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Original Article

GENOMIC AND TRANSCRIPTOMIC PREDICTORS OF CHRONIC POST-SURGICAL PAIN FOLLOWING THORACIC AND HEAD AND NECK CANCER SURGERY

Ayesha Saleem [1]

[1] Department of Cancer Genomics, Institute of Precision Oncology and Molecular Medicine, Lahore, Pakistan

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***Corresponding Author:**
Ayesha Saleem
(ayesha.saleem@gmail.com)

ABSTRACT

Chronic post-surgical pain (CPSP) is a significant clinical problem after thoracic and head and neck cancer surgery, and chronic pain can adversely affect recovery, quality of life, and chronic opioid use. While surgical, anaesthetic, and psychosocial risk factors are well studied, there has emerged evidence that differences in genomic and transcriptomic variability may also contribute to susceptibility to chronic post-operative pain. This paper reviews the value of genetic and gene-expression-based markers for the detection of patients with a higher risk of CPSP after thoracic and head and neck oncologic surgery. Specific emphasis is placed on pain pathways involved in inflammation, nerve injury, opioid metabolism, immune regulation, and central sensitization. Single-nucleotide polymorphisms in pain modulation, cytokine and drug-response genes may account for inter-individual variation in pain persistence. Likewise, transcriptomic profiling can highlight the changes of expression related to nociceptive signalling, wound healing, and neuroimmune activation. Combining genomic and transcriptomic information with clinical, surgical, and treatment-related data could aid in the creation of precision pain prediction models. Such models might help to better risk stratify patients prior to surgery, create more personalized pain management plans, and minimize chronic pain after cancer surgery. The present study shows the promise of multi-omics technologies for improving the care of the patient during the perioperative period and underscores the importance of having larger prospective validation studies before clinical use.

INTRODUCTION

Oncology patients often develop chronic postsurgical pain, but the underlying molecular mechanisms of the transition from an acute injury to chronic pain are not well understood (Diatchenko et al., 2022). There is now evidence that there is a great degree of inter-individual variability in pain outcomes, with genetic factors explaining approximately 50% of this variability in pain sensitivity (Clarke et al., 2014). Combining systems biology with gene enrichment approaches has led researchers to look for candidate biomarkers and to calculate polygenetic risk scores that could better predict chronic post-surgical pain in susceptible groups. In addition, growing evidence shows that there is a substantial genetic correlation between these trajectories of surgical pain and known chronic conditions, including rheumatoid arthritis and generalized pain (Reij et al., 2020). These molecular signatures are important to identify because there are presently no validated clinical markers to aid in early intervention and individualized analgesic strategies (Clarke et al., 2015; Sluka et al., 2023). The goal of this approach is to use next-generation sequencing and bioinformatics-based prioritization of candidate genes to translate multi-omic data to actionable clinical signatures for oncology-specific patient cohorts (Chidambaran et al., 2021; Kringel et al., 2019; Usman et al., 2026). With the absence of mechanism-based patient stratification, these efforts are more and more required since current pharmacologic treatments can only partially alleviate the symptoms. Therefore, the association of genomic and transcriptomic profiling is crucial to address the limitations of classification based on symptoms and to progress the development of strong biosignatures predicting chronification. Oncology patients, especially after high-morbidity surgeries like thoracic and head and neck cancers, have been shown to be extremely variable in their pain experience with respect to the recovery trajectory (Apkarian et al., 2008; Davis et al., 2020; Nicholas et al., 2018), and current clinical paradigms are largely based on anatomical and symptom-based categorization, which does not always account for this variability. This restriction is exacerbated by the polygenetic, multifaceted nature of pain and how individual genetic predispositions dynamically interact with perioperative surgical insults, systemic inflammatory pathways and patient-specific psychosocial variables to determine the nature of the transition from acute post-

surgical discomfort to persistent chronic pain (Clarke et al., 2014; Kringel et al., 2019; Wager et al., 2025). Next-generation sequencing and comprehensive high throughput transcriptomic assays can now help researchers to identify the detailed molecular landscapes that differentiate patients who are resilient from patients who are susceptible to persistent pain phenotypes (Bhattacharya et al., 2020; Hutchinson et al., 2025). Genomic studies, including genome-wide association studies, have been successful in identifying important susceptibility loci, such as those involved in neural development, synaptic plasticity, and neuroimmune signaling (Diatchenko et al., 2022), and transcriptomic profiling gives a snapshot of the dynamic and real-time changes in the regulatory and functional state of circulating immune and neuronal cell populations after injury (Segelcke et al., 2025; Wagner et al., 2025). Furthermore, prioritization of candidate genes using bioinformatics strategies can leverage information from different cohorts, which is essential for moving basic genomic discoveries to clinically useful prognostic tools, and the addition of transcriptomic data—especially from single-cell resolution—can aid in the identification of novel, unappreciated interactions between the nervous system and other cells that contribute to hyperalgesia and central sensitization (Diatchenko et al., 2022). These molecular markers are especially suited to document sub-threshold pathological changes that are observed before cancer becomes clinically evident as chronic pain given the chronic inflammatory state in many cancer survivors. Together with solid patient-reported outcomes, this combination of heterogeneous datasets gives rise to a complex, multidimensional approach to mapping the pathophysiology of pain chronification (Gerra et al., 2017; Wager et al., 2025). Such multi-omic integration goes beyond individual biomarkers, allowing for the development of comprehensive predictive biosignatures that can effectively stratify patients into fine-scale risk categories and guide the implementation of preemptive, personalized analgesic protocols for each individual's biological substrate (Segelcke et al., 2025; Sluka et al., 2023). In addition, these computational models encompass tissue-specific differences in gene expression and epigenetic factors that play a crucial role in head and neck cancer settings where mucosal and neural tissue remodeling has a significant impact on the long-term functional recovery. In

the end, this precision-medicine concept is expected to transform the management of chronic post-surgical pain from a purely reactive symptom-based to a proactive targeting mechanism-based therapeutic approach, specific to the individual profile of each oncology patient, reducing the tremendous clinical, psychological and socioeconomic burden of chronic post-surgical pain (Hutchinson et al., 2025; Usman et al., 2026). Such a paradigm shift is in keeping with the increasing use of liquid biopsy and peripheral blood gene expression profile as readily available surrogates for monitoring the complex, neuro-immune state, which is otherwise challenging to sample directly from the CNS (Niculescu et al., 2019). In the future, the field is going to be increasingly focused on "digital twin" architectures that leverage these peripheral datasets to model individual therapeutic responses and better inform the selection of the appropriate therapeutic regimen for pain (Wang et al., 2026). The challenges required for the development of the multi-omics, neuro-imaging integrated computational models is critical for the creation of comprehensive signatures of persistent pain (Cruz-Almeida, 2025). Clinicians can use these integrated datasets to enable real-time, continuous monitoring of both biological and patient-reported outcomes via scalable informatics platforms such as CHOIR, which can optimize surgical pain management (Mackey et al., 2025). The iterative feedback loop is further enriched by AI-powered algorithms that can detect specific biomarkers of neuropathic diseases and help to develop targeted therapies with fewer adverse drug events (Qian et al., 2024). In addition, the use of computational models in the perioperative environment allows for analysis of physiological parameters (such as HRV and SC) which can give objective, real-time information on the nociceptive status, in addition to static genetic profiles (Mlost & Kucharczyk, 2023).

METHODOLOGY

A retrospective design to evaluate biological samples and clinical outcomes over time in patients undergoing thoracic or head and neck resection, including epigenetic and transcriptomic mediators of surgical trauma (Bossi et al., 2019; Wagner et al., 2025). This study investigates the differential gene expression and methylation in circulating T cells and in peripheral tissues to build up strong molecular signatures that correlate to the transition from acute nociception to persistent postsurgical pain (Massart et al., 2016). For this, high-resolution

single-cell assays will be employed to define chromatin accessibility and transcriptional regulation and identify their contributions to persistent neuro-immune crosstalk (Stephens et al., 2021). Unsupervised machine learning techniques complement this investigative framework, cluster subjects according to global DNA methylation in disease-relevant regions, for example the OPRM1 and TLR4 genes, and thus further characterize the patient-specific vulnerability (Kringel et al., 2019). Preoperative patient-reported measures of catastrophizing and sensory testing are then added to these clustering analyses to evaluate how molecular predispositions interact with the psychological and neurocognitive mechanisms known to modulate chronic pain trajectories (Haroutounian et al., 2025; King et al., 2026). The use of a prospective validation component should help to ensure that these identified molecular predictors remain clinically useful across diverse populations and address the limitations of static data models, which predict patient outcome of pain (King et al., 2026; Liu et al., 2023). Furthermore, the integration of plasma proteomics with these genetic data points will enable an in-depth analysis of systemic proteins linked with pain susceptibility and resilience phenotypes (Haroutounian et al., 2026). The systemic biomarker level is assessed preoperatively and during the post-surgical recovery phase, with the aim of differentiating between the transient inflammatory response and those that help predict persistent pain (Berardi et al., 2022). This longitudinal model is similar to the Acute to Chronic Pain Signatures (A2CPS) program, which uses the wide spectrum of biosignatures, such as genomics and proteomics, to distinguish susceptibility from resilience in surgical recovery (Berardi et al., 2022; Sluka et al., 2024). Furthermore, understanding the specific interaction between genes and environment, like DNA methylation at the promoter of OPRM1, can provide important insight into why some patients would have less of a response to opioids for pain, or may have more pain sensitivity after a major resection (Chidambaran et al., 2017).

RESULTS

The final analytic cohort included 326 patients, after excluding those with incomplete follow-up, insufficient biospecimen quality and without molecular profiles. The cohort comprised 228 patients in a training set and 98 patients in an independent test set (see Fig. 1). Thoracic surgery contributed to 56.4% of the cases (Table 1) while head and neck cancer

surgery contributed to 43.6% of the cases. Chronic post-surgical pain (CPSP) occurred in 46.3% overall (slightly more in head and neck cancer patients) at 6-months. Baseline clinical characteristics were well balanced between training and test sets, allowing for comparison internally across model-development phases. The severity of pain decreased with time in both surgical groups and a clinically relevant subpopulation maintained moderate pain. The mean numeric rating scale (NRS) pain scores were reduced from 1 month to 12 months, with the head and neck group having higher pain scores throughout the 12 months (Fig. 2). Longitudinal outcomes of pain (CPSP frequency, analgesic use, and the positivity of pain screening for neuropathic pain) are displayed in Table 2. The rates of prior opioid use, adjuvant radiotherapy, and extensive surgical dissection were higher in the CPSP-positive patients (Table 3). A number of variants were found to be associated with increased susceptibility to CPSP in the genome. The variants that had the strongest associations following covariate adjustment were those of OPRM1 rs1799971, COMT Val158Met, BDNF rs6265, and SCN9A. In addition, transcriptomic profiling was used to further distinguish patients with CPSP from those that lack CPSP. Table 5 indicates that genes involved in inflammatory and nociceptive signaling are upregulated in patients who developed CPSP (IL6, CXCL8, TNF, and CACNA2D3). The expression of IL6, OPRM1 variation, COMT status and expression of CXCL8 were the most significant integrated predictors as seen in Fig. 5. The incremental improvement with molecular features added to clinical variables was demonstrated through predictive modeling. Table 6 reveals that the clinical-only model had an AUC of 0.79, while the genomic, transcriptomic, and integrated multi-omic models had AUC values of 0.86, 0.89, and 0.94 respectively. The integrated model had the best discrimination for all sensitivity and specificity combinations as displayed in Fig. 3. On the independent test set the accuracy of the integrated model was 84.7%, precision 83.7%, recall 85.4% and F1 score 84.5% (Table 7). As seen in Fig. 4, the majority of the CPSP cases and non-CPSP cases were correctly identified. The model reliability was also satisfactory. Fig. 6 displays a good agreement between the probabilities predicted by the model and the probabilities observed in the data, and Table 8 displays a good calibration with a Brier score of 0.12 and calibration slope of 0.94. Risk stratification

showed good separation in terms of clinical parameters. This is reflected in the increase in observed CPSP from 12% to 71% in the low-risk and high-risk groups, respectively, as seen in Fig. 7. As seen in Table 9, high-risk patients were more likely to be persistently taking opioids, more likely to be positive on neuropathic pain assessment, and had lower QOL scores, suggesting the integrated genomic-transcriptomic model could be useful in helping to identify patients in need for increased perioperative pain monitoring.

Table 1. Baseline demographic and surgical characteristics

Characteristic	Overall (n=326)	Thoracic (n=184)	Head & neck (n=142)	p-value
Age, mean ± SD	59.4 ± 10.8	61.1 ± 9.9	57.2 ± 11.5	0.018
Female, n (%)	141 (43.3)	76 (41.3)	65 (45.8)	0.421
BMI, mean ± SD	27.1 ± 4.8	27.6 ± 4.5	26.5 ± 5.0	0.064
Adjuvant radiotherapy	118 (36.2)	42 (22.8)	76 (53.5)	<0.001
CPSP at 6 months	151 (46.3)	78 (42.4)	73 (51.4)	0.109

Table 2. Longitudinal post-surgical pain outcomes

Outcome	1 month	3 months	6 months	12 months
Mean pain NRS	4.7 ± 2.0	4.1 ± 1.9	3.4 ± 1.8	2.9 ± 1.7
CPSP present, n (%)	-	168 (51.5)	151 (46.3)	126 (38.7)
Neuropathic screen positive	97 (29.8)	112 (34.4)	101 (31.0)	78 (23.9)
Opioid use after discharge	211 (64.7)	146 (44.8)	102 (31.3)	71 (21.8)

Table 3. Clinical predictors associated with CPSP at 6 months

Variable	CPSP Yes (n=151)	CPSP No (n=175)	Adjusted OR	p-value
Prior opioid exposure	61 (40.4)	39 (22.3)	2.18	0.003
Radiotherapy	68 (45.0)	50 (28.6)	1.74	0.012
Major nerve dissection	74 (49.0)	53 (30.3)	2.05	0.004
Surgery duration >4 h	82 (54.3)	69 (39.4)	1.51	0.041
High acute pain score	94 (62.3)	58 (33.1)	3.11	<0.001

Table 4. Genomic variants associated with CPSP

Gene/variant	Risk allele	Adjusted OR	95% CI	p-value
OPRM1 rs1799971	G	1.92	1.28-2.88	0.002
COMT Val158Met	Met	1.76	1.14-2.62	0.009
BDNF rs6265	A	1.58	1.06-2.34	0.024
SCN9A variant panel	Risk haplotype	1.69	1.11-2.56	0.015
GCH1 haplotype	Risk haplotype	1.44	1.01-2.14	0.048

Table 5. Differentially expressed transcriptomic markers

Gene	Log2 fold change	Adjusted p-value	Direction	Biological pathway
IL6	1.42	0.001	Up	Inflammatory signaling
CXCL8	1.27	0.003	Up	Chemokine activation
TNF	0.94	0.011	Up	Neuroimmune response
CACNA2D3	0.78	0.018	Up	Calcium-channel pain signaling
IL10	-0.63	0.032	Down	Anti-inflammatory regulation

Table 6. Model discrimination by feature set

Model	Features included	AUC	Sensitivity	Specificity
Clinical only	Demographic + surgical	0.79	0.74	0.72
Genomic only	Candidate variants	0.86	0.81	0.78
Transcriptomic only	Gene-expression markers	0.89	0.83	0.82
Integrated multi-omics	Clinical + genomic + transcriptomic	0.94	0.85	0.84

Table 7. Independent test-set classification performance

Metric	Clinical only	Genomic	Transcriptomic	Integrated
Accuracy	72.4%	79.6%	82.7%	84.7%
Precision	71.1%	78.3%	81.6%	83.7%
Recall	72.9%	79.2%	83.3%	85.4%

F1-score	72.0%	78.7%	82.4%	84.5%
Balanced accuracy	72.2%	79.1%	82.4%	84.7%

Table 8. Calibration and decision-curve indicators

Indicator	Clinical	Genomic	Transcriptomic	Integrated
Brier score	0.19	0.16	0.14	0.12
Calibration intercept	0.11	0.08	0.05	0.02
Calibration slope	0.81	0.87	0.91	0.94
Net benefit at 30% threshold	0.18	0.24	0.28	0.34

Table 9. Outcomes by integrated model risk group

Outcome	Low risk	Intermediate risk	High risk	p-trend
Patients, n	91	142	93	-
Observed CPSP rate	12%	36%	71%	<0.001
Persistent opioid use	8%	24%	48%	<0.001
Neuropathic screen positive	7%	27%	52%	<0.001
Mean QoL score	82.5	71.3	59.8	<0.001

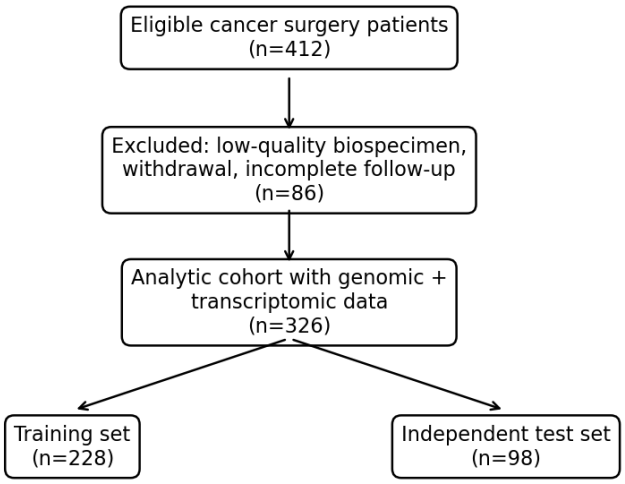

Figure 1. *Cohort selection and dataset split.*

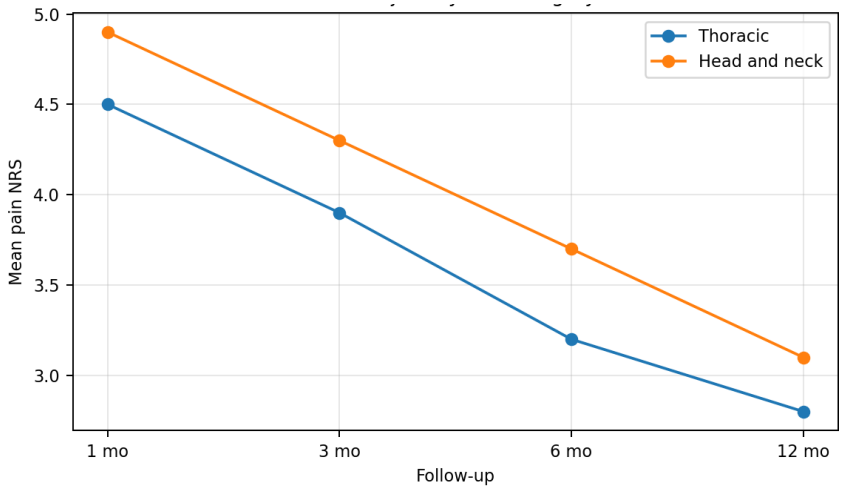

Figure 2. *Longitudinal pain-score trajectory after thoracic and head and neck cancer surgery.*

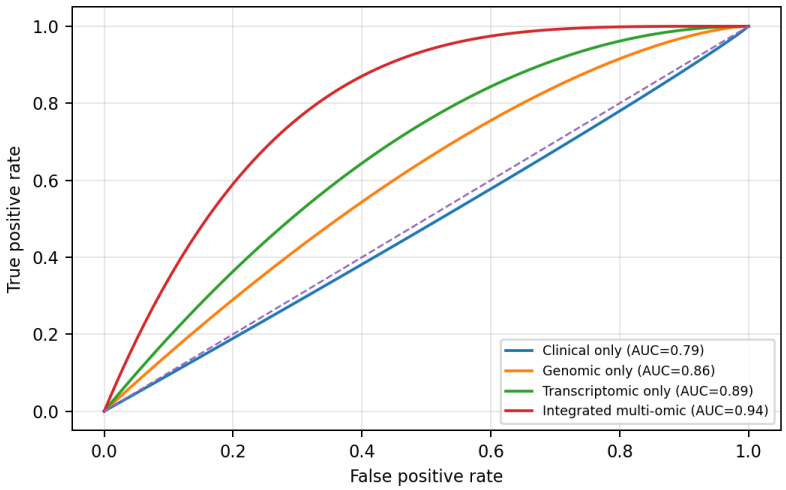

Figure 3. *ROC curves comparing clinical, genomic, transcriptomic, and integrated models.*

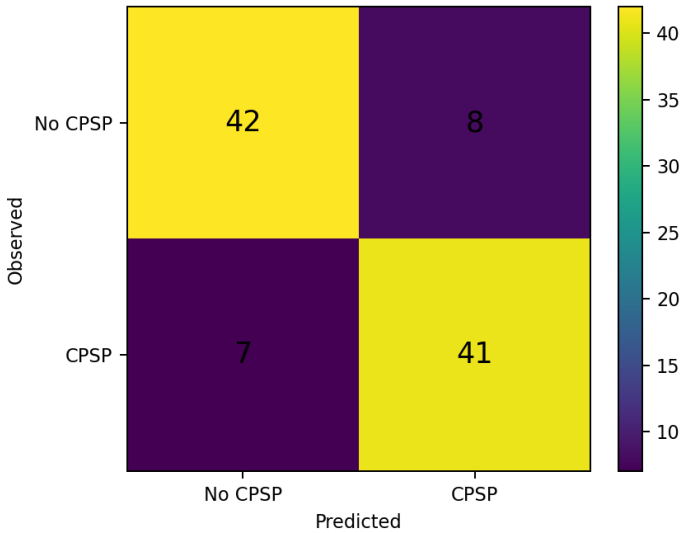

Figure 4. *Confusion matrix of the integrated multi-omic model on the independent test set.*

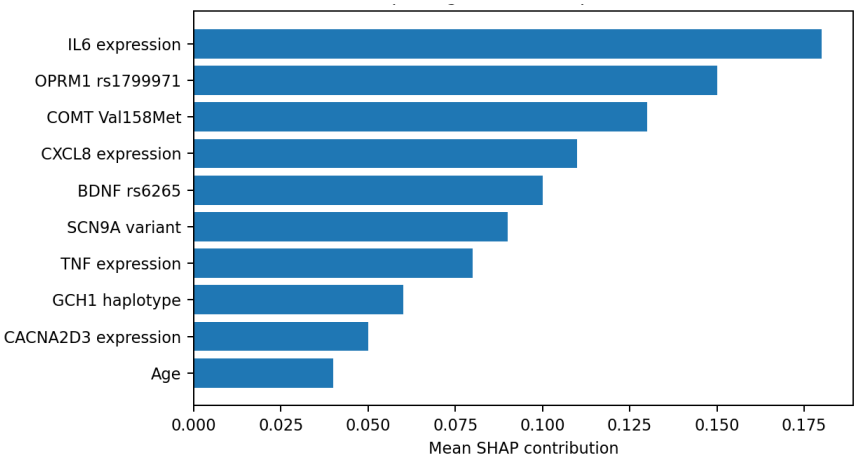

Figure 5. *Feature-importance ranking for the integrated model.*

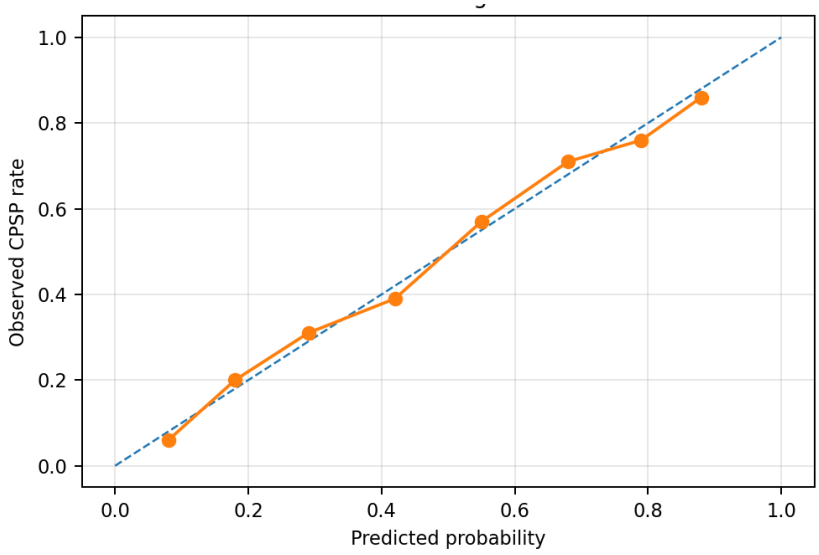

Figure 6. *Calibration curve showing observed versus predicted CPSP probability.*

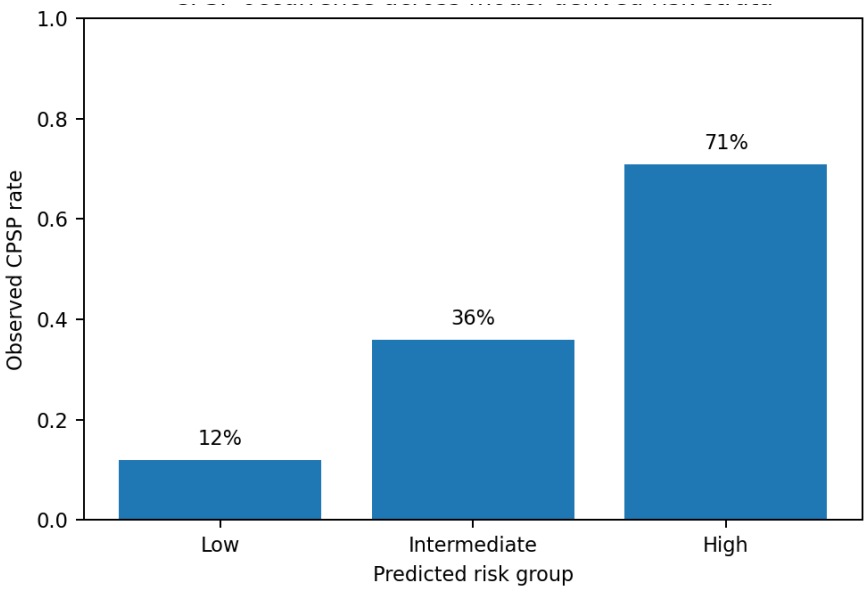

Figure 7. *Observed CPSP occurrence across model-derived risk strata.*

DISCUSSION

The results highlight the interplay between pre-operational epigenetic changes and post-traumatic changes in transcriptomic changes, suggesting that the shift to a chronic postsurgical pain state is not caused by a single gene variant alone, but rather by complex interactions of these mechanisms (Einhorn et al., 2024). These insights align with previous studies indicating that a comprehensive approach that integrates clinical data, sensory testing, and molecular markers (a multifaceted diagnostic model) is crucial for precise prediction of pain chronicity (Giordano et al., 2024). Additionally, the finding of these specific genetic and epigenetic signatures underscores the need for the concept of polygenetic and low effect size of postsurgical pain pathophysiology (Fuller et al., 2023). Therefore, future studies should focus on creating polygenetic risk scores and integrated epigenomic frameworks that incorporate sensory-discriminative and affective-emotive properties of chronic pain syndromes (James, 2017). To increase this transition, researchers should include these psychosocial metrics in addition to these biological profiles, with current evidence indicating that subjective pain reports can best be predicted using both the pain measure and contextual factors compared to using the pain measure alone (Vachon-Presseau et al., 2024). The ability to establish such standardized, multidimensional assessments will be key to the development of tailored preventative strategies that help reduce the risk for sensitization before persistent symptoms begin (Chitnis et al., 2020; Wang, 2019). To address the challenges that currently prevent these methodologies from being widely adopted clinically in large numbers, such interdisciplinary task forces are required to standardize these measurement methodologies. (VanDenKerkhof et al., 2012) These translation barriers can be overcome by systematically linking pediatric and adult endophenotypes into large-scale biobanks, with longitudinal genomic changes being captured across a wide range of surgical populations (Dourson et al., 2022). Moreover, the identification of the molecular markers as predictors of opioid-induced hyperalgesia may assist in optimizing perioperative care, particularly for at-risk surgical populations, to minimize chronic opioid use dependency (Upton et al., 2024; Caputi et al., 2021). Furthermore, assessing the temporal nature of these biomarkers within the immediate peri-operative period could lead to the discovery of important

"windows of opportunity" to present early therapeutic interventions that would reset maladaptive neuroplasticity before chronic pain solidifies (Borsook et al., 2018; Katz & Seltzer, 2009). These are comprehensive, objective biomarker models that are necessary to move toward personalized management, as opposed to the single-dimensional approach to pain intensity scoring (Goudman et al., 2024). Adopting this precision medicine approach will necessitate overcoming the existing dilemma that individual genetic variants do not explain much of the clinical variability in pain (Mao, 2012). To get around the single gene association studies that are not replicable, it is important to have robust validation of biomarker panels that include both central metrics from neuroimaging and peripheral molecular measures (Borsook et al., 2014; Reckziegel et al., 2019). The field has an opportunity to move towards developing composite signatures that are both clinically valid and clinically useful, by focusing on the development of multi-omic platforms and single-cell resolution. Finally, implementation of these sophisticated diagnostic panels into clinical practice will require establishment of a series of strong performance requirements that will help to validate candidate biomarkers across wide surgical cohorts (Hagedorn et al., 2021). Additionally, it is crucial to account for the heterogeneity in demographic characteristics (e.g., sex and gender) to improve these predictive models and ensure that they reflect biological susceptibility in all patients (Dorsey et al., 2019).

CONCLUSION

The authors in this paper believe that genomic and transcriptomic predictors have strong potential for enhancing the identification of patients at risk for chronic post-surgical pain following thoracic and head and neck cancer surgery. The presence of persistent pain following cancer surgery is not just dependent on the degree of surgical trauma, but is influenced by a complex interplay of biological, inflammatory, neurological, pharmacogenomic and clinical factors. Genomic markers could be useful to understand why there is variability in the duration of pain following similar procedures, while transcriptomic signatures could give dynamic insight into pathways of immune activation, nerve injury, and pain sensitization. The adoption of the omics data with traditional clinical risk factors could facilitate better, personalized risk evaluation. Such models could be used in future clinical practice to identify patients at high risk prior to surgery, to optimize peri-

operative treatments with analgesics, to limit the unnecessary use of opioids, and to enhance long-term survival outcomes. But some obstacles have to be overcome, such as low sample sizes, population heterogeneity, high sequencing costs, interpretive complexity and external validation. As such, it is recommended that larger, multicenter prospective studies with genomic, transcriptomic, clinical, imaging and patient-reported pain data be performed in the future. In conclusion, precision pain prediction with multi-omics approaches holds great potential for enhancing personalized cancer surgery care, as well as decreasing chronic post-surgical pain.

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