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The Application of Machine Learning and Artificial Intelligence in Patient Controlled Analgesia - Towards Personalized Pain Management

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Abstract

The application of artificial intelligence (AI) and machine learning in pain management after surgery is driven by advancements in communication technology, data analytics and real time monitoring technologies. These tools empower anaesthetists to develop dynamic, real-time pain management plans that adjust to the changing needs of patients throughout their recovery. Machine learning algorithms analyse extensive datasets, uncovering patterns and accurately predicting pain trajectories. By combining these predictions with patient-specific data, AI systems can recommend personalized pain management strategies, optimizing medication regimens and minimizing the risk of over- or under-treatment. This approach not only enhances pain control but also minimizes potential side effects and accelerates the recovery process.

This narrative review highlights the incorporation of machine learning predictions into development of patient-controlled anaesthesia (PCA), and offers a concise overview of postoperative pain management within the context of personalized medicine.

Keywords: Machine Learning; Artificial Intelligence; Patient Controlled Analgesia; Personalized Pain Management; surgery

Introduction

The recent extensive potential of artificial intelligence (AI) to transform healthcare has gained widespread recognition for its ability to analyse complex datasets, simulate human cognitive learning, and incrementally improve its performance. The application of machine learning, a subset of AI, in pain management research holds significant potential to revolutionize the field by developing personalized treatment strategies, supporting decision-making, and improving predictive health outcomes [1].

Personalised medicine is a rapidly growing field that has shown its prospects across a broad range of medical research areas. This paradigm moves away from the traditional one-size-fits-all model and customise healthcare based on individual profiles, clinical history and lifestyle choices, optimising treatment plans and offering more precise and effective healthcare solutions and better outcomes [2]. This approach is particularly important in pain management for enhancing patient safety and optimizing treatment efficacy.

The management of post-operative pain is a critical aspect of patient care, directly influencing recovery outcomes and overall patient satisfaction [3]. Traditional pain management approaches often rely on standardized protocols that may not adequately address the unique needs of individual patients. The advent of machine learning and artificial intelligence (AI) has heralded a new era in personalized medicine, offering promising solutions to tailor post-operative pain management to the specific characteristics of each patient.

This narrative review underscores the integration of machine learning prediction into personalized pain management, provides a brief overview of post-operative pain management within the framework of personalised medicine. It explores the development of patient controlled anaesthesia and prediction of patient outcomes in the respect of growing impact of AI and machine learning as pivotal tools in the evolution of anaesthetic precision.

Databases Search and Data Extraction

The PubMed and Embase were searched using combinations of the following keywords: machine learning, artificial intelligence, patient-controlled analgesia or PCA. All English language publications up to 17 July 2024 were eligible. Peer-reviewed articles, including abstracts and narrative reviews, were eligible for inclusion. Publications were screened through a meticulous assessment of titles and abstracts. After removing duplicate entries, the remaining articles were screened based on specific criteria. To be included, papers had to focus on the design or application of artificial intelligence algorithms specifically in post-operative pain management. Studies that broadly involved patient parameter monitoring but did not directly address post-operative pain management were excluded.

From Patient-Controlled Analgesia (PCA) to AI-Assisted PCA

Patient-controlled analgesia (PCA) has become one of the most effective techniques for treating multiple categories of pain, including acute, such as postoperative or labour pain, or chronic, such as palliative care or cancer pain [4,5].

The PCA pump was designed to deliver the patient's specific dose of pain medication on a schedule that is customized to each individual patient's needs because patients demonstrate marked individual variation in pain medication requirements. The revolutionary idea of PCA was first proposed by Sechzer et al. as “feedback loop” for analgesia [6], and it was put into practice in the mid-1970s following the emergence of microprocessors. PCA is now widely used in hospitals for the management of postoperative pain, especially for major surgeries [7].

The first generation PCA employed mechanical analgesia pumps, required a mechanical clock to control the timing. The development of electronic PCA pumps in the 1970s marked a significant leap forward [8, 9]. These devices allowed for precise control over dosage and timing, improving both safety and efficacy. They included features such as lockout intervals to prevent overdose and dosage limits tailored to individual patient needs.

Over the years, PCA pumps have incorporated various safety features, including alarms for low medication levels, infusion line occlusions, and unauthorized access. These advancements have enhanced the reliability and safety of PCA. The advances in real-time non-invasive monitoring and microprocessors have significantly enhanced the application of interactive smart systems in perioperative and post operative pain management [10-13]. In 2005, KK Women's and Children's Hospital in Singapore developed a smart-pump technology called computer-integrated patient-controlled epidural analgesia (CIPCEA) for management of labour pain. Labour is one of the most painful experiences a woman can undergo, influenced by both physical and psychological factors [14]. Although relatively invasive, with years of medical research and improved safety, neuraxial analgesia is now considered the gold standard of labour pain relief.

To provide the optimal management in labour analgesia, it is important to understand the dynamic and multifaceted nature of labour pain. CIPCEA system uses a laptop to adjust the epidural pump based on the frequency and history of patient demands. The CIPCEA algorithm varies the basal infusion rate proportionally to the number of demand boluses, which provides flexibility to accommodate the escalating analgesic requirements as labour progresses or as labour augmentation regimens are started. For example, if a patient required one, two, or three demand boluses in the last hour, the basal infusion rate would adjust to 5, 10, or 15 mL/h, respectively. By varying the basal maintenance doses, CIPCEA system closely mirror the evolving needs while allowing the patients the autonomy of self-administration of analgesics, improving analgesic effectiveness and optimizing local anaesthetic use [11].

In a randomized trial comparing CIPCEA with continuous epidural infusion using 0.1% ropivacaine with fentanyl 2 μg/mL, CIPCEA significantly reduced breakthrough pain without increasing anaesthetic consumption or side effects [11]. CIPCEA also led to higher maternal satisfaction scores compared to a conventional PCEA pump and a PCEA with a fixed basal infusion of 5 mL/h. The incidence of breakthrough pain was lower in the CIPCEA group (15%) compared to the conventional PCEA group (35%) [10,12].

The use of PCA offers numerous benefits: it empowers patients, is effective, typically has minor side effects and infrequent adverse events, is well-manageable, and is cost-efficient for specific conditions. However, contrary to the expected high analgesia efficiency, the Cochrane systemic review conducted in 2006 and 2015 showed that PCA only demonstrated marginal superiority (8%) over traditional methods of pain management [15,16].

One of the major problems with traditional PCA is decentralized information and inability to automatically collect and analyse postoperative analgesia data. PCA pumps are dispersed throughout patient wards, lacking direct or immediate connectivity with medical personnel. Nurses must spend time instructing patients on how to operate the pre-programmed PCA equipment. While this may not pose a problem when the equipment functions correctly, any mechanical malfunction or need for analgesia adjustment requires prompt attention from medical staff delays in response can compromise the analgesia efficiency [17]. Additionally, unresolved alarm sounds can provoke unnecessary anxiety or panic in patients.

The rapid advancement of communication technologies, particularly wireless communication, has given rise to the Internet of Things, facilitating instant information gathering and sharing. Wang and Wang proposed an intelligent analgesia system (AI-PCA) which connects intelligent electronic PCA pumps and other mobile terminals to a central computer server equipped with an information control system in a wireless environment [18]. It enables remote monitoring, intelligent alarms, intelligent analysis, and assessment of the PCA equipment, as well as automatic recording and storage of key information. The central information processing server received and analysed data from the analgesic pump via radio transmission. The AI-assisted PCA algorithm generated different alarm signals (insufficient analgesia, poor analgesia and blockage) which were sent back to the computer or mobile phone for the anaesthetists to address the issues in real time. The definition of "insufficient analgesia, poor analgesia" may vary according to local practice while 'blockage' was defined as an obstruction in the external infusion pipeline of the analgesic pump [19,20].

This information system solution integrates remote monitoring, information management, and high-precision infusion pumps for PCA. By transforming the traditional passive call mode— where patients rely on bedside alarms or staff-initiated interventions—into an active service, the AI-PCA system eliminates the fear and uncertainty caused by unexpected pain and delayed responses.

The results from Cao et al. indicated that the incidence of moderate to severe pain (NRS score ≥ 4) at rest and during motion was significantly lower in postoperative patients using AI-PCA. Additionally, side effects from analgesia, such as nausea and vomiting, were significantly reduced, and patient satisfaction was higher among those using AI-PCA [21]. Similarly, a recent report from Wang et al. found that the incidence of moderate to severe pain was significantly reduced in the AI-PCA group (21.7%) compared to the control group (26.3%), with a difference of 4.6% (95% CI, 3.2% to 6.0%; P < 0.001). The occurrence of total adverse reactions was similar between the groups [20]. In a randomized control trial comparing the pain score (NRS), Richards–Campbell Sleep Scale (RCSQ), and adverse outcomes at 8, 12, and 24 h after the operation in older patients after laparoscopic radical resection of colorectal cancer, the pain scores were significantly lower in AI-PCA group than that of the control group, while the RCSQ score of AI-PCA group was significantly higher than that of control group on the 1st and 2nd days after operation, showing less sleep disturbance. There were no significant differences in the incidence of dizziness and nausea, vomiting, and myocardial ischemia [19].

In summary, AI-PCA is an information system solution integrating remote monitoring, information management and high-precision infusion pump for PCA. The intelligent analysis of data by the wireless analgesia system solves the difficulties in the traditional management mode, and it can provide the better pain management under dynamic monitoring.

Predictive Model to Mitigate the Side Effects

Opioid-based intravenous patient-controlled analgesia (IV-PCA) is essential in many hospitals and plays a critical role in routine postoperative pain management. IV-PCA enhances safety through lockout intervals for time and dose, reduces nursing burden, and improves patient satisfaction by allowing immediate access to analgesia without waiting. Despite efforts to account for individual differences in pharmacodynamics and pharmacokinetics, some patients discontinue PCA due to intolerable side effects. The use of opioids is often accompanied by various side effects such as opioid-induced hyperalgesia, nausea, vomiting, respiratory depression, and sedation, postoperative ileus, bradycardia, pruritus, sedation, confusion, and urinary retention [22-26], which can vary widely among individuals.

Anaesthetists carefully balance the amounts of analgesics administered to avoid excessive amounts of opioids induced side-effects. To optimize pain management with the smallest effective yet adequate amounts of opioids, it is crucial to identify high-risk populations and predict the likelihood of adverse side effects for individual patients. This allows medical staff to promptly address side effects with prophylactic or regular administration of antiemetics or dexamethasone, preventing the discontinuation of IV-PCA [27]. Additionally, alternative analgesic strategies such as PCA with ketamine or nefopam, and surgery-specific nerve blocks (transversus abdominis plane block, ilioinguinal nerve block, iliohypogastric nerve block, etc.) should be considered [28,29]. These personalized analgesic plans can alleviate pain and reduce the risk of PCA discontinuation due to side effects.

The application of AI and machine learning in anaesthesia research holds significant potential to revolutionize the field by improving prediction, supporting decision-making, and developing personalized treatment strategies. In clinical practice, accurate prediction models enable better medical prognostication, early identification of high-risk patients, improved risk adjustment, optimal utilization of critical care resources, and more effective communication among patients, physicians, and families [30-32].

Recently, several groups attempted to develop machine learning models to predict postoperative nausea and vomiting (PONV) for patients under IV-PCA. PONV is the most common adverse event after general anaesthesia, affecting 40% of Asian and European American populations and up to 80% of high-risk cases [33, 34]. Shim et al. reported a predictive model of PONV using machine learning algorithms with AUC of 0.686 [35]. The recent results from Xie et al yielded an AUC of 0.947 which was significantly higher than that of the past models [36]. The best of their

ML model was used for external validation on patients at other hospital and generated the AUC of 0.821. The three key indicators—history of motion sickness and/or PONV, female sex, and low body weight—are particularly important for anaesthetists and surgeons to consider. The machine learning models offer a good preoperative prediction of PONV for patients using IV PCA.

Despite the publication of numerous comprehensive guidelines and risk assessment models, PONV remains a persistent issue for the surgical population. It is possible to reduce the incidence of PONV by using assessment tools to proactively guide clinical practice. Pysyk et al. reported that the incidence of PONV was reduced by providing annual performance feedback to anaesthetists, encouraging the use of antiemetic medications [37]. Rajan et al. concluded that identifying high-risk patients using predictive models for PONV, employing combinations of various antiemetic medications during and after surgery, and modifying anaesthesia techniques can significantly reduce the incidence of PONV [38].

Ethical Implications of AI in Healthcare

The integration of AI into clinical settings brings both significant benefits and challenges, along with important ethical and legal implications. Data privacy and security, the accuracy of predictive models, and the need for clinical validation are potential limitations to applying AI in clinical practice.

Protecting patient privacy and ensuring data security are critical, the need for establishing robust ethical guidelines and legal frameworks has emerged as an increasingly important subject. From a legal perspective, the entire lifecycle of data, including acquisition, storage, transfer, curation and analysis, must comply with all relevant laws, regulations, and legal obligations. On the other hand, the interpretation and enforcement of laws must continuously evolve to keep pace with the rapid advancements in technology [39]. Countries around the world have introduced laws to protect the data privacy of their citizens, such as the General Data Protection Regulation (GDPR) in Europe, Personal Data Protection Act in Singapore [40,41]. In addition, the European Union has become a leading player in medical AI innovation and has recognized the challenges that AI poses to existing liability frameworks. To promote consistency in liability principles and provide legal clarity, the European Commission introduced the Artificial Intelligence Act, one of the first legal frameworks specifically focused on AI. The Commission aims to foster the safe use of AI in critical sectors like healthcare while simultaneously driving technological innovation [42].

The legal framework regarding AI in healthcare is continuously evolving. Emerging laws and regulations are likely to address key issues such as liability. As AI technology advances, legal frameworks will adapt to promote ethical, transparent, and responsible use in healthcare. It is essential for healthcare professionals to remain well-informed about these changes to navigate complex legal terrain while maintaining accountability and ensuring high standards of patient care.

Another limitation of the utilization of AI in healthcare decision-making involved concerns about the accountability, the potential bias within predictive models, and the necessity of clinical validation. A recent systematic review evaluated the risk of bias in studies on prediction models developed using supervised machine learning techniques. The review concluded that most of these studies were prone to poor methodological quality and a high risk of bias. Key issues include small sample sizes, participant exclusion, inadequate handling of missing data, and failure to address overfitting. To enhance the clinical applicability of the prediction models, improvements in study design, execution, reporting, and validation are essential [43]. It is important to recognize that AI will not always outperform existing methods. Instead, AI should be taken as a tool that must be applied appropriately to address relevant questions or problems.

Summary and Future Directions

The field of anaesthesiology has a long history of integrating AI into its research. AI has the potential to transform clinical anaesthesia practices, including perioperative support, critical care delivery, postoperative and outpatient pain management. Modern anaesthesiology demands that anaesthetists gather, analyse, and interpret multiple data streams for each patient. With the healthcare system's shift from analogue to digital data, clinicians must now rely on increasingly data-intensive workflows to perform their daily tasks. AI and machine learning can enhance the safety and efficacy of PCA by leveraging large datasets from electronic health records and the anaesthesia information management system, patient histories, and real-time monitoring systems [44].

Fortunately, information management systems that automate the extraction of clinical variables (e.g., vital signs, drug delivery timestamps) have alleviated the documentation burden on anaesthetists. However, clinicians must now focus on effectively interpreting the growing volume of available data for anaesthetic and critical care delivery. The application of AI technologies should prioritize helping clinicians maximize the clinical utility of this electronically captured data.

The integration of AI in PCA is still in its early stages, with ongoing research focused on improving the accuracy and reliability of predictive models. Ethical considerations, such as data privacy and the need for rigorous clinical validation, are also critical. The comprehensive cybersecurity strategies and robust safeguards must be developed and implemented to protect patient data and ensure the security of critical healthcare operations. Collaboration among clinician, AI developer and regulatory bodies is essential for establishing clear guidelines and standards governing the use of AI algorithms in clinical decision-making. Anaesthetists should continue engaging with data scientists and engineers, offering their clinical expertise to ensure that AI is developed with real-world applicability. This collaboration helps guarantee that the data used to train algorithms is valid, representative of diverse patient populations, and that the resulting interpretations are clinically meaningful. Nevertheless, the potential of AI to revolutionize pain management and improve patient care is immense, making it a promising area of study and application in modern healthcare.

References

1. Char DS, Shah NH, Magnus D (2018) Implementing machine learning in health care - addressing ethical challenges. N. Engl. J. Med. 378: 981-3.

2. Dabbagh A, Sabouri AS (2021) The role of personalized medicine in current and future clinical practice of anesthesiology and perioperative medicine: Towards anesthesiomics. In: Dabbagh A editor. Personalized Medicine in Anesthesia, Pain and Perioperative Medicine. Cham: Springer International Publishing, 1-8.

3. Barnett S, Alagar R, Grocott M, Giannaris S, Dick J, Moonesinghe S. (2013) Patient-satisfaction measures in anesthesia: qualitative systematic review. Anesthesiology. 119: 452-78.

4. Evans JM, Rosen M, MacCarthy J, Hogg MI (1976) Apparatus for patient-controlled administration of intravenous narcotics during labour. Lancet, 1: 17-8.

5. Viscusi ER (2008) Patient-controlled drug delivery for acute postoperative pain management: A review of current and emerging technologies. Reg. Anesth. Pain Med. 33: 146-58.

6. Sechzer PH (1968) Objective measurements of pain. Anesthesiology. 29: 209-10.

7. Dolin SJ, Cashman JN, Bland JM (2002) Effectiveness of acute postoperative pain management: evidence from published data. Br J Anaesth. 89: 409-423.

8. Grass JA (2005) Patient-controlled analgesia. Anesth Analg, 101: S44-61.

9. Huang J (2009) Progress in application and nursing of patient-controlled analgesia pump after surgery. General Care, 7: 1483-5.

10. Sng BL, Sia AT, Lim Y, Woo D, Ocampo C (2009) Comparison of computer-integrated patientcontrolled epidural analgesia and patient-controlled epidural analgesia with a basal infusion for labour and delivery. Anaesth Intensive Care, 37: 46-53.

11. Sia AT, Lim Y, Ocampo CE (2006) Computer-integrated patient controlled epidural analgesia: a preliminary study on a novel approach of providing pain relief in labour. Singapore Med J. 47: 951-6.

12. Lim Y, Sia AT, Ocampo CE (2006) Comparison of computer integrated patient controlled epidural analgesia vs. conventional patient controlled epidural analgesia for pain relief in labour. Anaesthesia, 61: 339-44.

13. Sia AT, Leo S, Ocampo CE (2013) A randomised comparison of variable-frequency automated mandatory boluses with a basal infusion for patient-controlled epidural analgesia during labour and delivery. Anaesthesia, 68: 267-75.

14. R Melzack, R Kinch, P Dobkin, M Lebrun, P Taenzer (1984) Severity of labour pain: influence of physical as well as psychologic variables Can Med Assoc J, 130: 579-84

15. Hudcova J, McNicol E, Quah C, Lau J, Carr DB (2006) Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. Cochrane Database Syst Rev. 18: CD003348.

16. Monitoring Editor (2015) Cochrane Pain, Palliative and Supportive Care Group, McNicol ED, Ferguson MC, and Hudcova J. Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. Cochrane Database Syst Rev. 6: CD003348.

17. Herring ME, Shah SK, Gupta AK (2008) Current regulations and modest proposals regarding disposal of unused opioids and other controlled substances. J Am Osteopath Assoc. 108: 338-43.

18. Wang N, Wang JG (2019) Research on Intelligent Analgesia Pump. Procedia Comput Sci. 154: 256-9.

19. Liu D, Li X · Nie X, Hu Q, Wang J, Hai L, Yang L, Wang L, Guo P (2023) Artificial intelligent patientcontrolled intravenous analgesia improves the outcomes of older patients with laparoscopic radical resection for colorectal cancer. European Geriatric Medicine. 14: 1403-10.

20. Wang D, Guo Y, Yin Q, Cao H, Chen X, Qian H, Ji M, Zhang J (2023) Analgesia quality index improves the quality of postoperative pain management: a retrospective observational study of 14,747 patients between 2014 and 2021. BMC Anesthesiology, 23: 281.

21. Cao H, Huang W, Peng S, Xu L, Wang S, Zhang J, et al. (2018) Effect of intelligentized patientcontrolled analgesia management on quality of postoperative analgesia. Chin J Anesthesiol. 12: 1077-81.

22. Hollmann MW, Rathmell JP, Lirk P (2019) Optimal postoperative pain management: Redefining the role for opioids. Lancet. 393: 1483-5.

23. Simpson JC, Bao X, Agarwala A (2019) Pain management in enhanced recovery after surgery (ERAS) protocols. Clin. Colon Rectal Surg. 32: 121-8.

24. Ishikawa Y, et al. (2011) Evaluation of the side effects of intravenous patient controlled analgesia after spine surgery. Masui. 60: 920-3.

25. Paul AK, et al. (2021) Opioid analgesia and opioid-induced adverse effects: A review. Pharmaceuticals. 2021;14:11091. doi: 10.3390/ph14111091.

26. Motamed C. Clinical update on patient-controlled analgesia for acute postoperative pain. Pharmacy. 10: 10022.

27. Wakamiya R, et al. (2019) Effects of prophylactic dexamethasone on postoperative nausea and vomiting in scoliosis correction surgery: A double-blind, randomized, placebo--controlled clinical trial. Sci. Rep. 9: 2119.

28. Kim SH, et al. (2013) Opioid sparing effect of low dose ketamine in patients with intravenous patient-controlled analgesia using fentanyl after lumbar spinal fusion surgery. Korean J. Anesthesiol. 64: 524-8.

29. Moon JY, et al. (2016) The effect of nefopam on postoperative fentanyl consumption: A randomized, double-blind study. KJP. 29: 110-8.

30. Churpek MM et al. (2016) Multicenter comparison of machine learning methods and conventional regression for predicting clinical deterioration on the wards. Crit. Care Med. 44: 368-74.

31. Kwon JM, Lee Y, Lee Y, Lee S, Park J (2018) An algorithm based on deep learning for predicting in-hospital cardiac arrest. J. Am.Heart Assoc. 7: e008678.

32. Wu TT, Lin XQ, Mu Y, Li H, Guo YS (2021) Machine learning for early prediction of in-hospital cardiac arrest in patients with acute coronary syndromes. Clin. Cardiol. 44: 349-56.

33. Wu YH, Sun HS, Wang ST, Tseng CA (2015) Applicability of risk scores for postoperative nausea and vomiting in a Taiwanese population undergoing general anaesthesia. Anaesth. Intens. Care. 43: 473-8.

34. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N (1999) A simplified risk score for predicting postoperative nausea and vomiting: Conclusions from cross-validations between two centers. Anesthesiology. 91: 693-700.

35. Shim JG, et al. (2022) Machine learning for prediction of postoperative nausea and vomiting in patients with intravenous patient-controlled analgesia. PLoS ONE. 17: e0277957.

36. Xie M, Deng Y, Wang Z, He Y, Wu X, Zhang M, He Y, Liang Y, Li T (2023) Development and assessment of novel machine learning models to predict the probability of postoperative nausea and vomiting for patient-controlled analgesia. Sci Rep. 13: 6439.

37. Pysyk CL, Corsi DJ, Boet S (2019) The potential for anesthesiologist practice feedback to reduce postoperative vomiting in an academic centre. Can. J. Anaesth. 66: 609-10.

38. Rajan N, Joshi GP (2021) Management of postoperative nausea and vomiting in adults: Current controversies. Curr. Opin. Anaesthesiol. 34: 695-702.

39. Olsen HP, Slosser JL, Hildebrandt TT, Wiesener C (2019) What's in the Box? The Legal Requirement of Explainability in Computationally Aided Decision-Making in Public Administration. (June 12, 2019). iCourts Working Paper Series No. 162, 2019, University of Copenhagen Faculty of Law Research Paper No. 2019-84.

40. Yuan B, Li J (2019) The policy effect of the General Data Protection Regulation (GDPR) on the digital public health sector in the European Union: an empirical investigation. Int J Environ Res Public Health. 16: 1070.

41. Personal Data Protection Act (PDPA). Personal data protection commission Singapore.

42. Proposal for a Regulation of The European Parliament and of the Council Laying Down Harmonised Rules on Artificial Intelligence (Artificial Intelligence Act) and Amending Certain Union Legislative Acts; European Commission: Brussels, Belgium. 2021.

43. Andaur Navarro CL, Damen JAA, Takada T, Nijman SWJ, Dhiman P, Ma J, et al. (2021) Risk of bias in studies on prediction models developed using supervised machine learning techniques: systematic review. BMJ. 375: n2281.

44. Liem VGB, Hoeks SE, van Lier F, de Graaff JC (2018) What we can learn from Big Data about factors influencing perioperative outcome. Curr Opin Anaesthesiol, 31: 723-3