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Predicting postoperative pain in lung cancer patients using preoperative peak alpha frequency

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Table 1 Balance of possible confounding factors between groups. BIS, bispectral index; MAC, minimum alveolar concentration; SD, standard deviation.

	BIS 50		BIS 35	
	Delirium N=47	No delirium N=206	Delirium N=74	No delirium N=188
MAP (mm Hg), mean (SD)	83.4 (15.8)	85 (22.3)	81.0 (9.4)	80.9 (15.6)
Inotrope used, *n* (%)	32 (68)	101 (49)	52 (71)	135 (72)
Ketamine, *n* (%)	2 (4)	10 (5)	5 (7)	4 (2)
Dexmedetomidine, *n* (%)	3 (6)	7 (3)	0 (0)	14 (7)
Age-adjusted MAC, mean (SD)	0.66 (0.19)	0.73 (0.18)	1.01 (0.30)	0.96 (0.27)

been significant reported separation between groups in depth of anaesthesia.[3]

We look forward to the publication of further randomised studies that test the possible causative mechanisms mentioned, so that anaesthetists can be guided by sound evidence. Meanwhile, we maintain that our study was balanced.

Declarations of interest

KL is a member of the editorial board and LE is a member of the associatee editorial board of the *British Journal of Anaesthesia*. The other authors declare that they have no conflicts of interest.

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Predicting postoperative pain in lung cancer patients using preoperative peak alpha frequency

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Editor—Thoracotomy incisions used to gain access to the thoracic organs, lead to chronic pain in an estimated 25–60% of cases.[1] Considerable nerve damage is common in thoracotomy, as rib retractors used in this operation block conduction of intercostal nerves near the incision by 50–100%.[2] Video-assisted thoracoscopic surgery (VATS), an alternative to conventional thoracotomy, involves less nerve damage owing to smaller incisions and no rib retraction, and is associated with increased tolerability for patients and better patient outcomes.[3] However, even with VATS many

patients still suffer from moderate to severe postoperative pain.[3]

Sensitivity to acute postoperative pain is amongst the most significant risk factors for development of chronic postsurgical 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 postoperative 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 EEG. PAF is a stable heritable trait within individuals.[8]

In healthy participants, before the induction of a prolonged (but temporary) painful experience, PAF is negatively related to their pain ratings.[9,10] Furman and colleagues[9] found a relationship between PAF and experimental pain sensitivity, and that PAF can predict pain sensitivity for multiple pain models even months later.[10] These findings suggest that PAF can serve as a reliable biomarker for pain ratings, and could be a powerful clinical tool.

In this pilot study, we directly investigated if PAF can be used as a clinical tool to stratify pain-sensitive patients. Specifically, we investigated whether preoperative PAF, measured using cEEGrids (TMSi, Oldenzaal, The Netherlands; https://ceegrid.com), correlated with postoperative pain severity in 16 patients (6 female; mean [standard deviation] age=67.5 [4.4] yr; range, 59–73 yr) undergoing surgery for lung cancer. Written consent, PAF, and baseline pain were collected up to 4 weeks before surgery (8.6 [6.4] days) during standard preoperative assessments. Within 72 h after surgery, patients were asked to report their present, average, and

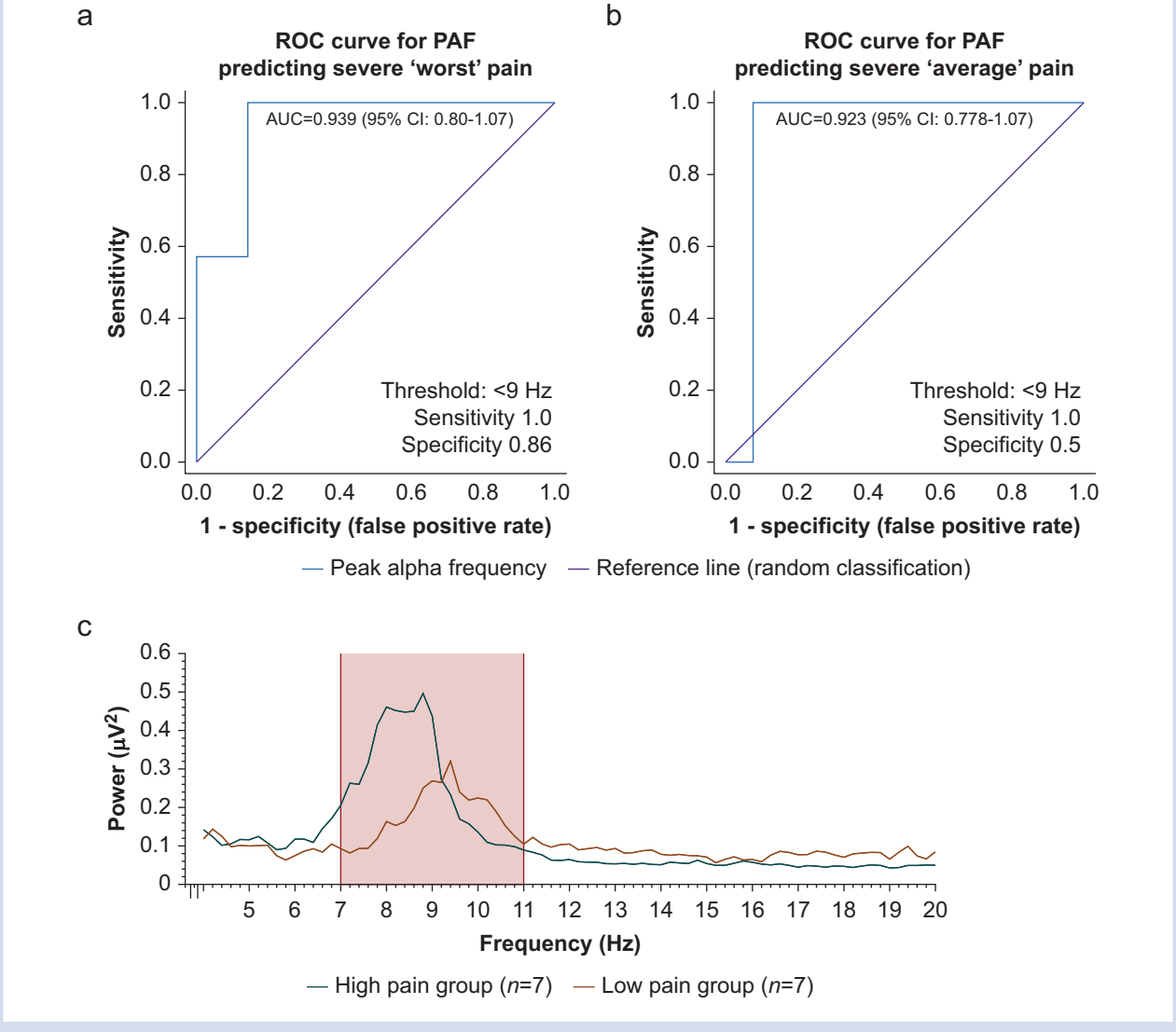

Fig 1. The receiver operating characteristic curve of preoperative peak alpha frequency (PAF) in (a) classifying severe (>7/10) postoperative pain, and (b) classifying individuals reporting severe 'average pain experienced in the last 24 h' (c). The frequency spectrum of patients (n=14) median split according to their worst postoperative pain, showing that the high pain group had slower PAF. AUC, area under the curve; CI, confidence interval; ROC, receiver operative characteristic.

worst pain in the past 24 h (see Supplementary Material A for detailed methods).

Use of EEG in a clinical setting is 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 preoperative PAF was negatively correlated with present (n=16), average and worst (n=14) postoperative pain (all P<0.02; Supplementary Material C). Postoperative complications prevented assessment of average and worst postoperative pain for two patients. Postoperative pain was not associated with preoperative pain (Supplementary Material D), operation type (13 VATS, 3 thoracotomy), analgesic type (10 paravertebral catheter, 5 patient-controlled analgesia [PCA], 1 epidural catheter), age, or sex (Supplementary Material E).

For classification, we used the receiver operative characteristic (ROC) curve to assess the sensitivity and specificity of preoperative PAF in identifying patients reporting severe 'worst' postoperative pain (Fig. 1a). The area under the curve (AUC) was 0.939 (standard error [SE]=0.077; P<0.001; 95% confidence interval [CI], 0.80–1.07). A PAF of <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' postoperative pain (Fig. 1b), the AUC was 0.923 (SE=0.074; P<0.001; 95% CI, 0.778–1.07). A PAF of <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.

We found that a median split of worst postoperative pain ratings revealed significant differences in PAF across patients (Fig. 1c). A Mann–Whitney U-test showed that preoperative PAF was significantly faster (W=74, P=0.004) for those with lower worst postoperative pain (median, 9.25 Hz; range, 8.65–9.41 Hz) compared with those with higher worst postoperative 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 were also collected for some participants at 6 weeks and ~15 months postoperatively (Supplementary Material F).

Although our work remains to be replicated in a larger population of patients, if PAF is shown to be a sensitive and specific biomarker of pain sensitivity, it would allow surgeons and anaesthetists to identify patients at risk of severe acute postoperative pain preoperatively. This identification would enable provision of targeted interventions with pre-emptive analgesic strategies for chronic postoperative pain (e.g. small incision, regional analgesic nerve block, 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 postoperative pain could move the focus away from pain treatment and towards pain prevention; preoperative PAF is a prime candidate that warrants further investigation.

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Declarations of interest

DS, AF, and AM have a patent pending (PCT/US2018/058889) for "A Simple and Portable Biomarker for Pain Sensitivity." AF and AM are shareholders and DS, AF, and AM serve as advisors to Empower Therapeutics, a University of Maryland/University of Birmingham spin-out company commercializing this IP to create pain management technology. No conflicts of interest, financial or otherwise, are declared by the remaining authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.03.006.

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