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Application of Kaplan-Meier Estimator Model for Validation of AURKC as an Early Biomarker for Kidney Cancer

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Abstract: Artificial neural networks are very powerful algorithms for predicting cancer survival results but evaluating their accuracy is vital and required for successful clinical application. This research introduces an enhanced Kaplan -Meier estimator model that contains new additional features for better validating AURKC as an early-stage prediction marker in kidney cancer. The enhancements include using a larger sample size (530 kidney cancer cases) and integrating additional variables such as AURKC expression, disease stage -1, follow-up threshold up to 150 months, sex, and race. These enhancements focus on improving predictive accuracy. Using public datasets TCGA, EGA, and GEO, genes linked to survival changes outcomes were detected. Log rank regression revealed AURKC as the top prognostic gene with a hazard rate of 2.36. High levels of AURKC linked to shorter survival in stage-1 were found in white male patients. In conclusion, integration of multi database analysis and advanced statistical models validates the identification and prioritizing of AURKC as a promising biomarker and as a target for drug development in malignancies, as well as kidney cancer.

Keywords: Kidney, Renal, AURKC, K-M plotter, Prediction, Public, Dataset

Introduction

Kidney cancer is the most common form of adult kidney cancer. It is classified among the top ten most common cancers in developed countries (Cairns et al., 2010; Warren et al., 2018). Its incidence has been regularly increasing globally (Siegelet al., 2017). The disease shows significant gender disparity, attacking men at twice the rate of women, with several genetic factors, such as proteins or genes overexpression, playing a crucial role in its development (Peired et al., 2021).

Early detection of kidney cancer is important for improving patient outcomes and reducing treatment costs (Dinesh et al., 2023). Advancements in human genome project and computational techniques have improved diagnostic accuracy and shortened the time required for diagnosis. Among these methods, machine learning, artificial intelligence, and Kaplan Meier statistical analysis. Machine learning and artificial intelligence methods concentrate on developing algorithms from data for prediction purposes (Matta et al., 2022). Techniques such as neural networks, are designed to estimate survival probability of cancer patients (Mahootiha et al., 2024). Deep learning, a subset of machine learning, incorporates statistical knowledge to build models for cancer prognosis (Kwang-Hyun et al., 2021; Chi et al., 2024). However, these methods require to be evaluated for their accuracy before they can be considered in clinical

settings. One promising approach is the application of Kaplan Meier estimator; a traditional method used in survival analysis. Although traditionally employed to estimate survival probabilities, recent studies have investigated its potential for analyzing data to detect disease at early stages (Jager et al., 2008, Zwyea, 2019; Alinia et al., 2024).

Previous studies often rely on machine learning classifiers, deep learning models trained on large datasets (Park et al., 2013; Lal et al., 2024). For example, Choudhury et al., 2020 employed convolutional neural networks to classify brain tumor. However, these methods require labeled datasets. Alternatively, survival analysis techniques like Kaplan Meier provide a statistical framework for understanding cancer progression over time, which can complement imaging based methods (Gyorffy et al., 2024). The current traditional KM model is the standard gold test for survival estimation. However, KM analysis considers only one patient characteristic at a time. In this study, refinements to K-M estimator model were introduced for renal cancer prediction at early stages. The enhanced KM model can assess conditional survival probabilities based on multiple known patient characteristics. Incorporating additional variables (or features) into the refined K-M model helps improve its capacity to render more patient's specific survival estimates capturing dependencies between patient features and survival times. Ultimately, this allows for more patient survival predictions. The enhanced model has the potential to provide more accurate; patient specific survival estimates and to detect better survival differences between subgroups limitations of the traditional KM method.

In prior research (Almansouri et al., 2020), expression profiling was utilized to compare the patterns between renal cancer tumors and matched normal tissues. Building on these results, custom renal cancer-specific microarrays containing 530 mRNA samples from renal cancer were created. The primary aims of this study were twofold: first, to identify gene level signatures that distinguish the patient's outcomes with renal cancer subtypes; and second, to discover new molecular subgroups. Additionally, analyzing the relationship between molecular changes, clinical and pathological variables, and patient outcomes to identify novel diagnostic and prognostic biomarkers for renal cancer.

Method

Data Preparation

A comprehensive, unbiased national dataset comprising patients registered between May 1, 2025, and June 20, 2025, from TCGA, EGA, and GEO was utilized. The data were incorporated into an enhanced Kaplan Meier (KM) model following the protocol, based on parameters such as sex (male or female), disease stage, follow-up threshold, and racial subgroup (Gyorffy et al., 2024). Since all patient information was not-identified, ethical approval from the review board for this study was not required in USA; referencing specific articles was sufficient for handling non-identified patient data. The dataset included 530 male and female. The model's performance was then compared to an available dataset from the human protein atlas, which included 100 patients, as well as to previous studies employing deep learning approaches for predicting survival in renal cancer patients. In K-M refined estimator model and the protein atlas, expression of AURKC, a protein crucial in cancer development, used as primary variable to categorize patients. Those with low AURKC mRNA expressions were considered to have better prognosis, while high AURKC expression was associated with a poorer prognosis. The log rank test was employed to check the statistical difference between AURKC level and patient's survival, significance set at a P value less than 0.05 (Harrington et al., 2005).

Kaplan-Meier Model Refinement

In this study using the K-M estimator model, the outcomes of 530 patients with renal cell carcinoma were tested. The enhanced model incorporates additional remarkable new prognostic variables, which are appointed in Table 1. First the data were arranged into sub-groups based on these variables, and then separate K-M plots were generated for each subgroup so it will give a better understanding of how these factors influence renal cancer prognosis and patient survival outcomes. Additionally, log rank test was utilized to compare the survival among sub-groups, focusing on determining if each variable has an effect and independently impacts early prognosis and whether there are statistical differences in survival among studied sub-groups. Survival time variable indicates the number in months from date of diagnosis to the end of the study because of death. Overall survival times were divided into two curves: first curve for patients with low AURKC mRNA levels (black color) and the other curve for those with high AURKC mRNA levels (red color). The refined model was used here because it improves the accuracy of survival analysis in censored data. It's also enhanced ability to accurately estimate survival across different sub-groups, so it can provide a better

understanding and comprehending of the prognostic factors impacting the outcomes of kedney cancer. Additionally, it demonstrated a closer fit to data from previous deep-learning based studies (Sun et al., 2007; Akram et al., 2021) and the human protein atlas (Nagy et al., 2021), as evidenced by comparison of their results. Thereby confirming the predictive accuracy of the K-M estimator model.

Even though software approaches for survival analysis are widely used, the enhanced model integrating multiple prognostic variables into refined K-M framework, enabling more detailed sub-groups analyses, survival predictions, and outcome estimates (Ching et al., 2018; Wei et al., 2022). The functions describing actual survival time $f(t)$, survival probability $s(t)$, hazard rate $h(t)$, and the overall survival model are expressed as functions of $s(t,x)$, which predict the likelihood that a patient with characteristics x will survive beyond time than t. here, T denotes the interval between treatment and death, and these are estimated as follows:

$$S(t,x) = (T > t/x) \quad (1)$$

$$h(t)\,dt = \frac{f(t)dt}{s(t)} \quad (2)$$

$$h(t) = \int_0^1 h(u)du \quad (3)$$

$$S(t) = e^{-H(t)} \quad (4)$$

Table 1. The data inputs for the refined estimator model

Method	Factor	Description
Refined Kaplan Meier Estimator Model	Larger sample size	Datasets from TCGA,EGA, and GEO
	Fellow up threshold	Up to 150 months
	Cutoff value	Cutoff value set at 27
	Histological stage	Kidney renal clear cell carcinoma Stage -1-
	AURKC	Probe Gene expression range between 5 and 87
	Male	Gender subgroup
	White	Racial subgroup

Results and Discussion

Assessment of the Refined Kaplan-Meier Estimator Model's Performance

Conventional Kaplan-Meier (K-M) model unable to detect renal cancer at early stages. To enhance its ability larger sample size was used and features were expanded by adding additional factors along with AURKC probe for expression (Table 1). The total data consist of 7489 patients. Among these, 530 patients were used for the enhanced model. The data of all 530 patients were then divided into subsets, to facilitate analysis, built on each added independent factor (histological stage, race, and gender) and generate a plot of the data for each subset to evaluate the performance of our enhanced K-M survival model. The findings indicated that within each subset, patients were categorized into two groups based on AURKC levels: one with high AURKC probe level and the other with low AURKC probe expression. Notably, among stage 1 patients, those with high AURKC expressions appeared to have the poorest prognosis, whereas patients with low AURKC expression experienced better and longer survival times (exceeding 150 months), as illustrated in figure 1A. In Figure 1B, white race patients with high AURKC expression also showed the worst prognosis result (p=1.1 x 10-7). Similarly, male patients with elevated AURKC levels indicated to have the poorest outcomes result (p=0.041), as shown in (Figure 1C). Overall, these results propose a significant and remarkable improvement in early disease prediction. Furthermore, a significant strong correlation and connection was observed between AURKC expression and patient survival in the early stages, with the logistic rank test showing a p value less than 0.05 (p=0.0026). The hazard ratio was computed (2.36), within the range of 1.01 to 5.52, indicating an increased probability of risk of death post-treatment for patients with high AURKC expression. To our knowledge, AURKC is often unregulated in various cancers due to mutations in its coding sequences, which can activate downstream signaling pathways involved in carcinogenesis. These findings highlight AURKC as a potential new

prognostic marker for early-stage kidney cancer patients. Additionally, the observed significant survival differences between subgroups suggest outcomes in kidney cancer patients within the studied cohort.

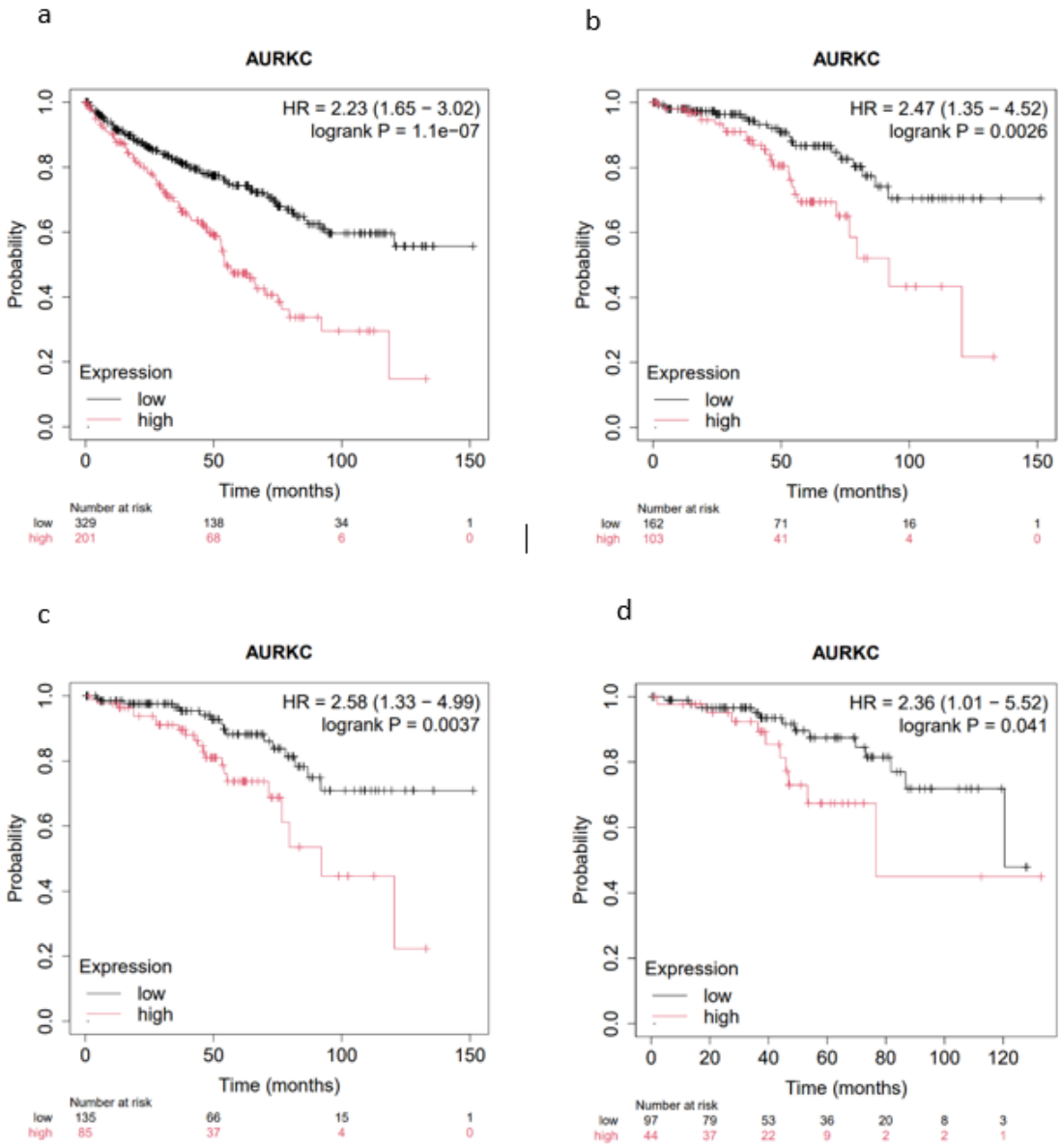

Figure 1. (a), Performance of K-M estimator model in kidney cancer (b), Performance of K-M estimator refined model in kidney cancer using stage 1 (c), Performance of K-M estimator refined model in kidney cancer using stage 1 and white race (d), Performance of K-M estimator refined model in kidney cancer using stage 1, white race and male gender.

Evaluation of the Kaplan-Meier Estimator Performance Using Public Datasets

To assess the refined model, the results were compared with data obtained from the human protein atlas, comprising 100 kidney cancer patients (77 alive, 23 dead; both males and females aged between 17-86 years) (Nagy et al., 2021). After normalizing the data and excluding missing values, we included the same variables used AURKC probe expression and stage1 and conducted survival analysis. The refined K-M model closely aligned with the dataset findings, showing that stage1 patients with high AURKC expression had the poorest prognosis and shortest survival,

whereas those with low expression experienced longer survival (Figure 2). The logistic test results in a p value of 0.0078, underscoring the significance. These results reinforce AURKC as a potential early-stage prognostic marker for kidney cancer. Further investigation into AURKC overexpression revealed, via RNA sequencing data (Figure 3), that mRNA level is significantly higher in patients compared to healthy individuals, suggesting that increased AURKC mRNA may promote tumor development in kidney tissues.

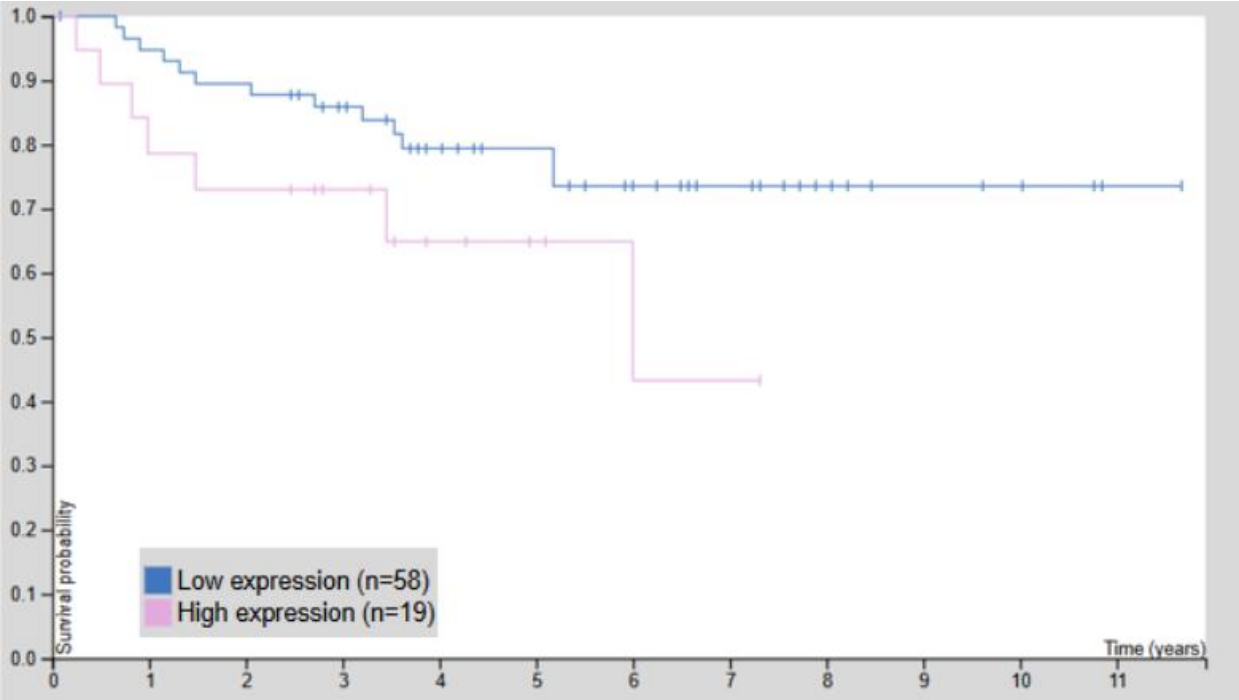

Figure 2. Performance of K-M estimator evaluated by public dataset

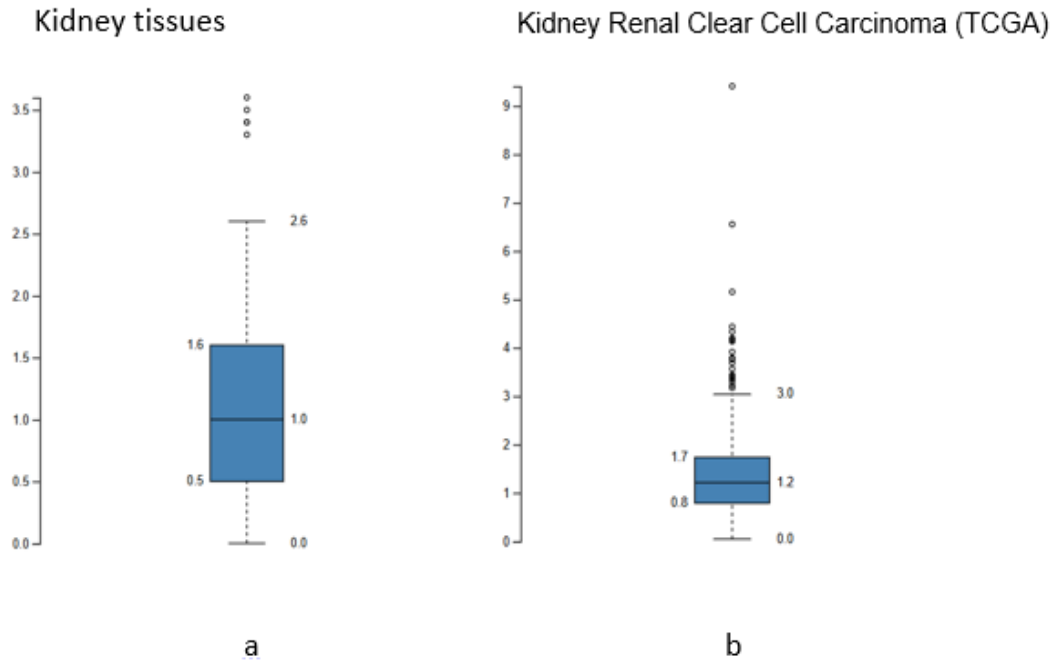

Figure 3. (a), RNA seq data of AURKC level in normal individuals (b), RNA seq of AURKC level in renal cancer patients

Comparison of Results from the Proposed Kaplan-Meier Model with Previous Deep Learning Studies

Our Kaplan-Meier (K-M) survival model were compared with previous deep learning based studies that used imaging and feature extraction methods (Wang et al., 2019; Courtiol et al., 2019; Chen et al., 2022; Srikantamurthy et al., 2023), as summarized in Table 2 for example, one study using CT scans of overian cancer achieved a C-index of 0.71, indicating good predictive accuracy, especially for patients with grade 1 tumors. Another study using histopathology images of mesothelioma had a lower C-index of 0.64, but still provided useful survival predictions, benefiting from the inclusion of clinical factors. A third study combined multiple data modalities to enhance performance. While we did not use multi-model approaches, our model outperformed some previous methods in early-stage survival prediction. Overall, Table 2 highlights the diverse deep learning techniques applied across different cancer types.

Table 2. Summary of comparable deep learning studies

Research study	Methods	Datasets	Performance
Our model	Biomarkers such as AURKC, stage-1, male gender and white race	TCGA, EGA, and GEO	-The outputs used to assess correlation significance between AURKC and patients survival, p value= 0.041 for the identification of kidney cancer but limiting the use of advanced methods (fusion of multiple models)
Wang et al. (2019)	Five customized 2D convolutional layers filter counts of 24,16,16,16, and 16 respectively.	Images from Ct scan	-The outputs from the CNN were used to construct the cox model and the c index of 0.71
Courtiol et al. (2019)	2D ResNet 50 for features extraction -each slide divided into 10000 tiles -3 classes for each tile	H and E slides	-MesoNet did not perform better than the regression model.
Chen et al. (2022)	A fusion model that integrates CT and gene data	CT images and gene expression	-The output used to identify imaging biomarker and survival the c index was 0.73
Srikantamurthy et al. (2023)	- A combination of CNN and long short-term memory (LSTM) recurrent neural network is utilized. - Both CNN and LSTM employ transfer learning method.	The Break His dataset includes 2480 benign and 5429 malignant samples.	- An Overall accuracy of 99% was achieved for binary classification, while 92.5% accuracy was obtained for Multiclass-classification

Conclusion

In this study, the effectiveness of the Kaplan-Meier (K-M) survival estimator in predicting early stage renal cancer was highlighted. By identifying AURKC as a novel biomarker, we support its use in renal cancer survival analysis.

The traditional K-M model was enhanced by integrating additional prognostic variables, resulting in more accurate survival predictions based on datasets from TCGA, EGA, and GEO. This refined model, which uses logistic hazard-based estimation, provides dependable and reliable survival curves than traditional Cox regression models. Interestingly, the enhanced K-M model has the potential to provide more precise and accurate survival estimates and reveal variances between patient's sub-groups that the conventional KM model is unable to detect. These findings and results suggest that enhanced K-M can effectively detect and identify AURKC as a predictive biomarker for renal cell carcinoma, supporting clinical decision making, treatment planning, and clinical trial design. However, a pitfall and restriction of public datasets utilizing is narrowing the opportunity to apply and use advanced methods like deep learning fusion models (Joshi et al., 2023; Maha et al., 2022). Overall, our research consistent with other studies that use deep learning and advanced statistical techniques for cancer prognosis, adds new insights and perception and future research directions into biomarker discovery in medical science.

Recommendations

Future studies and research can be explored such as the integration of hybrid (deep learning-based fusion) models and biological data. Incorporating additional predictive markers such as genetic mutations and immune profiles can improve survival predictions. Moreover, applying feature engineering strategies, such as special context assessment, may help detect heterogeneity within datasets. The integrated models might provide more accurate predictive biomarkers in renal cancer.

Data Availability

* The dataset links: https://kmplot.com and https://www.proteinatlas.org.

Scientific Ethics Declaration

* The authors declares that the scientific, ethical, and legal responsibility for this article published in EPSTEM journal held by the authors.

Conflicts of interest

* The authors declare that they have no conflicts of interest.

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