.39$, $df = 2$).

Table S1. Patient characteristics, comorbidities, and medications, grouped according to a median split of low and high worst post-operative pain. Comorbidities and medications are displayed by order of frequency, followed by alphabetical order.

		Low worst post-op pain (n = 7)	**High worst post-op pain (n = 7)**
Sex (%)	Male	4 (57.14)	5 (71.43)
	Female	3 (42.86)	2 (28.57)
Age (years)	Mean (SD)	66.57 (5.19)	67 (3.96)
	Range	59-73	59-71
Operation type (%)	Thoracotomy	1 (14.29)	2 (28.57)
	VATS	6 (85.71)	5 (71.43)
Intra-operative anaesthesia (%)	Paravertebral catheter	4 (57.14)	5 (71.43)
	Patient controlled analgesia (PCA)	3 (42.86)	1 (14.29)
	Epidural	0 (0)	1 (14.29)
Comorbidities (%)	Smoking	4 (57.14)	6 (85.71)
	Hypertension	4 (57.14)	4 (57.14)
	Hypercholesterolaemia	3 (42.86)	5 (71.43)
	Arthritis/Osteoarthritis	4 (57.14)	3 (42.86)
	Obesity	2 (28.57)	4 (57.14)
	Anticoagulant therapy	2 (28.57)	1 (14.29)
	COPD	1 (14.29)	2 (28.57)
	Atrial fibrillation and flutter	0 (0)	2 (28.57)
	Diabetes type 2	0 (0)	2 (28.57)
	Chronic ischaemic heart disease	0 (0)	1 (14.29)
	IBS	0 (0)	1 (14.29)
	Peripheral vascular disease	1 (14.29)	0 (0)
	No data	1 (14.29)	0 (0)
Routine Medications:	**Pain (ordered by frequency)**		
	Paracetamol	5	4
	Codeine phosphate	4	3
	Morphine sulphate	1	5
	Aspirin	2	1
	Ibuprofen	1	2
	Gabapentin		2
	Tramadol	1	
	Other medications (ordered by frequency)		
	Docusate sodium	5	6
	Senna	5	6

Atorvastatin	3	1
Carbocisteine	1	2
Omeprazole	1	2
Amlodipine	2	
Clopidogrel	2	
Bisoprolol	1	1
Lansoprazole	1	1
D3 supplement	1	
Co-amoxiclav	1	
Glyceryl trinitrate	1	
Ondansetron	1	
Quinine sulphate	1	
Tamsulosin	1	
Umeclidinium	1	
Amiodarone		1
Apixaban		1
Atenolol		1
Beclometasone		1
Bezafibrate		1
Carbocisteine		1
Aclidinium bromide		1
Empagliflozin		1
Fluticasone		1
Furosemide		1
Gliclazide		1
Glycopyrronium		1
Levofloxacin		1
Loratadine		1
Macrogol		1
Metformin		1
Mirtazapine		1
Pravastatin		1
Ramipril		1
Salbutamol		1
Simvastatin		1
Thiamine		1
Vitamin B compound		1
No data	**2**	**1**

Supplementary Material F

Post-operative pain follow up

Post-operative pain follow ups were conducted for seven patients, six weeks after their operation. This follow up included basic questions on whether patients had none, a little, quite a bit, or a lot of pain in their chest, arm or shoulder, or other parts of their body during the past week. Six reported having a little pain, either in their chest, arm or shoulder, or elsewhere (i.e. around the wound, under breast, and lung). Only one of the seven patients assessed reported having no pain. The average pre-operative PAF of the six patients reporting pain was 8.63 Hz (SD = 0.48, range: 7.81-9.15 Hz), while the PAF of the patient reporting no pain was 9.29 Hz. This indicates that pre-operative PAF has potential to predict presence of post-operative pain at a six week follow up. However, further research with larger sample sizes would be required to assess this.

A second post-operative pain follow up was conducted for all 16 patients, on average 15 months (range: 8-20 months) after the operations. Two patients reported still experiencing some pain at this follow up, neither of which were assessed at the six-week post-operative follow up. Nine patients reported having no pain, and follow up was unattainable from three patients that died as well as from two additional patients for other reasons. Of the two patients still reporting pain, one reported back, shoulder, and pain where the surgical chest drain had been 17 months post-operatively. This patient had undergone a thoracotomy with a paravertebral catheter as analgesia, their pre-operative PAF was relatively high at 9.29 Hz, and their worst post op pain was low at 2/10. The other patient reported pain 18 months after their operation, the exact location was not recorded. They had a received a video assisted thoracoscopy surgery (VATS) and patient controlled analgesia (PCA), their pre-operative PAF was at 9.04 Hz and their worst acute post-operative pain was low at 3/10.

From the information we have, we are not able to draw conclusions regarding PAF and the development of chronic pain. We replicate the experimental work in terms of a relation to future pain sensitivity over relatively short time periods (i.e. within 72 hours, and possibly six weeks), but whether this is linked to chronic pain development is still undetermined. Future work should implement thorough 3, 6, and 9-month post-operative pain follow ups to assess patients' pain development.

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