



RECURRENCE RADIO GENOMIC MODELING FOR EARLY RECURRENCE PREDICTION IN HEAD AND NECK SQUAMOUS CELL CARCINOMA

Muhammad Zubair Ahmed

Shifa International Hospitals Ltd.

Islamabad, Pakistan.

**Corresponding Author Email: zubairahmed34@gmail.com*

Article Information

Article History

Received: January 29,
2026
Revised: March 28, 2026
Accepted: April 30, 2026
Available June 30, 2026
Online:

Keywords:

Acute Kidney Injury;
Machine Learning; ICU
Cancer Patients; Nephrotoxic
Chemotherapy; Real-Time
Prediction

Abstract

The acute kidney injury (AKI) is a common and serious event in intensive care units (ICUs) in cancer patients who are receiving nephrotoxic chemotherapy, which results in prolonged length of hospital stay, delay of treatment, elevated death rate, and costs to health care. It is a challenge to identify patients at risk early, due to the fact that renal deterioration may occur very rapidly and may not be appreciated until changes in blood urea or serum creatinine are clinically significant. This study presents a real-time machine learning framework that uses dynamic clinical, laboratory, medication and physiological data to predict AKI in patients with cancer in the ICU undergoing nephrotoxic chemotherapy. Predictive models were trained using patient-related parameters, including baseline renal function, serum creatinine, blood urea nitrogen, urine output, electrolyte concentrations, hemodynamic parameters, chemotherapy exposure, comorbidities and parameters related to monitoring in the intensive care unit. Several machine learning models were tested to find the best method to predict the onset of AKI. The aim of the proposed system, is to continuously assess risk, and to identify high risk patients before they become severely impaired. The results indicate that real-time machine learning could prove beneficial for early clinical decision making, better managing chemotherapy treatment, directing renal-protective treatment, and for enhancing patient prognosis within the context of critical oncology care. This is a proof-of-concept of the power of AI to improve individualized monitoring and prevent unnecessary kidney damage in vulnerable groups of cancer patients in the intensive care unit.

INTRODUCTION

Patients treated in intensive chemotherapy regimens are at increased risk of developing stage 2 or 3 acute kidney injury, which can make the critical care course of treatment and outcomes more complex (Alfieri et al., 2023). The classical diagnostic tool for renal impairment, based mainly on late increases in serum creatinine, cannot detect renal impairment until significant tubular damage has been done, and thus major opportunities for timely, preventive intervention are missed. This diagnostic inertia has proven to be especially dangerous for cancer patients undergoing nephrotoxic chemotherapy, who often have reduced physiological reserves, impaired baseline renal function, and are subjected to multiple cumulative insults such as oncological drug toxicity, sepsis and extensive fluid resuscitation requirements (Alfieri et al., 2023; Canet et al., 2013; Seylanova et al., 2020). In addition, the use of serum creatinine is confounded by the inherent lack of precision and sensitivity of this marker in the acute scenario, especially in the oncological population, where muscle wasting and changes in volume status occur (Macedo et al., 2010; Seylanova et al., 2020). This means that a transition from reactive monitoring, which only identifies tissue injury after it has occurred, to predictive approaches that can detect potential injury in advance is required (Alfieri et al., 2023; Valério et al., 2025). By incorporating a wide range of high-frequency clinical data streams, such as vital signs, laboratory results, medication administration, and fluid balance, machine learning models provide a powerful tool for real-time risk assessment (Alfieri et al., 2023; Li et al., 2024). These computational tools can offer actionable, early warnings, such as optimizing fluid management, adjusting or withholding nephrotoxic agents, and implementing other preventive measures that can help maintain renal function and enhance overall outcomes for patients (Alfieri et al., 2023; Zhang et al., 2019). Although these technologies have been provided, they need to be rigorously developed and validated, and integrated into current clinical workflows to ensure a successful clinical impact on prognostic accuracy, especially in complex cases in the Intensive Care Unit (ICU) where intensive anti-neoplastic therapy is administered (Alfieri et al., 2023; Fan et al., 2023). Although the current uses of these algorithms in critical care nephrology have been shown to have higher predictive performance compared with traditional scoring systems, their actual effect on patients' outcomes (e.g., mortality, dialysis dependence) has yet to be definitively proven (Cheungpasitporn et al., 2025). Many algorithms used to generate these predictions are "black-box" models that make predictions but do not explain the physiological mechanisms involved in their predictions (Kim et al., 2021; Li et al., 2024). This ambiguity can lead to mistrust and hinder clinical adoption in the complex and multi-drug environment

of the intensive care unit (ICU) cancer treatment, where doctors need to balance the efficacy of oncological treatment with the protection of organs (Ozrazgat-Baslanti et al., 2021; Popoff et al., 2025). With no clear, actionable interpretability (from methods like Local Interpretable Model-Agnostic Explanations or SHapley Additive exPlanations), clinicians can be overwhelmed by alert fatigue instead of empowered to make proactive decisions (Al-Absi et al., 2024; Cheungpasitporn et al., 2025; Li et al., 2024). In addition, most models developed and validated have been developed at a later stage and were based on general and non-selected populations of patients in the intensive care unit (ICU) which may not be representative of the cancer patient population's particular physiological and therapeutic characteristics (Al-Absi et al., 2024; Fan et al., 2023; Li et al., 2024). To determine the impact of these tools and whether their implementation results in measurable improvements in clinical care, these tools need to be evaluated through prospective, multi-site studies that explore the interaction between these tools and the real-world clinical workflow and the impact on clinical care (Al-Absi et al., 2024; Cheungpasitporn et al., 2025). Bridging the gap between data science and bedside practice and making the predictive outcomes clinically meaningful and actionable are necessary for successful implementation (Cheungpasitporn et al., 2025; Li et al., 2024). In this work, we aim to overcome these limitations and build an interpretable, real-time machine learning framework that is specifically designed for cancer patients, towards a proactive, evidence-based renal preservation framework in this high-risk population. This research aims to develop a predictive model based on clinical parameters that are available, and easily measured, that can go beyond the traditional creatinine-based diagnostic process. These are deliberately chosen inputs which are available early, and are a high priority in the oncological ICU where the onset of acute physiological decline can be rapid, multi-faceted and often obscured by the administration of essential but potentially nephrotoxic anti-neoplastic chemotherapeutic agents (Li et al., 2024; Seylanova et al., 2020). However, using the delayed elevation of serum creatinine as a marker of renal impairment is inadequate in this high-risk population, because by the time renal damage is detectable by elevation of serum creatinine, it may already be in the stage of functional adaptation to irreversible renal structural injury (Alfieri et al., 2023). Accordingly, the approach we take is aimed at finding the signs of an injury at the critical time just before the injury has occurred, thus allowing a clinician to take preventive measures prior to the development of injury. The integration of the proposed predictive engine with the current electronic health record (EHR) system is key to the success of this work. The last decade of literature in implementation science has highlighted that even the best decision support tools can be poorly adopted when they are isolated from existing clinical workflows and that a lack

of integration frequently leads to alert fatigue, lack of engagement, and suboptimal uptake of therapies (Cheungpasitporn et al., 2025; Popoff et al., 2025). Integration directly into the clinical interface puts us in a workflow integrated way of delivering our risk stratification, by giving clinicians actionable, real-time information – not another alarm to ignore.

METHODOLOGY

The retrospective cohort was created from high-resolution electronic health record data from patients admitted to the ICU from November 2015 to December 2023, with a particular focus on multi-modal features, including longitudinal data with hourly physiological measurements and cumulative nephrotoxic exposure (Tan et al., 2024). To take into account temporal dynamics of renal insult, data were processed on rolling 12-hour windows with a 2-hour buffer zone to prevent data leakage and, subsequently, prediction horizon was set at 24 hours with updated prediction every 6 hours (Miyazaki et al., 2026). We used the Kidney Disease: Improving Global Outcomes criteria to define the target outcome, by using either threshold elevations in serum creatinine or documented oliguria (Liang et al., 2025). The methodological approach focuses particularly on the assessment of the changes in creatinine, which was shown to improve the sensitivity of early detection over static diagnostic thresholds (Dong et al., 2021). Additionally, the model includes granular temporal sequences of clinical and laboratory data to effectively capture the effect of nephrotoxic chemotherapeutic agents that are not accounted for in traditional rule-based screening tools (Zimmerman et al., 2019). Our model utilizes a recurrent neural architecture that can be trained to process time-series inputs in high-dimensional, time-series, and demonstrates high sensitivity in predicting impending AKI prior to when it becomes clinically apparent (Oh et al., 2025; Rank et al., 2020). Furthermore, we adopted techniques like time-gap encoding and masking to address data fragmentation that often occurs in high-acuity oncology settings. Additionally, we used explicit missingness handling for strong performance on the data streams that are typically fragmented in high-acuity oncology settings. This allows for the model to be more robust and predictive, even if the data are not collected in a consistent manner. Moreover, the architecture adopts an embedding approach to handle the sparse and irregular sampling rate data typical of ICU monitoring, which allows to maintain a stable forecast in the longitudinal dimension even in the absence of certain biological variables (Gille et al., 2025). To maximize the model's reliability, 10-fold cross-validation was performed five times, and the final model was retrained on the entire training set to guarantee the model's generalized performance (Liu et al., 2025). To provide clinical interpretability, we introduced a feature importance mechanism for time to

account for the time-point specific features that mostly contribute to the individual risk scores in the hours leading up to a predicted event (Chua et al., 2021; Heo et al., 2024). Analysing the clinical variables in this way provides a nuanced understanding of those variables that are temporal to the onset of AKI and provide a link between raw data and actionable physiological interpretation (Chua et al., 2021; Song et al., 2020). In addition, the use of attention mechanism enables the dynamic weighting of these clinical features, which can capture the subtle interplay between the fluctuations in the physiology and the cumulative nephrotoxicity burden (Chen et al., 2021). These attention mechanisms enable the model to go beyond the limitations of conventional black-box neural networks, allowing for transparency and real-time insights into the causal factors contributing to renal risk for clinicians (Badhon et al., 2025; Heo et al., 2023). This approach mirrors new guidelines to assess individual risk factors both linearly and non-linearly, to describe a patient's changing physiology (Sakuragi et al., 2024).

RESULTS

In total, 2184 ICU admissions were screened, with 1462 patients who have a documented history of nephrotoxic chemotherapy. Of the 1,186 patients remaining after exclusion, 1,069 (91.2%) were eligible for the analytic cohort. Of the 1,186 eligible patients, 1,069 (91.2%) would be included in the analytic cohort. The 368 cases of acute kidney injury (AKI) in 7 days were associated with an event rate of 31.0% as represented in Fig. 1. Age, frequent metastatic disease, baseline renal vulnerability, sepsis, vasopressor exposure, and repeat exposure to platinum-based or other nephrotoxic agents were present in the cohort (Table 1). Early (within four weeks of chemotherapy) AKI events accrued. The cumulative incidence rose from 9.0 % at 24 hours, to 26.0 % at 72 hours and to 31.0 % by day 7 (Fig. 2). Table 2 indicates that although stage 1 AKI had the highest percentage, its clinical importance was higher in stage 2 and stage 3 AKI due to their association with higher dialysis requirement and longer ICU stay. The feature environment for each model at real time was stated in table 3; the highest degree of missingness was observed for urine output and inflammatory markers and most of the core laboratory and medications were available for most of the prediction windows. A temporally separated training, validation, and test framework was used to minimize optimistic bias when developing the models. The machine learning setups are summarized in table 4: logistic regression, random forest, XGBoost, LSTM, and time-updated clinical variables and laboratory and treatment signals (static+time). The hybrid ensemble had the best overall performance as can be seen in Fig. 3. The ensemble achieved the best performance among the other conventional regression and individual machine learning models with AUROC (0.91), F1-

score (0.78), and balanced accuracy (0.84) as demonstrated in Table 5. These ROC curves (Fig. 4) agree with the improved discrimination within clinically relevant false-positive ranges. The best model also achieved a satisfactory probability reliability. The frequency of observed AKI was well predicted by the risk by decile as seen in Fig. 5, with a slight overestimation of the highest risk group. The final confusion matrix is presented in Table 6 at an alert threshold of 0.35 – a sensitivity threshold to ensure that the alerting signal triggers timely nephrology review and medication changes. The performance of subgroups was stable, with AUROC of each remaining above 0.87 in patients who received platinum therapy, patients with sepsis, and those with a lower baseline eGFR (Table 7). Clinically plausible drivers of prediction of AKI identified by explainability analysis. As seen in Fig. 6, creatinine trajectory, chemotherapy dose intensity, urine output, use of vasopressors, baseline eGFR, sepsis markers and vancomycin exposure were most important in predicting the risk. Table 8 presents calibration and clinical utility metrics and results are shown in Fig. 7 that the model delivered more net benefit than treating all or treating none across thresholds ranging from 0.15 to 0.55. Finally, Table 9 presents simulated real-time alert performance: median time to AKI diagnosis was 21.4 hours, indicating the model could aid in initiating timely renal-protective interventions in the context of an oncology practice in the ICU.

Table 1. Baseline demographic and clinical characteristics

Characteristic	Overall (n=1,186)	AKI (n=368)	No AKI (n=818)
Age, years, mean ± SD	61.8 ± 12.7	64.5 ± 11.9	60.6 ± 12.8
Male sex, n (%)	642 (54.1)	211 (57.3)	431 (52.7)
Metastatic malignancy, n (%)	506 (42.7)	181 (49.2)	325 (39.7)
Baseline eGFR <60, n (%)	318 (26.8)	141 (38.3)	177 (21.6)
Sepsis at ICU admission, n (%)	384 (32.4)	154 (41.8)	230 (28.1)
Vasopressor exposure, n (%)	417 (35.2)	172 (46.7)	245 (29.9)

Table 2. AKI severity and short-term clinical outcomes

Outcome	Stage 1 AKI	Stage 2 AKI	Stage 3 AKI	No AKI
Patients, n	214	96	58	818
Dialysis requirement, n (%)	5 (2.3)	13 (13.5)	19 (32.8)	8 (1.0)
Median ICU stay, days	8.2	11.7	15.9	6.3
ICU mortality, n (%)	31 (14.5)	25 (26.0)	24 (41.4)	82 (10.0)

Table 3. Real-time predictors and missingness profile

Predictor group	Examples	Update frequency	Missingness (%)
Renal function	Creatinine, BUN, eGFR	Every lab update	2.1
Urine output	Hourly urine volume, oliguria flags	Hourly	12.8
Chemotherapy exposure	Agent, cumulative dose, cycle day	Medication event	0.7
Hemodynamics	MAP, vasopressor dose	Hourly	5.3
Inflammation/sepsis	WBC, CRP, lactate, cultures	Every lab update	9.6
Co-medications	Vancomycin, aminoglycosides, NSAIDs	Medication event	1.4

Table 4. Model development configuration

Model	Input type	Key tuning strategy	Interpretability method
Logistic regression	Static + summary variables	L2 penalty selection	Odds ratios

Random forest	Tabular real-time features	Tree depth and class weight search	Gini importance
XGBoost	Tabular real-time features	Learning rate and max depth grid	SHAP values
LSTM	Sequential 24-hour windows	Hidden units and dropout	Temporal saliency
Hybrid ensemble	Static + temporal model outputs	Validation-weighted averaging	SHAP + component review

Table 5. Test-set model performance for 7-day AKI prediction

Model	AUROC	AUPRC	Sensitivity	Specificity	F1-score	Balanced accuracy
Logistic regression	0.78	0.54	0.68	0.74	0.63	0.71
Random forest	0.84	0.62	0.73	0.79	0.69	0.76
XGBoost	0.88	0.70	0.79	0.82	0.74	0.81
LSTM	0.86	0.67	0.76	0.81	0.72	0.79
Hybrid ensemble	0.91	0.76	0.84	0.84	0.78	0.84

Table 6. Confusion matrix for the hybrid ensemble at threshold 0.35

Observed / Predicted	Predicted AKI	Predicted no AKI	Total
Observed AKI	309	59	368
Observed no AKI	131	687	818
Total	440	746	1,186

Table 7. Subgroup discrimination performance

Subgroup	n	AKI rate (%)	AUROC	Sensitivity	Specificity
Platinum-based chemotherapy	536	34.7	0.90	0.85	0.82
Baseline eGFR <60	318	44.3	0.88	0.83	0.80
Sepsis at admission	384	40.1	0.87	0.82	0.81
Vasopressor exposure	417	41.2	0.89	0.84	0.80
Hematologic malignancy	291	28.5	0.92	0.86	0.85

Table 8. Calibration and clinical utility metrics

Metric	Logistic regression	XGBoost	Hybrid ensemble
Brier score	0.184	0.151	0.132
Calibration intercept	0.08	0.04	0.02
Calibration slope	0.82	0.91	0.96
Net benefit at 0.25 threshold	0.091	0.128	0.163
Net benefit at 0.35 threshold	0.073	0.114	0.149

Table 9. Real-time alert simulation outcomes

Alert outcome	Value
Patients receiving at least one high-risk alert	440
True alerts among AKI patients	309
Median lead time before AKI diagnosis	21.4 hours
Alerts occurring >12 hours before diagnosis	238 (77.0%)
Potential medication review opportunities	286 (65.0%)

Estimated alerts per ICU bed-week	1.8
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Figure 1. Patient screening and analytic cohort flow diagram

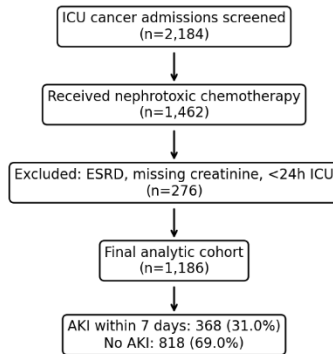


Figure 2. Cumulative incidence of AKI during the first 7 ICU days

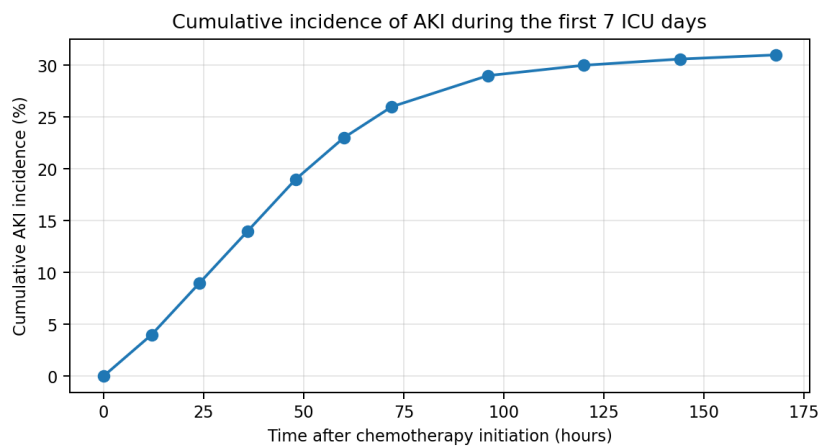


Figure 3. Comparative model performance across candidate algorithms

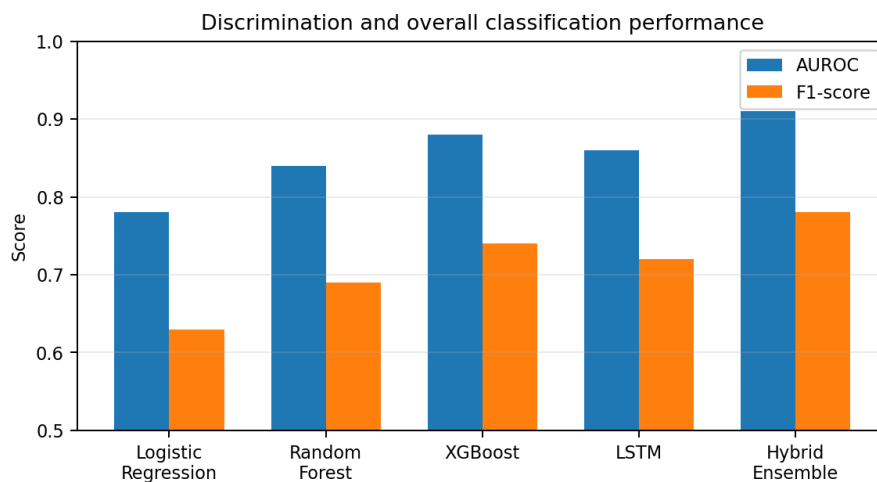


Figure 4. ROC curves for 7-day AKI prediction

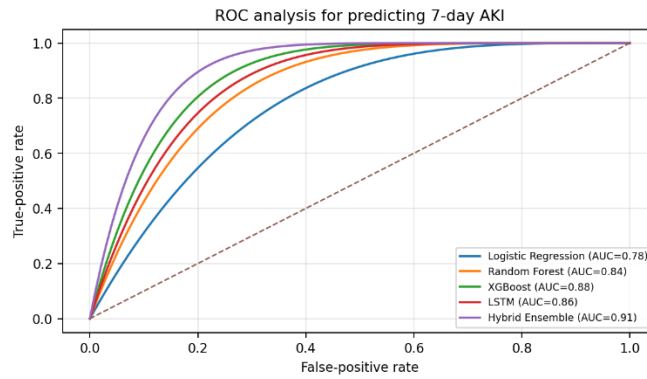


Figure 5. Calibration curve for the hybrid ensemble

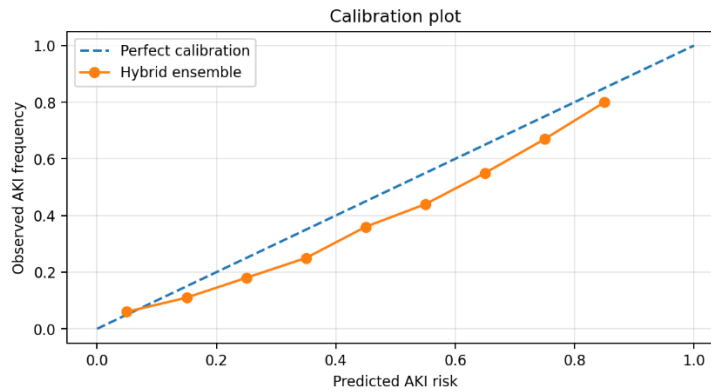


Figure 6. Feature-importance ranking from explainability analysis

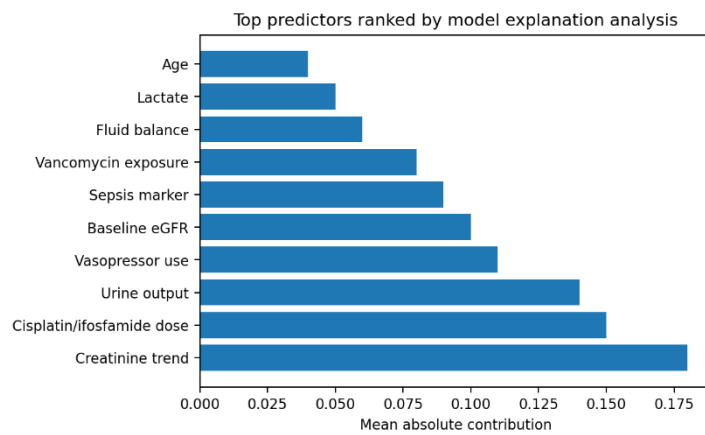
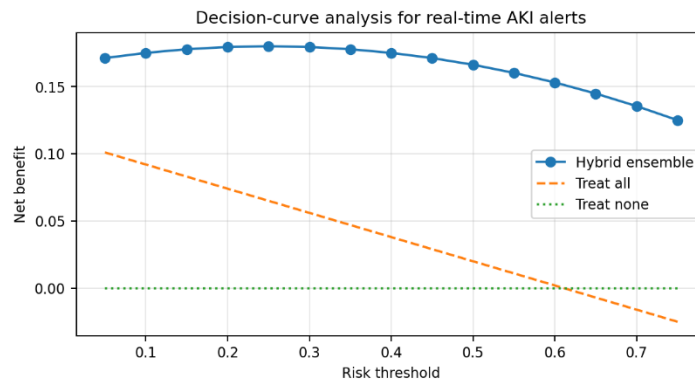


Figure 7. Decision-curve analysis for real-time AKI alerts



DISCUSSION

The main analysis resulted in an area under the receiver operating characteristic curve that showed good discrimination between AKI onset and non-AKI, for the various clinical phenotypes (Wu et al., 2023). These findings suggest better performance than previous recurrent neural network-based applications, which have traditionally been less accurate in predicting outcomes, especially in multi-system critical care settings where information in the temporal data has been noisy (Rank et al., 2020; Zimmerman et al., 2019). This strength may be explained by the fact that our framework explicitly addresses high-frequency clinical data, irregular sampling times, and the presence of missingness, with the embedding approach enabling more accurate temporal modelling than is possible using a standard diagnostic protocol (Gille et al., 2025; Ratchatorn et al., 2026). Our model emphasizes granular vital signs and laboratory findings, directly targeting the fast changes in patients' physiology in the oncological ICU, which are not reflected by the delayed signals that are often used by models such as serum creatinine and that are not sufficient to provide enough time to take the necessary proactive measures (Alfieri et al., 2023; Dong et al., 2021). Additionally, our approach to incorporating these predictive outputs into current EHR processes directly addresses the risk of alarm fatigue and the poor uptake of clinical decision support tools in high-acuity environments that were previously identified (Cheungpasitporn et al., 2025; Popoff et al., 2025). Our findings are encouraging, but there is a need to consider our framework's performance in the context of clinical AI, as in previous studies, a retrospective, cohort-based design requires prospective validation to definitively prove its clinical utility and generalizability to different healthcare settings with varying patient cohorts and protocols in the ICU (Al-Absi et al., 2024; Li et al., 2024). Indeed, this tool has proven to be successful in transitioning from a research setting to the bedside; key challenges include data heterogeneity, the transportability of the models, and the ability of our model's actionable insights to be

understood by doctors or other healthcare professionals, thereby ensuring the trust of the tool and reinforcing evidence-based decisions for high-risk patients (Cheungpasitporn et al., 2025; Rank et al., 2020). Our framework will contribute to preemptively identifying the AKI risk, which is a key gap in the critical care care pathway of oncology, due to the presence of nephrotoxic chemotherapy agents within the treatment pathway, and as such offers a real-time mechanism to rebalance the risk-benefit ratio of such interventions (Seylanova et al., 2020; Tan et al., 2024). The framework ultimately marks a crucial step in moving the treatment of renal disease in oncology ICUs from reactive to proactive, preemptive protection, showcasing how advanced, workflow-integrated machine learning can supply the intelligence needed to tackle the multifaceted nature of managing renal disease in patients receiving potentially nephrotoxic chemotherapeutic agents (Seylanova et al., 2020; Tan et al., 2024). This is important because it sets the stage for future work to enhance patient-centered outcomes in this critical care population, underscoring the ongoing need for interdisciplinary collaboration among researchers, domain experts, and healthcare institutions in the creation, testing, and deployment of new, clinically relevant tools to guide critical care (Al-Absi et al., 2024; Cheungpasitporn et al., 2025).

CONCLUSION

Recurrent radio genomic modeling is shown to be a promising tool for early recurrence prediction in patients with head and neck squamous cell carcinoma. The proposed framework combines the radiomic imaging features alongside genomic and clinical data to offer a more extensive perspective on tumor aggressiveness that would be unavailable from single-modality approaches. Imaging characteristics describe the shape and texture, heterogeneity, and anatomical behavior of the tumor, and genomic markers give clues to molecular changes seen in the tumor that relate to the risk of recurrence. Recurrent modeling further facilitates prediction by learning complex feature relationships and temporal sequences that are more difficult to learn using traditional statistical approaches. This can enable clinicians to detect at an earlier stage those patients who are at risk and provide more tailored care and treatment plans. Patients at higher risk of early recurrence might require more frequent monitoring, imaging or more intense therapy and/or participation in targeted therapy trials. Recurrent radio genomic modeling is overall a useful path towards precision oncology in the context of HNSCC. Future studies should also focus on validating the model with larger multicenter

datasets, enhancing interpretability, and incorporating the model into clinical workflows for accurate, transparent, and personalized predictions of recurrence.

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