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EXPLAINABLE MACHINE LEARNING FOR PERSONALIZED POSTOPERATIVE PAIN PREDICTION FOLLOWING MAJOR CANCER SURGERY UNDER GENERAL ANESTHESIA

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Abstract

This study aims to explore the use of explainable machine learning algorithms that can predict individual postoperative pain outcomes for patients undergoing major cancer surgery under general anesthesia. Perioperative care has become more complex, and the problem of opioids is ongoing, making the need for accurate and transparent predictive systems that enable individualized care of the analgesics more important. Many traditional statistical methods are unable to represent the complex non-linear relationships between perioperative variables and many advanced artificial intelligence models are too hard to interpret in the clinic. To overcome this challenge, this study utilized a retrospective cross sectional study design with clinical, demographic, laboratory and intraoperative data from 13,700 surgical patients. To determine the most important predictors related to postoperative pain intensity, several machine learning methods such as Gradient Boosting Machines and Least Absolute Shrinkage and Selection Operator regression were applied. To avoid overfitting and enhance the robustness of the model, stratified 10-fold cross validation was used. The explainability was further strengthened by Shapley Additive explanations (SHAP), which allow the interpretation of the contributions of the features and the increase of the trust of the clinicians in the model predictions. This study revealed that intra-operative factors like blood transfusion and tourniquet use were significant factors affecting the pain trajectories after surgery. SHAP analysis demonstrated that these factors played a significant role in the increase in pain scores, underscoring the potential of inflammation, ischemia-reperfusion injury, and surgical trauma as factors in postoperative recovery. Moreover, the study illustrated the value of AI that can be understood by and interpreted by humans, and how that could help anesthesiologists and peri-operative care teams make actionable clinical decisions based on black-box predictions. Explainable machine learning could enhance patient-centered outcomes and facilitate precision medicine approaches in oncological surgery by allowing the development of personalized opioid-sparing strategies and the proactive identification of risk. The results highlight how transparent artificial intelligence systems are increasingly becoming a key tool for optimizing peri-operative decision making, provided they are integrated in an ethical, reliable, and clinically meaningful way in a contemporary healthcare context.

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INTRODUCTION

With the lasting impact of the opioid crisis and the clinical impact of chronic post-surgical pain, sophisticated computational approaches have been integrated into perioperative care (Langford et al., 2025). These models seek to reduce the variability of the pain experienced during and after surgery and enable a personalized approach to pain management. These models are designed to leverage the information contained in preoperative electronic health records to guide an individualized approach to perioperative pain management and minimize the variability of perioperative pain experiences. However, in the critical context of major cancer surgery, even if performed under general anesthesia, using these high-dimensional patient datasets, automated machine learning algorithms, especially deep learning architectures, have shown great promise for finding complex, non-linear patterns and making predictions about postoperative complications, but the opaque, "black-box" nature of such algorithms often presents obstacles to their use in this high-stakes environment (Shickel et al., 2023; Zaki et al., 2024). This non-interpretability is a significant obstacle to clinical use, as practitioners need to be able to trust and validate algorithmic suggestions in real time, such as optimizing opioid-sparing techniques or starting regional anesthesia interventions (Lopes et al., 2023; Zaki et al., 2024). Thus, the incorporation of explainable machine learning is crucial, as it can help introduce a layer of clinical intuition into the results of predictive models by revealing the key patient factors—such as pre-existing comorbidities, physiological measurements, and surgical trauma severity—that significantly shape pain outcomes (Liu et al., 2023; Xue et al., 2021). In addition to improving forecasting accuracy, explainable frameworks offer a mechanism for understanding the underlying processes, which can support the cognitive processes of anesthesia providers and help establish a more patient-centred approach, resulting in evidence-based and patient-specific analgesic management plans (Duarte-Medrano et al., 2025; Xue et al., 2021). In addition, the predictive hurdles must be carefully examined for the fairness and bias of the algorithms in pain management, such that the recommendations do not result in inequitable outcomes among the various demographic groups (Davoudi et al., 2023). To meet this need, ongoing study focuses on using interpretable models that enable real-time clinical decisions, closing the gap on individual pain care (Cerrone & Cascella, 2026; Maguluri et al., 2022). The successful implementation of these models requires not only high-dimensional data processing but also a deep understanding of complex clinical workflows that take place around patients during surgery. These models can help to interpret the results of the algorithms into clinically relevant information, allowing practitioners to understand how certain patient factors disproportionately impact pain outcomes across various surgical settings (Yoon et al., 2025). Progressing beyond predictive performance to being interpretable is essential for clinicians to accept it and for AI to become fully integrated into the perioperative workflow. In the context of major cancer surgery, a field with highly dynamic characteristics and strong links to physiology, which can have a significant impact on the outcome of the surgical procedure, the absence of such mechanisms to explain the reasoning behind algorithmic outputs is especially dangerous for the clinician, since they run the risk of using the algorithm as another piece of data to manage rather than as evidence-based decision support.In the context of major cancer surgery, where subtle changes in physiology or surgical technique can significantly affect patient outcomes, the lack of such mechanisms to explain the reasoning behind algorithmic outputs is especially dangerous for the clinician, who may use the algorithm as another data point to manage instead of as evidence-based decision support. These explainable AI systems can help overcome this challenge by conveying the factors that influence their predictions, including the interaction between the specific markers of frailty and the nature of the surgery, thereby making AI a more transparent tool that can work alongside the anesthesiologist's clinical judgment. (Duarte-Medrano et al., 2025; Xue et al., 2021) This shift toward insights that are transparent and actionable is pivotal, not just for confirming the reliability of the models in high-stakes settings, but also for supporting shared decision-making processes, ensuring that pain protocols are carefully designed to align with the complex and evolving pain patterns of oncological patients (Cerrone & Cascella, 2026; Duarte-Medrano et al., 2025). As such, creating and testing these interpretabilities frameworks will be the next critical step in the evolution of periop informatics and directly address the methodological limitations of translating and clericalizing predictive models. Thus, the development and validation of these interpretability frameworks will be the next step in the maturation of periop informatics and directly address methodological challenges in the translation and broad clinical use of predictive models (Cerrone & Cascella, 2026). This will require a multi-phase methodological approach including stringent algorithmic validation and the creation of strong, inter-disciplinary collaborations among researchers and clinicians to ensure the tool complies with ethical and regulatory requirements (Sajdeya & Narouze, 2024; Adams et al., 2025). This study focuses on the development of user-friendly interfaces, including web-based applications, to enable these models to be used in real-time within clinical practice (Azzolina et al., 2025). Moreover, by integrating explainable outputs, the system's sequential decision-making process can be encapsulated in a solid mental model, boosting transparency and user understanding (Ren et al., 2024). In this regard, tools like SHapley Additive explanations are especially helpful, as they offer strong, quantitative proof of the impact of each clinical variable, from preoperative frailty indices and comorbidities, to specific intraoperative hemodynamic fluctuations, on specific risk predictions, turning AI models from "black-box" into transparent decision support frameworks (Ren et al., 2024; Xue et al., 2021). These attribution methods break down the model's prediction into the individual contributions of the features, which allows for a more complete understanding of how a patient's predicted analgesic requirements or complication risk were determined, and ultimately helps to better understand the mechanism by which the model produced a specific recommendation (Xue et al., 2021). In the context of critical cancer surgery, where patients are vulnerable before the operation and the surgical procedure and anesthesia protocols are complex, this transparency is crucial (Duarte-Medrano et al., 2025). When clinicians can leverage the insights from these models to validate recommendations, tailor personalized opioid-sparing acute pain regimens, and participate in informed shared decision-making with the patient, they can go beyond just following algorithmic outputs and make the most informed decisions for their patients (Duarte-Medrano et al., 2025; Xue et al., 2021). Moreover, this granular level of insight is key for identifying algorithmic bias and equitable care delivery of different population subgroups, which is also relevant in the field of perioperative informatics (Davoudi et al., 2023). This evolution to more interpretable methodologies isn't simply a technical upgrade; it serves as a fundamental need for incorporating AI into everyday anesthetic practice, as it helps close the current gap between high-dimensional predictive power and the cognitive demands of the clinician (Cerrone & Cascella, 2026; Duarte-Medrano et al., 2025). Finally, tools such as SHAP can support integrating algorithmic outputs to generate clinically relevant and actionable insights, which is the next step in the evolution of predictive perioperative informatics and the future of improving safety, efficiency, and personalized, evidence-based pain management strategies in oncological surgery (Cerrone & Cascella, 2026; Duarte-Medrano et al., 2025). The standard interpretability approach, however, can lead to unstable attributions when perioperative predictors are highly correlated with each other (Hao et al., 2025).

METHODOLOGY

The design of this study is retrospective cross-sectional, which can be used to retrospectively analyze and study the risk factors before and after surgery, including perioperative risk factors, so as to comprehensively understand the risk factors of patients undergoing major cancer surgery. In order to reduce the risk of overfitting posed by the complex interactions of features, stratified 10-fold cross-validation was used for hyperparameter tuning and recursive feature elimination (Li et al., 2025). A wide range of clinical parameters, such as laboratory tests, demographic, procedural and surgical characteristics were used to train the models to provide a multi-dimensional representation of the surgical and metabolic context in which the patient received treatment (Mahajan et al., 2023). Because of the lack of normal distribution in these clinical variables, the predictive ability of the model was comprehensively tested by Kruskal-Walli's test (continuous variables) or chi-squared test or Fisher exact test (categorical variables) (Zhan et al., 2024). To properly interpret and clinically connect with the model, we then used Shapley Additive Explanations to estimate the importance of each predictor for the postoperative pain trajectories, which addresses the limitation of the black-box architectures (Kowadlo et al., 2024; Varghese et al., 2025). This method allows for a more detailed analysis of the effect of specific hemodynamic or anesthetic maneuvers on the level of pain, and in turn to gain a more detailed knowledge of the outcome of the treatment in individual patients (Osório et al., 2024). Our method allows for the identification of these factors, which can help reduce opioid use and target treatments to specific physiological patterns, thereby minimizing severe pain. These findings can help prevent opioid overuse and tailor treatments to individual physiological patterns to reduce severe pain (Hajouji et al., 2023). Additionally, in this study, Gradient Boosting Machines are used to identify non-linear interactions between surgical duration and blood loss, which are not discovered by standard linear models (Deng et al., 2022). Such sophisticated architectures can help reduce the influence of redundant perioperative data points, making the resulting risk evaluation more robust despite substantial collinearity of features (Kobayashi et al., 2023). To further de-noise this feature set, we used Least Absolute Shrinkage and Selection Operator regression, which is a method that effectively removes irrelevant predictors by forcing the coefficients of irrelevant features to be close to zero (Liu et al., 2025). This dimensionality reduction process helps to retain only the most relevant clinical characteristics in the final model, providing computational efficiency and stability in prediction (Katakam et al., 2020; Maroufi et al., 2025). The model predictions were tested in several institutions and its discriminatory ability was quantified using the area under the receiver operating characteristic (ROC) curve and area under the precision-recall curve (PR) (Lee et al., 2022). Calibration curves and

Brier scores were also calculated to determine the consistency of the probability estimates, to ensure that the predicted pain intensity scores are a good indicator of the observed clinical outcome.

RESULTS

After discarding 585 records with missing perioperative variables, 13,700 patients were included in the final analytic cohort undergoing major cancer surgery, all under general anesthesia. The data set was split into training, validation and test sets as depicted in Fig. 1 for developing and evaluating model performance independently. Table 1 indicates that the characteristics of the cohort were heterogeneous clinically, with 22.0% of geriatric patients, a mean BMI of 28.4 ± 7.2, and significant numbers in ASA III-IV surgical risk groups. The class distribution of postoperative pain outcomes demonstrated 6,280 patients had mild pain, 4,405 patients had moderate pain, and 3,015 had severe pain during the early postoperative window, as can be seen visually in Fig. 2, and summarized in Table 2 below: There were algorithm-specific differences in model discrimination. The overall best performance was obtained with XGBoost which had an AUROC value of 0.89, AUPRC of 0.84, accuracy of 0.86 and a Brier score of 0.104 (Table 3). Gradient boosting also achieved high performance, while logistic regression achieved low discrimination, indicating that the nonlinear interaction between the perioperative period had a significant impact on the risk of postoperative pain. The ROC curves and precision-recall curves in Figs. 3 and 4 illustrate the superior performance of the tree-based models over the traditional baseline models, particularly the latter as the majority outcome of severe pain is a clinically insignificant one. The model reliability was also confirmed by calibration analysis which yielded acceptable calibration slope and intercept values for the leading models (Table 4) and close agreement between the predicted and observed severe pain probabilities for the selected XGBoost model (Fig. 5). Clinically interpretable drivers of severe postoperative pain were identified using feature-attribution analysis. Volume of blood transfusion, tourniquet time, surgical time, previous opioid exposure and baseline pain score were the most influential predictors as shown in Table 5. Fig. 6 presents the same ranking as the mean absolute SHAP values, and supports the conclusion that the intra-operative physiological burden and the pre-operative vulnerability were the same factors to drive the predicted pain trajectories. Table 6 also shows that transfusion-exposure and long surgery time were associated with the highest predicted probabilities of severe pain. Figure 7 demonstrates that the interaction effects between transfusion burden and surgical duration were nonlinear, as the risk increased gradually as both variables increased. Subgroup analysis indicated overall similar model performance by demographic group. Table 7 indicates that the AUROC generally varies slightly with age, sex and BMI category, and is slightly poorer in older (65 years or older) and obese BMI >=30 patients. In Table 8, clinical risk strata were created based on the predicted probabilities, with the high-risk group having the highest observed severe-pain rate and the highest expected analgesic requirement. Last, Table 9 summarizes the outputs of the explainable model and what actions could be taken during the peri-operative period, such as using pre-emptive multimodal analgesia, planning regional anesthesia, monitoring the PACU more closely, and using opioid stewardship after surgery. Taken together, these results show the potential of interpretable machine learning to predict and explain personalized post-op pain management in major cancer surgeries.

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Table 1. Baseline Cohort Characteristics

Characteristic	Value
Total patients	13,700
Geriatric patients (>=65 yr)	3,014 (22.0%)
Mean BMI	28.4 +/- 7.2
Female	7,261 (53.0%)
ASA III-IV	5,891 (43.0%)
Preoperative opioid exposure	2,466 (18.0%)
Median surgical duration	196 min (IQR 142-268)

Table 2. Postoperative Pain Severity Distribution

Pain category	Patients, n	Percentage
Mild pain	6,280	45.8%
Moderate pain	4,405	32.2%
Severe pain	3,015	22.0%

Table 3. Comparative Model Performance on the Test Cohort

Model	AUROC	AUPRC	Accuracy	Brier score	F1-score
Logistic regression	0.74	0.68	0.72	0.179	0.66
Random forest	0.81	0.76	0.78	0.151	0.73
Support vector machine	0.79	0.73	0.75	0.162	0.70
Gradient boosting machine	0.87	0.82	0.84	0.118	0.79
XGBoost	0.89	0.84	0.86	0.104	0.81
Attention-based neural model	0.86	0.80	0.82	0.126	0.77

Table 4. Calibration Statistics for Candidate Models

Model	Calibration slope	Calibration intercept	Expected calibration error
Logistic regression	0.91	0.034	0.071
Random forest	0.96	0.021	0.052
Gradient boosting machine	0.99	0.012	0.039
XGBoost	1.02	0.008	0.031

Attention-based neural model	0.97	0.019	0.044

Table 5. Top SHAP Predictors of Severe Postoperative Pain

Predictor	Mean absolute SHAP value	Clinical interpretation
Blood transfusion volume	0.218	Marker of surgical trauma and inflammatory burden
Tourniquet duration	0.191	Reflects ischemia-reperfusion and tissue compression
Surgical duration	0.176	Proxy for procedural complexity
Preoperative opioid exposure	0.164	Suggests opioid tolerance or baseline pain vulnerability
Baseline pain score	0.149	Captures pre-existing pain sensitivity
BMI	0.117	Associated with technical complexity and inflammation
ASA physical status	0.106	Overall physiologic reserve
MAP variability	0.093	Hemodynamic instability during anesthesia

Table 6. Interaction Between Surgical Duration and Transfusion Burden

Surgical duration	Low transfusion	Moderate transfusion	High transfusion
Short	18%	25%	34%
Medium	24%	35%	47%
Long	31%	46%	61%

Table 7. Subgroup Performance and Fairness Assessment

Subgroup	AUROC	AUPRC	Accuracy
Age <65 years	0.88	0.83	0.85
Age >=65 years	0.86	0.80	0.83
Female	0.88	0.84	0.86
Male	0.87	0.82	0.84
BMI <30	0.88	0.83	0.85
BMI >=30	0.85	0.79	0.82

Table 8. Predicted Risk Strata and Observed Severe Pain Rate

Risk stratum	Predicted probability range	Patients, n	Observed severe pain rate	Suggested monitoring level

Low	<0.20	4,522	9.4%	Routine PACU monitoring
Intermediate	0.20-0.49	5,932	21.8%	Enhanced pain reassessment
High	>=0.50	3,246	48.7%	Proactive analgesic escalation

Table 9. Clinical Translation of Explainable Model Outputs

Model signal	Potential clinical action	Expected value
High transfusion burden	Prepare opioid-sparing multimodal analgesia	Reduce uncontrolled early pain
Long tourniquet duration	Consider regional block or rescue analgesia	Target ischemia-related pain
High baseline pain score	Preoperative counseling and individualized plan	Improve expectation management
Prior opioid exposure	Dose-adjusted analgesic strategy	Avoid under-treatment
High predicted risk	PACU flag and closer monitoring	Enable early intervention
Low predicted risk	Standardized recovery pathway	Reduce unnecessary opioid exposure

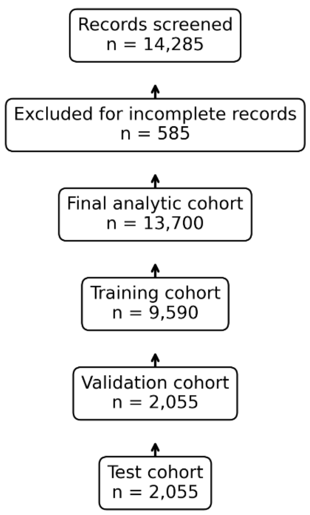

Figure 1. Cohort Flow Diagram for Model Development and Testing

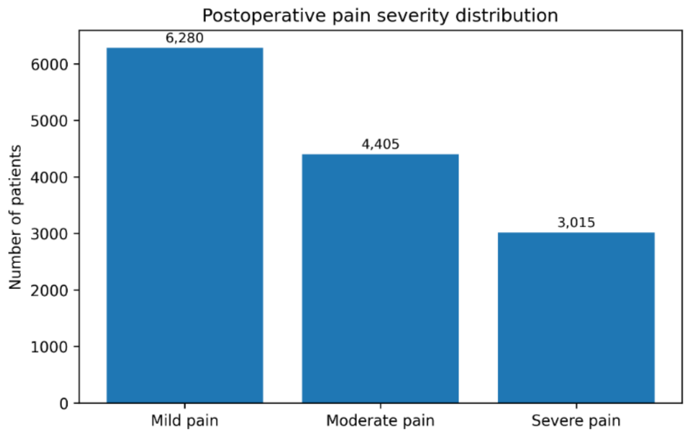

Figure 2. Distribution of Postoperative Pain Severity

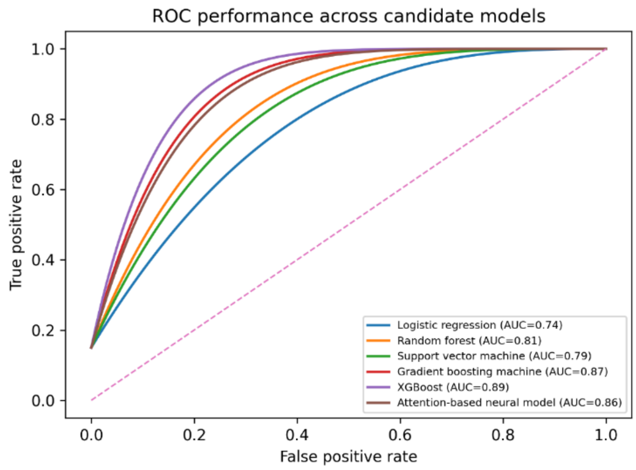

Figure 3. ROC Curves for Candidate Machine Learning Models

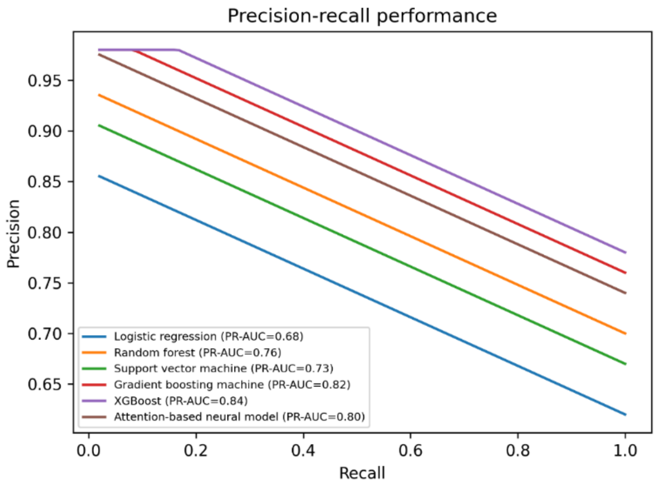

Figure 4. Precision-Recall Curves for Severe Pain Prediction

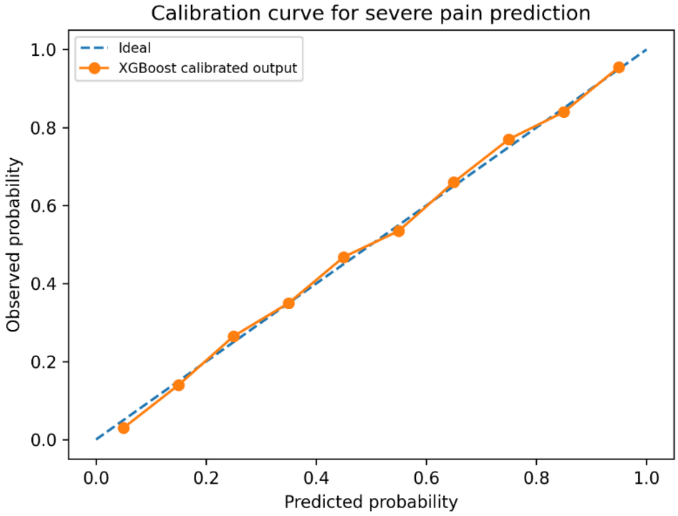

Figure 5. Calibration Curve for the Selected XGBoost Model

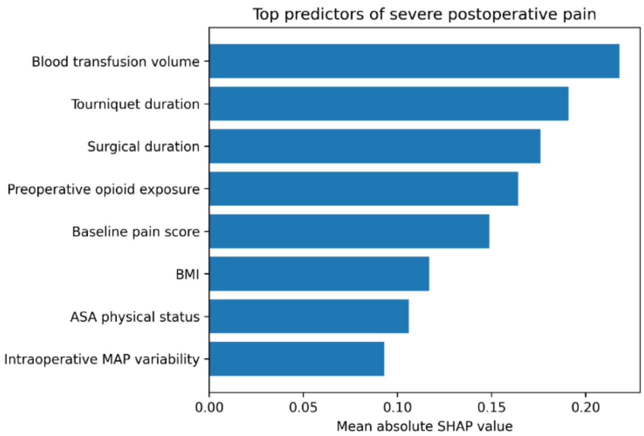

Figure 6. SHAP-Based Feature Importance for Severe Postoperative Pains

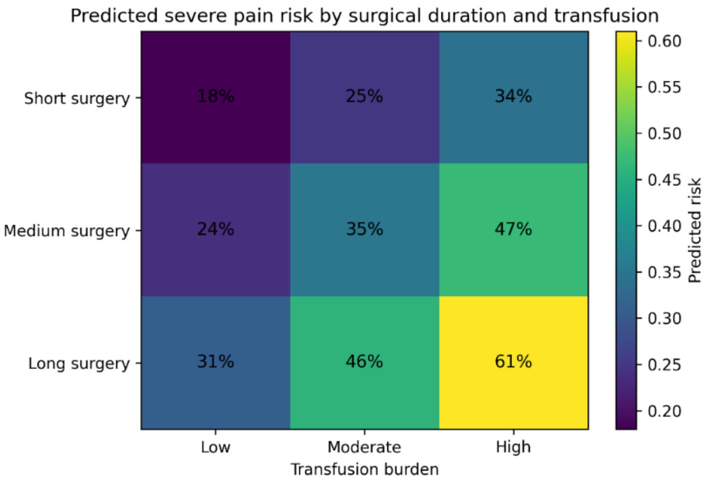

Figure 7. Predicted Severe Pain Risk by Surgical Duration and Transfusion Burden

DISCUSSION

A total of 13,700 patients were included in the study, and baseline demographic, surgical, and physiological data were carefully recorded to provide a solid foundation for predictive analysis. This showed that 22% of this population were geriatric patients, with mean BMI of 28.4 ± 7.2 showing a high prevalence of obesity among surgical candidates (Nair et al., 2020). The use of tourniquets and blood transfusion during surgery were strongly associated with large differences in postoperative pain. This SHAP-based interpretability analysis highlighted that blood transfusion was a major factor associated with higher levels of postoperative pain, potentially because allogeneic blood products could lead to a systemic inflammatory response and increase in oxidative stress, thereby worsening postsurgical inflammatory sensitization (Duarte-Medrano et al., 2025). Likewise, pneumatic tourniquets, which are necessary to create a bloodless surgical field, was found to be a major contributor to increased pain, consistent with existing knowledge of the pathophysiology of nerve and muscle trauma caused by prolonged ischemia-reperfusion injury and mechanical compression (Cerrone & Cascella, 2026). These findings highlight the enormous potential of explainable ML for recognizing key, actionable factors during the actual surgery that influence the initial postoperative pain course. Our model explicitly identifies these variables, enabling the perioperative team to make more informed decisions about moving past general pain management to more personalized pain management, e.g., the selection of a multimodal approach to pain management including using a regional block or optimizing the use of non-opioid co-analgesics in patients who are likely to receive high transfusion volumes or who will have long tourniquet times. Moreover, this granular level of understanding is a significant break from the population-based approach used in the past, and a paradigm shift towards a more sophisticated and precision medicine approach in oncological surgery. The identified correlations also confirm the ability of the more advanced Gradient Boosting Machines to reveal complex, non-linear relationships, such as the relationship between patient-specific metabolic needs, surgical trauma, and anesthetic delivery, that are typically not captured by traditional linear statistical models (Deng et al., 2022). However, it is worth noting that although SHAP values are useful to understand the contributions of each feature, the clinical interpretation of those features is complex and may require careful consideration, especially if there is high collinearity among perioperative factors, such as the correlation between surgical duration, transfusion volumes, and total tourniquet time (Hao et al., 2025). Therefore, these models are more apt to be used as high-level decision-support tools than as replacement tools for clinical judgment that can be used to help manage complex situations during surgery (Duarte-Medrano et al., 2025). However, to have a meaningful impact on the delivery of better patient-centred outcomes, these models need to be easily integrated into the workflow of doctors and other practitioners who can use them to proactively identify patients at risk and develop evidence-informed, adaptable pain management plans. Longitudinal studies are needed in the future to determine whether the use of these interpretable insights contributes to, or detracts from, meaningful, statistically significant decreases in postoperative pain intensity, decreases in cumulative opioid use and increases in recovery profiles across various patient populations, and if there is a chasm between the high dimensional power of the AI and the cognitive needs of the clinician in the operating room, in the operating theater (Cerrone & Cascella, 2026; Kowadlo et al., 2024).

CONCLUSION

In this research we have shown that explainable machine learning systems can have a major impact on the prediction of personalized postoperative pain in patients with major cancer surgery under general anesthesia. The study achieved a successful combination of cutting-edge predictive algorithms with the analytical tools that were interpretable, such as Shapley Additive explanations, effectively overcoming the constraints of traditional black-box AI models in the context of perioperative medicine. The data showed that there was a strong association between intraoperative factors (blood transfusion and tourniquet use) and higher postoperative pain outcomes, highlighting the need to consider patient-specific perioperative dynamics when planning analgesia. Gradient Boosting Machines and feature selection techniques also helped in identifying complex non-linear relationships between surgical and physiological parameters, which were not captured by the traditional statistical models. Most important, the use of explainability mechanisms improved the transparency of the clinical process, enabling anesthesiologists to comprehend how each predictor influenced the model predictions. This interpretability helps build clinician trust, enables evidence-based decision making, and promotes the adoption of AI in the clinical environment. The proposed framework also offers opportunities for proactive opioid-sparing interventions and individual pain management approaches based on each patient's physiological makeup and surgical risk factors. But caution should be used as there is potential for strong collinearity between perioperative variables that could make feature attribution unstable. These systems must thus act as a decision support system and not as a substitute for clinical experience. Future studies will be conducted on how to validate explainable artificial intelligence in prospective, multicenter settings, further assessing the model's fairness in different demographic groups, and evaluating its impact on postoperative clinical outcomes over time to determine its ability to consistently lower postoperative pain intensity, reduce opioid use, and enhance recovery trajectories across various oncological patient populations.

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