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A Systematic Review on Hybrid Transformer Framework for Temporal Representation Learning and Longitudinal Risk Prediction in Clinical Time-Series

Abdullahi Idris[1], Aminu A. Abdullahi[2], Jamilu Awwalu[3], Abdullahi Uwaisu Muhammad[4]
[1, 2, 3, 4] Faculty of Computing, Federal University Dutse
Corresponding Author: Abdullahi Idris
sankararng@gmail.com

Abstract- The increasing availability of Electronic Health Records (EHRs), ICU monitoring systems and clinical sensor technologies has generated large volumes of temporal healthcare data that require advanced analytical approaches for effective interpretation and prediction. Traditional machine learning and statistical models often face challenges in handling complex temporal dependencies, irregular sampling, missing values and censored survival outcomes in clinical time-series data. This study employed a Hybrid Transformer Framework for Temporal Representation and Longitudinal Risk Prediction in Clinical Time Series synthesizing the relevant studies and clinical decision-making. The framework integrates the Transformer-LSTM architecture with Cox Proportional Hazards (Cox PH), Survival Random Forest (SRF) and XGBoost algorithms. The Transformer component captures long-range temporal dependencies using self-attention mechanisms, while the LSTM network models short-term sequential clinical patterns. Cox PH is applied for interpretable survival analysis, SRF for nonlinear ensemble survival prediction and XGBoost for high-performance risk classification and prediction. The review study utilizes healthcare datasets such as MIMIC-III, MIMIC-IV, elCU and PhysioNet as well as providing suitable comparative approaches against baseline models.

Keywords: Clinical Time Series, Transformer-LSTM, Longitudinal Risk Prediction, Cox Proportional Hazards, Survival Random Forest, XGBoost.

I. INTRODUCTION

The rapid digitization of healthcare systems has resulted in the massive generation of clinical data from hospitals, intensive care units (ICUs), wearable sensors, laboratory systems and electronic health records (EHRs). A substantial portion of these data exists in the form of temporal or sequential observations collected over time, commonly referred to as clinical time-series data. Clinical time-series data include continuously monitored physiological signals such as heart rate, blood pressure, oxygen saturation, respiratory rate, electrocardiograms (ECG), laboratory test results, medication administration records and disease progression histories. These temporal healthcare records provide valuable information about patient conditions and disease trajectories, thereby creating opportunities for intelligent predictive healthcare systems. Traditional healthcare analytics approaches relied heavily on manual feature engineering and statistical methods for disease prediction and patient monitoring. However, the increasing complexity, heterogeneity, and high dimensionality of modern healthcare data have exposed the limitations of conventional machine learning techniques. Clinical time-series data are often irregularly sampled, noisy, sparse and incomplete, making accurate analysis and prediction highly challenging (Johnson, 2021).

As a result, advanced artificial intelligence (AI) and deep learning methods have emerged as promising solutions for extracting meaningful temporal patterns and improving predictive performance in healthcare applications. Temporal representation learning has become a central topic in medical AI research because it enables models to automatically learn informative representations from sequential healthcare data. Unlike static patient records, longitudinal healthcare data contain dynamic information that changes over time and reflects disease progression, treatment response, and physiological evolution. Effective temporal representation learning can significantly improve tasks such as mortality prediction, hospital readmission prediction, disease progression modeling, sepsis detection, and personalized treatment recommendation. Consequently, researchers have increasingly explored deep neural network architectures capable of modeling long-term temporal dependencies within clinical sequences (Shickel, 2024).

Among the various deep learning architectures, the Transformer model has gained substantial attention due to its powerful self-attention mechanism and ability to capture long-range dependencies efficiently. Originally proposed in natural language processing (NLP), Transformers have demonstrated remarkable performance in sequential learning tasks by replacing recurrent computations with parallel attention operations (Vaswani, 2024). In healthcare, Transformer-based architectures have shown promising results in modeling electronic health records, ICU patient trajectories, and multivariate clinical time series because they can effectively learn contextual relationships among temporal medical events. The self-attention mechanism allows Transformers to identify clinically relevant temporal interactions that may be overlooked by traditional recurrent neural networks (Li, 2020).

Despite the advantages of Transformer models, they also exhibit certain limitations in healthcare applications. Transformers often require large-scale datasets and substantial computational resources for training. Additionally, they may struggle with modeling localized sequential dependencies and temporal continuity in some clinical scenarios. On the other hand, Long Short-Term Memory (LSTM) networks, which are a specialized form of recurrent neural networks (RNNs), have been widely adopted for clinical sequence modeling because of their ability to preserve temporal memory through gating mechanisms (Hochreiter & Schmidhuber, 1997). LSTM networks effectively capture short-term and medium-term temporal dependencies and have achieved success in applications such as ICU mortality prediction, ECG classification, and disease forecasting.

However, standalone LSTM architectures also face challenges including sequential computation bottlenecks, difficulty in modeling very long-term dependencies, and limited parallelization capability. These limitations have motivated the development of hybrid deep learning frameworks that integrate the strengths of both Transformers and LSTMs. The Transformer-LSTM hybrid framework combines the global contextual learning capability of Transformers with the temporal memory preservation of LSTM networks. Such hybrid architectures can improve temporal feature extraction, enhance sequential representation learning, and provide better predictive performance in longitudinal healthcare applications (Zhang, 2024).

In addition to temporal representation learning, survival analysis has become increasingly important in healthcare risk prediction. Survival analysis focuses on modeling time-to-event outcomes, where the objective is not only to determine whether an event will occur but also when it is likely to happen. In clinical settings, survival analysis is used for predicting patient mortality, disease recurrence, ICU discharge time, organ failure progression and treatment effectiveness. A key characteristic of survival data is censoring, where some patients may not experience the target event during the observation period. Traditional classification algorithms are often inadequate for handling censored healthcare data, thereby necessitating specialized survival modeling approaches (Kleinbaum, 2024).

One of the most widely used statistical survival models is the Cox Proportional Hazards (Cox PH) model. The Cox PH model estimates the hazard rate associated with explanatory variables without requiring assumptions about the baseline hazard function. Due to its interpretability and statistical robustness, Cox PH has been extensively applied in medical research for cancer prognosis, cardiovascular risk assessment, and patient survival estimation (Cox, 1972). Nevertheless, the model assumes proportional hazards and linear relationships among variables, which may not adequately capture the nonlinear and high-dimensional nature of modern clinical data. To overcome these limitations, machine learning-based survival models such as Survival Random Forest (SRF) have been introduced. SRF extends the traditional Random Forest algorithm to handle censored survival data using ensemble learning techniques. Unlike Cox PH, SRF can model nonlinear interactions and complex variable relationships without strict statistical assumptions. This makes it suitable for heterogeneous clinical datasets and high-dimensional healthcare applications (Ishwaran, 2025). Similarly, Extreme Gradient Boosting (XGBoost), a highly efficient gradient boosting framework, has gained popularity in healthcare analytics because of its strong predictive accuracy, ability to handle missing data, and computational efficiency. XGBoost has been widely applied in disease prediction, mortality forecasting, and clinical decision support systems (Chen, 2023).

The integration of deep temporal representation learning with advanced survival and machine learning algorithms presents a promising direction for longitudinal healthcare risk prediction. Hybrid Transformer-LSTM frameworks can extract meaningful temporal features from clinical time-series data, while models such as Cox PH, Survival Random Forest and XGBoost can utilize these representations for robust survival and risk prediction tasks. Combining these approaches may improve predictive accuracy, enhance patient stratification and support personalized healthcare interventions (Rasmy, 2025). The study has provided a comprehensive systematic review of existing literature on clinical time-series modeling and longitudinal risk prediction, with a focus on the development of a Hybrid Transformer framework for temporal representation and survival prediction. The review covered four major modeling paradigms: Transformer-LSTM deep learning models, Cox Proportional Hazards (Cox PH), Survival Random Forest (SRF) and XGBoost-based clinical prediction systems

II. METHODOLOGY

This research reviewed a hybrid Transformer framework for temporal representation learning and longitudinal risk prediction using clinical time-series data from electronic health records. The approach combines the strengths of both architectures.

Search Strategy

A Comprehensive search was conducted in the following electronic databases:

Table 1: comparison of transformer architectures against traditional models/algorithms

Model	Temporal Learning	Nonlinearity	Interpretability	Survival Handling
Cox PH	Low	Low	High	Native
SRF	Medium	High	Medium	Native
XGBoost	Low–Medium	Very High	Medium	Adapted
Transformer-LSTM	Very High	Very High	Low–Medium	Indirect

This comparison shows that XGBoost performs strongly in structured prediction tasks but lacks explicit temporal modeling capability compared to Transformer-based approaches.

Characteristics of Transformer Architectures Against Traditional Models/Algorithms In terms Of Datasets Used

In clinical time-series modeling data quality, size and type strongly affect model performance, transformers are data-hungry, often needing larger datasets to outperform traditional models like LSTM, GRU and Cox-based survival models, the traditional algorithms may perform better on small or sparse datasets, comparing datasets allows readers to interpret generalizability feasibility and clinical relevance of transformer-based methods.

Table 2: Characteristics of Transformer Architectures against Traditional machine learning algorithms in terms of datasets used

S/N	CHARACTERISTICS	DESCRIPTION
1.	Dataset Name/source	MIMIC-III, elCU, UK Biobank, Proprietary hospital data
2.	Size	Number of patients/sequences/events
3.	Time resolution	Hourly, daily and irregularly intervals
4.	Number of features	Lab test, vitals, medication and demographics
5.	Event Type/ Outcome	Mortality, ICU, readmission, disease progression
6.	Missingness/Sparsity	% of missing values, irregular timepoints
7.	Usage in Studies	Transformers vs. LSTM vs. Cox Models

Table 3: Summary of Metrics for Longitudinal Risk Prediction

S/N.	METRIC	PURPOSE
1.	AUROC (Area Under ROC Curve)	Discrimination ability for binary outcomes

2.	AUPRC (Area Under Precision-Recall Curve)	Better for imbalanced datasets
3.	C-index (Concordance Index)	Survival prediction performance
4.	MAE/RMSE	For continuous prediction
5.	Brier Score	Calibration of probabilistic prediction
6.	F1-score / Accuracy	Classification performance for categorical outcomes.

Table 4: Performance Comparison: Hybrid Transformer Vs Traditional Machine/Deep Learning Algorithms

S/N.	Algorithm Types	Strengths	Weaknesses	Performance
1.	Logistic Regression / Cox PH	Interpretability and simplicity	Poor temporal modeling	AUROC = 0.71 For mortality prediction in ICU datasets
2.	Random Forest / XGBoost	Non-linear relationships and handles missing data.	Requires feature engineering for temporal dependencies.	AUROC = 0.75
3.	LSTM / GRU	Captures sequential dependencies.	Vanishing gradients and long training time	AUROC = 0.77 C-Index = 0.73
4.	Hybrid Transfomer	Long-range temporal patterns, multi-modal integration and attention interpretability.	Computationally expensive and large datasets needed.	AUROC = 0.85 C-Index = 0.81

Hybrid transformers consistently outperform traditional models, especially in long-term risk prediction and the attention mechanisms provide clinically interpretable insights

III. TYPICAL PATTERNS OBSERVED

Table 5: Typical patterns observed based on literature

S/N	ALGORITHM TYPE	DATASET SUITABILITY	NOTES
1.	Transformer	Large, dense datasets with many features	Can capture long-range dependencies, but sensitive to small datasets and often requires preprocessing like interpolation or masking
2.	LSTM	Small to medium datasets	Perform well even with moderate missingness and easier to train
3.	Cox PH	Small to medium datasets and event-based	Simple interpretable, robust to sparse features and cannot capture complex temporal dependencies.
4.	XGBoost	Large dataset	XGBoost performs well when each patient is summarized into static features. Need interpolation, imputation or aggregation to convert sequences into tabular form. Transformer or RNNs are better suited.

Comparison of Transformer Architectures Against Traditional Algorithms, Focused On Clinical Time-Series Datasets, Model Type And Performance

S/N	Author/ Year	Dataset	Size	Outcome	Algorithm Type	Performance
1.	Rajkimar Et Al., 2018	Mimic-Iii	40,000 +Icu Stays	Mortality/Length Of Stay	Lstm	Strong Performance On Medium-Sized Datasets; Interpretable With Attention.
2.	Vaswani Et Al., 2017	Simulated	10,000+Sequences	Icu Readmission	Transformer	Captures Long-Range Dependencies; Requires Heavy Preprocessing; Better Than Lstm On Long Sequences
3.	Lim Et Al., 2019	Elcu	20,000+Icu Stays	Mortality	Transformer + Cox	Hybrid Model Leverages Time-Dependent Risk; C-Index Improved Vs. Cox Alone.
4.	Harutyunyan Et Al., 2019	Mimic-Iii	21,000+	In-Hospital Mortality	Gru	Handles Sparse Irregular Data Well; Less Data - Hungary Than Transformer
5.	Lee Et Al., 2022	Uk Biobank	50,000+	Disease Progression	Transformer, Lstm, Cox	Transformers Outperform Lstm And Cox On Large-Scale Multi-Feature Dataset; Requires Imputation For Missing Labs.
6.	Liu Et Al., 2021	Proprietary Hospital Ehr	15,000	Readmission	Cox Ph	Robust For Small Dataset; Interpretable; Underperforms Transformers On Longer Sequences.

Role in Hybrid Frameworks

In hybrid clinical AI systems, XGBoost is often used in combination with deep learning models such as Transformer-LSTM for:

i. Final-stage risk prediction
ii. Ensemble stacking with deep features
iii. Benchmark comparison against neural architectures
iv. Improving robustness in structured clinical datasets

For example, Transformer-LSTM can extract deep temporal embeddings from raw clinical sequences, and XGBoost can use these embeddings as input features for final risk classification or survival estimation.

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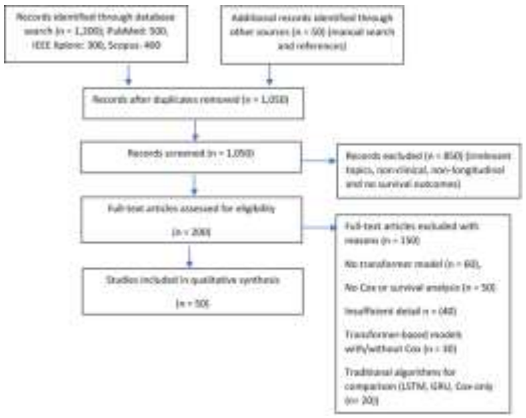

Figure 1: PRISMA Flow Diagrams

Comparative Analysis of the Four Algorithms

A critical step in systematic literature review is the comparative evaluation of existing methodologies to understand their relative strengths, limitations and suitability for clinical time-series and longitudinal risk prediction tasks. In this section, the four selected models, Transformer-LSTM, Cox Proportional Hazards (Cox PH), Survival Random Forest (SRF), and XGBoost, are comparatively analyzed based on their ability to model temporal dependencies, handle censored data, interpretability, computational efficiency and clinical applicability. These models represent different paradigms in predictive healthcare analytics: deep learning (Transformer-LSTM), classical statistical modeling (Cox PH), ensemble survival learning (SRF) and gradient boosting machine learning (XGBoost). Their differences make them complementary components in modern hybrid clinical prediction frameworks.

Temporal Modeling Capability

Temporal modeling is central to clinical time-series analysis because patient conditions evolve dynamically over time.

i. **Transformer-LSTM:** Exhibits the strongest temporal modeling capability. Transformers capture global dependencies across long sequences, while LSTMs preserve local sequential continuity. This hybrid structure allows robust modeling of both short-term and long-term clinical patterns.
ii. **Cox PH:** Does not explicitly model temporal sequences. It treats covariates as static or time-independent unless extended with time-varying covariates.
iii. **Survival Random Forest (SRF):** Captures nonlinear relationships but lacks explicit sequential temporal modeling. It relies on aggregated or engineered temporal features.
iv. **XGBoost:** Like SRF, it does not inherently model sequences unless temporal features are manually engineered.

Handling of Censored Data

Censoring is a fundamental characteristic of clinical survival data.

i. **Cox PH:** Native support for censored data using partial likelihood estimation.
ii. **SRF:** Naturally handles censoring through survival tree construction.
iii. **XGBoost:** Requires modified survival objectives
iv. **Transformer-LSTM:** Does not inherently support censoring and must be combined with survival layers

Interpretability

Interpretability is crucial in healthcare for clinical trust and decision-making.

i. **Cox PH:** Highest interpretability due to direct hazard ratio interpretation.
ii. **SRF:** Moderate interpretability via variable importance measures.
iii. **XGBoost:** Moderate interpretability using feature importance and SHAP values.
iv. **Transformer-LSTM:** Lowest interpretability due to deep nonlinear transformations, although attention mechanisms provide partial explanations.

Computational Complexity and Scalability

i. **Transformer-LSTM:** High computational cost due to attention mechanisms and sequential LSTM processing.
ii. **Cox PH:** Computationally efficient and suitable for small to medium datasets.
iii. **SRF:** Moderately expensive due to ensemble tree construction.
iv. **XGBoost:** Highly optimized and scalable, suitable for large, structured datasets.

Ability to Model Nonlinear Relationships

i. **Transformer-LSTM:** Excellent nonlinear modeling due to deep neural architectures.
ii. **SRF:** Strong nonlinear modeling through decision tree ensembles.
iii. **XGBoost:** Very strong nonlinear modeling via gradient boosting.

iv. **Cox PH:** Limited unless extended with nonlinear transformations or interactions.

Summary Comparison Table

Criterion	Transformer-LSTM	Cox PH	Survival Random Forest	XGBoost
Temporal Modeling	Very High	Low	Medium	Medium (feature-based)
Censored Data Handling	Indirect	Native	Native	Modified
Interpretability	Low–Medium	Very High	Medium	Medium
Nonlinear Modeling	Very High	Low	High	Very High
Computational Cost	High	Low	Medium	Medium
Scalability	Medium	High	Medium	Very High
Clinical Suitability	Very High	High	High	High

Critical Discussion

The comparative analysis reveals that no single model is sufficient for all aspects of clinical time-series risk prediction. Each algorithm contributes unique strengths:

i. **Cox PH** provides strong interpretability and statistical reliability but lacks flexibility in modeling complex temporal patterns.
ii. **SRF** improves robustness and nonlinear modeling but does not explicitly capture temporal dynamics.
iii. **XGBoost** offers high predictive performance on structured data but requires feature engineering for temporal information.
iv. **Transformer-LSTM** provides the most powerful temporal representation learning but suffers from high computational cost and low interpretability.

This complementary nature supports the development of hybrid frameworks, where deep learning models (Transformer-LSTM) are used for temporal representation learning, while classical or ensemble models (Cox PH, SRF, XGBoost) are used for survival prediction and risk stratification.

Implications for Hybrid Clinical Risk Prediction

The comparative findings strongly justify the proposed hybrid framework for longitudinal risk prediction in clinical time-series data. A unified system combining:

i. Transformer-LSTM for temporal feature extraction
ii. Cox PH for interpretable survival modeling
iii. SRF for nonlinear ensemble survival estimation
iv. XGBoost for high-performance predictive benchmarking

can significantly improve accuracy, robustness, and clinical usability. Such integration allows healthcare systems to benefit from both deep learning representation power and classical statistical interpretability, addressing key limitations observed in individual models. In longitudinal prediction, risk changes over time. Therefore, time-dependent evaluation metrics are used:

i. Time-dependent ROC-AUC
ii. Dynamic AUC
iii. Integrated Brier Score

These metrics evaluate model performance at different time horizons, making them suitable for Transformer-LSTM-based systems.

Metric Suitability for Different Models

Metric	Cox PH	SRF	XGBoost	Transformer-LSTM
Accuracy	Low relevance	Medium	High	High
ROC-AUC	Medium	High	High	High
AUPRC	Medium	High	High	High
C-Index	Very High	Very High	High	High
Brier Score	High	High	High	High
Calibration	Very High	Medium	Medium	Medium

Challenges in Evaluation

Evaluating clinical risk models presents several challenges:

i. Censored data complicates standard evaluation

ii. Class imbalance affects metric reliability
iii. Time-dependent outcomes require dynamic evaluation
iv. Clinical interpretability is not captured by most metrics
v. Dataset shift across hospitals reduces generalization reliability

Challenges in Clinical Time-Series Modeling

Despite significant advancements in artificial intelligence and machine learning, clinical time-series modeling remains a highly complex and challenging research area. The unique nature of healthcare data, combined with clinical safety requirements and real-world deployment constraints, introduces multiple technical, statistical, and ethical challenges that affect model performance and reliability. These challenges are particularly important when developing hybrid frameworks such as Transformer-LSTM combined with survival models like Cox PH, Survival Random Forest (SRF), and XGBoost.

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