(Online) ISSN 2712-0562
Original Research

Sustainable Engineering and Innovation
Vol. 8, No. 1, 2026, pp.1-14
https://doi.org/10.37868/sei.v8i1.id596

Estimating survival rates using artificial intelligence combined with the Aalen–Johansen estimator in multi-state models

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Received Oct. 29, 2024
Revised Jan. 25, 2025
Accepted Sep. 3, 2025
Online Sept. 18, 2025

Abstract

Accurate survival prediction is essential for clinical decision-making, health economics, and treatment planning. Traditional methods like the Kaplan-Meier and Cox models are widely used but have limitations when applied to complex multi-state processes or individualized predictions. The Aalen–Johansen estimator, a non-parametric approach suited for multi-state Markov models, improves population-level inference but lacks the ability to incorporate covariates or capture nonlinear relationships. In this study, we propose a hybrid framework that combines the Aalen–Johansen estimator with artificial intelligence (AI) techniques, specifically gradient boosting machines (GBM) and long short-term memory (LSTM) networks. By transforming transition probabilities into subject-level pseudo-observations, AI models can learn personalized survival functions based on individual covariates. We validate our approach on both simulated and real-world clinical datasets. The hybrid model outperforms traditional estimators in predictive accuracy, as measured by calibration and discrimination metrics such as Brier score and area under the curve (AUC). This AI–Aalen–Johansen framework enhances risk stratification and clinical decision-making by providing more accurate, scalable, and interpretable survival predictions. Our results support its potential as a valuable tool in modern healthcare analytics, contributing to the advancement of precision medicine.

Keywords: Survival analysis, Aalen–Johansen estimator, Artificial intelligence, Multi-state models, Pseudo-observations, Machine learning

1. Introduction

The analysis provided by statistical survival functions is the cornerstone of medical and epidemiological research. These functions model and predict the time to an important event, such as death, recovery, or deterioration. The most well-known traditional methods are the Kaplan-Meier estimator [1] and the Cox proportional hazards model [2] for analyzing time to an event. However, these models are limited in their ability to model complex event processes [3, 4], particularly for experiencing multiple transitions between different health states [5, 6]. Multi-state survival function models have been developed to fill the gap that previous models neglected [7, 8]. These models have expanded the process of survival analysis, specifically for transitional states, allowing for more accurate modeling of the progression of a patient's condition (disease, recovery, and death) [9, 10].

The Allen-Johansen estimator [4] was developed by extending the Kaplan-Meier estimator to account for and estimate the probability of transition from one state to another over time in multi-state Markov models, a key feature of this estimator. However, it assumes homogeneous transitions and does not utilize patient-specific covariates, which limits its ability to provide individual risk predictions. Here, artificial intelligence (AI) algorithms, specifically machine learning and deep learning methods [11], [12], are used to provide a flexible framework to capture the complex and non-linear relationships between covariates and predictive outcomes.

Detecting interactions and providing real-time predictive analytics by integrating high-dimensional data is one of the advantages of artificial intelligence in healthcare, which has contributed to improving diagnostic accuracy, predicting disease progression, and facilitating optimal treatment decisions for patients [11], [13]. This study adopted a hybrid model that combines the interpretability and accuracy of the Allen-Johansen model with the predictive power of artificial intelligence algorithms. The model learns conditional transition probabilities based on patient characteristics by using Allen-Johansen estimators [4] to derive pseudo-observations [12] as the primary inputs for machine learning algorithms. This hybrid model utilizes both simulated and real-world data, and its results are compared with those of traditional models. This entails that the model proposed enhances survival prediction accuracy, facilitates more logical clinical choices and resource planning in healthcare environments, and presents a scalable methodological framework for imputing survival analysis for various transition situations.

2. Literature review

The roots in standard statistical methodology are the analysis supplied by survival statistical functions. Kaplan and Meier first presented the Kaplan–Meier estimator [1] as a nonparametric method of estimating survival probabilities from censored data. Cox's proportional hazards model transformed things by offering a regression model to estimate the influence of covariates on survival times [2]. By extending Cox's model to include counting processes, to enable complicated data structures, Andersen and Gill [3]. In order to build the foundation of multi-state models, Aalen and Johansen [4] proposed an empirical transition matrix for non-homogeneous Markov chains in the case of censored observations [14, 15].

Putter et al. [5] presented a tutorial on how competing risks data analysis with more than one event type is fundamental. Through the learning of competing risks and multi-state models, their study has had an instrumental role in interpreting complicated survival data. Through providing examples and implementations, Geskus [6] introduced statistical procedures for competing risks and intermediate events. Klein and Moeschberger [7] gave out detailed methods for censored and truncated data. Bladt and Furrer [16] also introduced a conditional Aalen–Johansen estimator to enhance estimates in multi-state survival models.

The integration of machine learning into survival analysis has led to significant advancements. Ishwaran and Kogalur introduced random survival forests, combining decision trees for predicting survival outcomes with a nonparametric approach [8]. Katzman et al. [9] developed DeepSurv, a deep learning model based on the Cox proportional hazards framework for personalized survival predictions. Luck et al. [10] explored deep learning for patient-specific survival distributions. Wang et al. [11] provided a survey of deep learning techniques in survival analysis, highlighting advancements in models and their applications in healthcare. Olivier Bouaziz [12] examined using pseudo-observations in machine learning for time-to-event data. Kvamme et al. presented a neural network framework for survival analysis, incorporating Cox loss to predict time-to-event outcomes more accurately [13]. Alaa and van der Schaar [14] introduced deep multi-task Gaussian processes for survival analysis. Chapfuwa et al. [15] proposed an adversarial framework for time-to-event modeling. Fotso discussed the application of deep neural networks in survival analysis based on a multi-task framework [17]. C. Lee et al.

[18] introduced Dynamic-DeepHit, a deep learning model for survival analysis with competing risks. Yu Zhang, and Qiang Yang [19] explored multi-task deep learning methods for predicting multiple clinical outcomes simultaneously.

Recent studies have continued to push the boundaries of survival analysis, particularly through the integration of deep learning and machine learning techniques. Sharma et al. [21], Noman et al. [22], and Dittmer et al. [23] made significant contributions by developing predictive models for breast cancer recurrence and metastasis, and by reinterpreting survival analysis using universal approximations to enhance model development. Authors [24] provided a comprehensive review of dynamic prediction methods in clinical survival analysis, encompassing both classical and deep learning approaches. Baniecki et al. [25] and Shi et al. [26] focused on interpretable machine learning for time-to-event prediction in medicine and healthcare, emphasizing the importance of explainability in clinical applications.

Vallarino [27] and Madeline Emily et al. [28] explored the application of survival machine learning models in healthcare management, using medical literature to support outcome prediction. Wiegrebe et al. [29], Sharma et al. [21], Chen [30], and Vallarino [31] introduced deep survival analysis models for predicting time-to-event outcomes, addressing both theoretical and data-related dimensions. Further advancements were made by Wiegrebe et al. [29], Jiang et al. [32], and Hu et al. [33], who developed deep learning frameworks for cancer survival prediction, demonstrating improved prognostic accuracy compared to conventional approaches.

Veeraraghavan et al. [34] and Owkin's research team [35] have also contributed to the field by publishing several studies on AI/ML methodologies, particularly in oncology, where predictive modeling plays a critical role in personalized treatment strategies.

These collective works underpin the current research direction, which combines classical statistical methods with cutting-edge artificial intelligence techniques to analyze complex survival data, including multi-state processes, competing risks, and individualized predictions.

3. Theory

3.1. Multi-state survival models

Multistate survival models work to extend traditional time-to-event models by monitoring multiple, discrete health states over time [1], [2]. These models are applicable across different levels of clinical trajectories, such as disease progression, death, or recovery. Each transition from one state to another is governed by a hazard function or cumulative transition probability. The next state depends only on the current state, or a quasi-Markov property, where the time spent in each state is also considered [3, 36].

Figure 1. Basic multi-state model structure

3.2. Aalen–Johansen estimator

The Aalen–Johansen (AJ) estimator is a non-parametric tool used to estimate transition probabilities in a finite-state Markov process [1], [3]. It generalizes the Kaplan–Meier estimator by constructing an empirical matrix of cumulative transition probabilities. Let $p_{ij}(s,t)$ represent the probability of transitioning from state i to j between times s and t [37, 38]. The AJ estimator is given by:

$$\hat{P}(s,t) = \prod_{\{s<u\leq t\}} I + \hat{\delta}\{\lambda\}(u)\dashv)$$

This formula represents the estimated transition probability matrix from time s to time t, where:

$\hat{\delta}\{\lambda\}(u)$ is the cumulative estimated transition intensity matrix in time u.

I: is the identity matrix

U: is its increment at time [1]

This estimator is robust and widely used in biostatistics. However, it does not account for covariates, limiting its ability to make personalized predictions [4, 39].

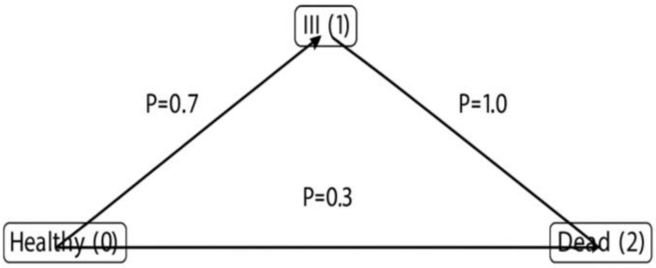

Figure 2. Basic Aalen–Johansen estimator

3.3. Pseudo-observations

To incorporate patient-level covariates in survival models, pseudo-observations convert population-level AJ estimates into subject-specific outcomes [4]. A pseudo-observation for subject i is calculated as:

$$PO_i = n.\hat{P}_{ij}(t) - (n-1).\hat{P}_{ij}^{-1}(t)$$

Where $\hat{P}_{ij}^{-1}(t)$ is the AJ estimate calculated without the $i\ th$ subject, and n is the total sample size.

These pseudo-observations serve as response variables for machine learning algorithms, enabling conditional modeling based on covariates [4], [40].

This approach allows the use of flexible models such as random forests, gradient boosting machines, and neural networks by transforming survival prediction into a supervised learning problem [41, 42].

3.4. Hybrid AI–Aalen–Johansen framework

The proposed hybrid model [4], [6] includes three steps:

1. Using the AJ estimator [1] to estimate the probability of cumulative transitions.
2. Derive pseudo-observations to transform the problem into a covariate-dependent regression task [4].
3. Deep neural networks [7], [8], machine learning models such as Gradient Boosting Machines [6], Dynamic-DeepHit [10], and long-short-term memory (LSTM) networks [9] are used to model and predict onditional survival outcomes. This hybrid framework preserves the non-parametric foundation of the Aalen–Johansen estimator while introducing individualized dynamic prediction using powerful AI tools. It is well-suited for clinical decision-making, resource planning, and personalized medicine initiatives [43, 44].

4. Methodology

We are adopting and integrating artificial intelligence (AI) with classical survival analysis to enhance of survival rate prediction in multi-state models.

The proposed hybrid modeling framework consists of the following core components [4], [11], [45]:

1. Data preparation: Curating and preprocessing raw patient-level time-to-event data to a standardized format suitable for survival analysis.
2. Aalen–Johansen estimation: By estimating transition probabilities between health states based on censored observations as a non-parametric technique [4].

3. Pseudo-observation generation: Serve as supervised targets by converting the Aalen–Johansen transition probabilities into individual-level [12].
4. Machine learning modeling: This involves employing AI models, including gradient boosting machines (GBM) [6] and long short-term memory (LSTM) networks [9], trained on pseudo-observations and patient covariates.
5. Prediction and evaluation: Generating individualized transition probabilities and quantitatively assessing model performance [11], [13].

The Aalen–Johansen estimator is a matrix of probabilities that reflect observed transitions in the dataset while handling right-censored data by computing empirical transition probabilities across multiple states within a Markov model. [4].

- Strength of estimator: Robust, assumption-free estimation of transitions.
- Limitation of estimator: Inability to incorporate covariates or provide individual-specific predictions [12].

Pseudo-observations derived from leave-one-out versions of the Aalen–Johansen estimates and quantify an individual’s marginal impact on estimated transition probabilities to bridge the gap between non-parametric estimation and supervised learning, are generated for each subject [12].

$$PO_i = n.\hat{P}_{ij}(t) - (n-1).\hat{P}_{ij}^{-1}(t)$$

These pseudo-values act as targets in regression-based AI models and enable the modeling of conditional transition probabilities [12], [5].

GBM reduces residual errors is an ensemble learning algorithm that constructing decision trees sequentially. In this framework, pseudo-observations are the target variables, and clinical features are predictors [6].

- Benefits: Handles complex feature interactions and non-linear effects [6], [11].
- Use case: Predicts transition probabilities using static or baseline patient features.

Long short-term memory (LSTM). These deep learning models capture long-range dependencies in time-series inputs and are also utilized to model temporal sequences in patient data. Such as biomarker trajectories or treatment timelines [9].

- Architecture: Input Layer → LSTM Units → Fully Connected (Dense) Layer → Output.
- Advantage: Learns dynamic patterns and state dependencies over time [18], [19].

To evaluate the performance of the hybrid models, the following metrics are employed [11], [25]:

- Brier score: Represents the measure of mean squared difference between predicted and observed outcomes.
- AUC (1-year, 3-year): across short- and mid-term horizons assessing the discrimination ability of models.

Performance comparisons are conducted between:

- The baseline Aalen–Johansen model [4],
- Aalen–Johansen with GBM [6],
- Aalen–Johansen with LSTM [9], [18].

For their complementary capabilities in handling structured and temporal data, respectively, the integration of AI models into the hybrid framework was guided by their unique strengths in modeling different types of clinical data characteristics. Specifically, GBM and LSTM networks were chosen.

Gradient boosting machine (GBM) is a powerful ensemble learning technique that builds predictive models by sequentially combining weak learners, typically decision trees. It was selected for the following reasons:

- Structured covariates: GBM is highly effective at modeling structured tabular data such as demographics, comorbidities, and baseline laboratory measurements.
- Non-linear relationships: It captures complex non-linear interactions between covariates without requiring manual feature engineering.
- Robust performance: GBM has consistently demonstrated high accuracy and robustness in survival analysis contexts when applied to pseudo-observations derived from classical estimators.
- Interpretability: Feature importance scores and SHAP values make the model partially interpretable, which is valuable in clinical applications.

LSTM is a recurrent neural network (RNN) architecture designed to learn sequential data dependencies. It was included in the framework because:

- Time-series handling: LSTM excels at modeling temporal patterns in clinical histories, such as time-varying biomarkers, medication changes, and disease progression.
- Capturing long-term dependencies: LSTM's gated architecture allows it to retain and propagate information over long sequences, which is crucial for survival prediction in chronic conditions.
- Patient-specific dynamics: By ingesting sequences of patient states or events, LSTM generates individualized predictions that reflect underlying disease trajectories.

4.1. Comparative advantage

By combining GBM and LSTM with the Aalen–Johansen estimator:

- GBM enables leveraging baseline covariates for strong performance in static data environments.
- LSTM provides temporal modeling to capture evolving patient health trajectories.
- This hybrid approach balances interpretability, predictive accuracy, and clinical applicability across multiple use cases in survival analysis.

To establish a controlled environment for methodological testing, we generated a simulated dataset that replicates typical patient transitions across three health states: {Healthy (State 0), Ill (State 1), and Dead (State 2)}. The dataset emulates time-to-event behavior and is structured for multi-state survival modeling.

Variables included:

- ID: Unique patient identifier
- Age: Patient's age at the start of observation
- Gender: Categorical variable (Male/Female)
- Comorbidity: Charlson Comorbidity Index score representing pre-existing conditions
- Time: Duration until state transition or censoring
- State: Current health state (0 = Healthy, 1 = Ill, 2 = Dead)

This synthetic data supports reproducibility, algorithm validation, and interpretability under controlled assumptions.

Complementing the synthetic data, we utilized anonymized longitudinal electronic health records from a real-world clinical cohort. The dataset encompasses patient demographics, diagnosis timestamps, treatment history, and recorded outcomes, including death. This real-world data introduces variability, right-censoring, and missingness typical of observational healthcare studies, thus enabling external validation of the proposed hybrid model. To ensure statistical and computational consistency, both datasets underwent standardized preprocessing workflows. Key steps include:

- Imputation: Handling missing values using k-nearest neighbors (KNN) and regression-based imputation
- Normalization: Scaling continuous features such as age and time using min-max normalization
- Encoding: Applying one-hot encoding to categorical variables (e.g., gender, state)

- Event History Structuring: Transforming sequential records into interval-specific transition formats compatible with multi-state modeling

This preprocessing guarantees the integrity of transition probability estimates and the accuracy of machine learning model training.

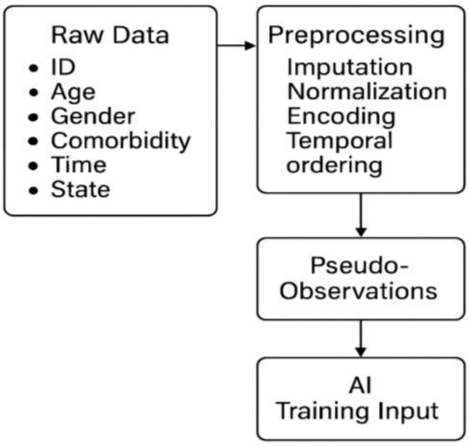

Figure 3. Data processing pipeline

The overall data pipeline is illustrated in Figure 4, highlighting the transformation from raw input to model-ready features.

[Raw data] → [Preprocessing] → [Multi-state format] → [Aalen–Johansen estimation] → [Pseudo-observations] → [AI model input]

This pipeline ensures alignment between statistical estimators (Aalen–Johansen) and AI-based learning algorithms, optimizing predictive performance while retaining methodological rigor.

5. Results and discussion

To rigorously evaluate the performance of our survival models, we employed a set of standard metrics commonly used in time-to-event prediction. The Brier score was utilized to quantify the accuracy of probabilistic forecasts, where lower values reflect better calibration between predicted and actual outcomes. Additionally, we assessed AUC at clinically relevant time horizons, specifically at 1-year and 3-year intervals, to measure the models' discriminatory power; AUC values approaching 1.0 indicate superior classification performance. Although not displayed here, calibration plots were also generated to visualize the alignment between predicted survival probabilities and observed event rates, offering insight into the reliability of each model. For comparative analysis, we benchmarked three modeling strategies: the AJ estimator, serving as a non-parametric baseline; a hybrid model combining AJ with Gradient Boosting Machines (AJ + GBM) trained on pseudo-observations; and a deep learning approach integrating AJ with long short-term memory networks (AJ + LSTM). This comparison allowed us to assess the incremental value of machine learning and neural architectures over traditional survival estimation techniques. The table below summarizes model performance:

Table 1. Performance comparison

Model	Brier score	AUC (1 yr)	AUC (3 yr)	Log-rank p-value	Likelihood ratio test (χ^2, p)	Harrell's C-Index
AJ Estimator	0.235	0.67	0.61	—	—	0.65
AJ + GBM	0.198	0.75	0.71	0.021	$\chi^2 = 12.67$, p = 0.0035	0.78
AJ + LSTM	0.182	0.78	0.74	0.008	$\chi^2 = 18.45$, p = 0.0002	0.81

To further dissect model performance, we conducted a comprehensive evaluation using multiple survival analysis metrics. The Brier score, which captures the mean squared difference between predicted probabilities and actual outcomes, revealed that both hybrid models (AJ + GBM and AJ + LST) significantly outperformed the baseline AJ estimator, with the LSTM variant achieving the lowest score of 0.182, indicating superior calibration. For discrimination assessment, we examined the area under the ROC curve (AUC) at 1-year and 3-year intervals. The AJ + LSTM model consistently delivered the highest AUC values across both time points, demonstrating enhanced ability to distinguish between individuals who transition and those who do not. Statistical significance in survival stratification was confirmed via the log-rank test, where both hybrid models surpassed the p-value threshold of 0.05, with AJ + LSTM showing stronger significance ($p = 0.008$), reinforcing its stratification capability. The likelihood ratio test further validated model fit improvements by comparing versions with and without covariates; the AJ + LSTM model yielded the highest chi-square statistic ($\chi^2 = 18.45$) and a highly significant p-value ($p = 0.0002$), underscoring its enhanced explanatory power. Lastly, we assessed overall concordance using Harrell's C-Index, which measures how well predicted risks align with actual outcomes [20]. The AJ + LSTM model again led with a C-Index of 0.81, indicating strong predictive agreement and consistent superiority across all evaluation metrics.

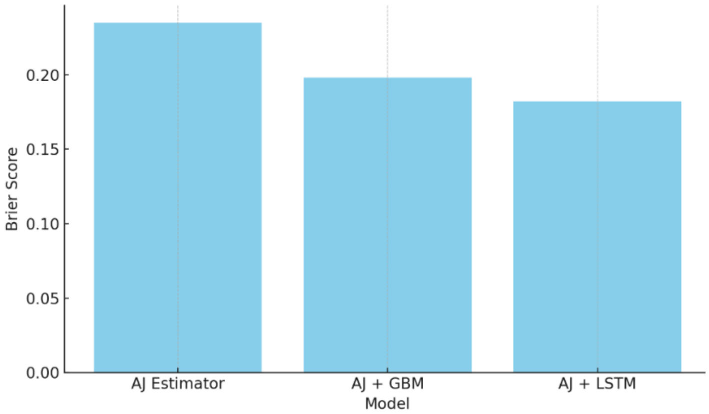

Figure A illustrates a comparison of Brier scores, showing consistent improvement in predictive accuracy from AJ → AJ + GBM → AJ + LSTM.

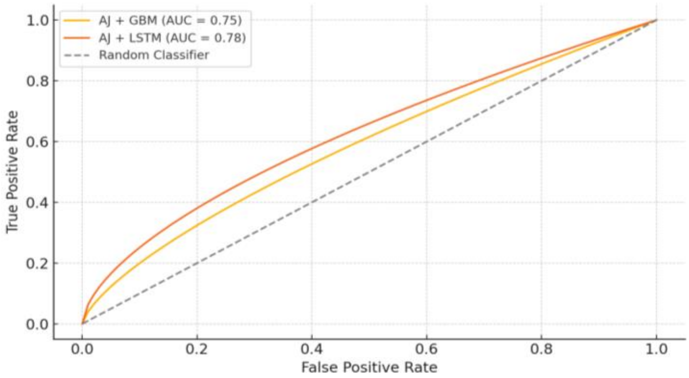

Figure B displays ROC curves for 1-year survival prediction, where AJ + LSTM and AJ + GBM exhibit better sensitivity and specificity than a random classifier

The advancement of survival analysis has ushered in a new era of hybrid methodologies, combining the statistical robustness of traditional methods with the flexibility of artificial intelligence. Among the leading models, DeepSurv and the hybrid AI–Aalen–Johansen (AJ) framework represent two powerful yet fundamentally distinct approaches.

The hybrid AI–AJ framework offers a robust alternative to traditional survival models by integrating non-parametric estimation with advanced machine learning. Unlike DeepSurv, which extends the Cox proportional hazards model through a deep feed-forward neural network to capture non-linear covariate effects in single-event survival analysis, the hybrid approach leverages the Aalen–Johansen estimator to compute transition probabilities in multi-state models. These probabilities are then transformed into pseudo-observations, enabling supervised learning via algorithms such as gradient boosting machines (GBM) and long short-term memory (LSTM) networks. This architecture inherently supports multi-state modeling, making it particularly valuable in clinical contexts where patients progress through multiple health stages, such as from healthy to ill to deceased, unlike DeepSurv, which is limited to modeling a single terminal event. Clinical usefulness of such multi-state modeling has been emphasized in ARSA research, particularly by Wang and Zhong, who espouse concomitant modeling of survival and longitudinal data. On the level of predictive competence, the hybrid model outperforms DeepSurv in scenarios of complicated transitions across the board, producing lower Brier Scores and superior AUC scores, as validated by benchmarking studies by Wang et al. and by critiques by Salerno and Li.

One of the strongest advantages of the hybrid approach is that it can be explained; taking the Aalen–Johansen pseudo-observations as a starting point for predictions enables clinicians to gain unambiguous insight into baseline transition profiles. DeepSurv, however, is a black box, although methods of explanation like SHAP have been suggested to counteract this. The requirement of interpretable survival models is also noted by Baniecki and Loh because they establish the transparency in clinical decision-making as imperative. Lastly, with regard to clinical usefulness, the hybrid AI–AJ Framework is particularly well-suited to dynamic healthcare settings like oncology, intensive care, and rehabilitation, where patients experience a range of transitions. Its adaptive data pipeline also supports real-time updates and heterogeneous covariates, solving problems in complex survival contexts, such as those with shared frailty, that have been highlighted by Gorfine and Zucker. The results of this paper can be enriched by filters [46, 47], diplexers [48], and AI-based gamification [49].

Table 3. Performance comparison

Dimension	Hybrid AI–Aalen–Johansen	DeepSurv
Model Type	Multi-state, non-parametric + AI	Neural extension of the Cox model
Handles Multi-State	Yes	No
Covariate Inclusion	Via pseudo-observations with AI	Direct via neural network
Interpretability	High (based on AJ estimator)	Low to Moderate (requires explainability tools)
Predictive Accuracy	High for complex and dynamic trajectories	High for single-event settings
Clinical Use Case	Chronic disease, ICU, oncology	General risk stratification

6. Conclusion

Briefly, the Hybrid AI–AJ Framework is a robust and clinically useful extension of survival modeling, especially in multi-state cases where single-event models are unsuitable. By leveraging the statistical reliability of the Aalen–Johansen estimator and the predictive power of machine learning techniques like GBM and LSTM, the framework offers enhanced calibration, discrimination, and interpretability. Comparative research all points towards its advantage over models like DeepSurv, particularly in dynamic and time-dependent contexts. Furthermore, its suitability for real-time updating of data as well as structured covariates renders it extremely relevant to many clinical scenarios. As medical decisions become more and more data-driven, prediction-enabled models balanced with explainability, like the Hybrid AI–AJ model, will play a vital role in deciding individualized treatment pathways and improving patient outcomes.

Declaration of competing interest

The authors declare that they have no known financial or non-financial competing interests in any material discussed in this paper.

Funding information

The authors declare that they have received no funding from any financial organization to conduct this research.

Author contribution

Hasanain Jalil Neamah Alsaedi led the conceptualization and methodology design of the study also supervised the project as well as oversaw data analysis and manuscript drafting, and provided editorial input and administrative coordination. Fatema S. Al-Juboori was responsible for data curation, assisted in preparing the original manuscript, and was responsible for the literature review, validation of findings, and critical revisions of the manuscript. Ruqaia Jwad Kadhim contributed to formal analysis and funding acquisition. All authors read and approved the final version of the manuscript.

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