

Cox Model Improvement Using Residual Blocks in Neural Networks: A Study on the Predictive Model of Cervical Cancer Mortality

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ABSTRACT

Cervical cancer is the fourth most common cancer in women worldwide, and more than 604,000 new cases were reported in 2020 alone, resulting in approximately 341,831 deaths. The Cox regression model is a major model widely adopted in cancer research, but considering the existence of nonlinear associations, it faces limitations due to linear assumptions. To address this problem, this paper proposes ResSurvNet, a new model that improves the accuracy of cervical cancer mortality prediction using ResNet's residual learning framework. This model showed accuracy that outperforms the DNN, CPH, CoxLasso, Cox Gradient Boost, and RSF models compared in this study. As this model showed accuracy that outperformed the DNN, CPH, CoxLasso, Cox Gradient Boost, and RSF models compared in this study, this excellent predictive performance demonstrates great value in early diagnosis and treatment strategy establishment in the management of cervical cancer patients and represents significant progress in the field of survival analysis.

Keywords : Cervical Cancer, Survival Prediction Model, Cox Proportional Hazards, Machine Learning, Deep Neural Networks, ResNet

신경망 내 잔여 블록을 활용한 콕스 모델 개선: 자궁경부암 사망률 예측모형 연구

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요 약

자궁경부암은 전 세계적으로 여성에게 발생하는 암 중 네 번째로 흔한 암이며, 2020년 한 해 동안 60만 4천 건 이상의 신규 케이스가 보고되었고 이로 인한 사망자 수는 약 34만 1천 831명에 달했다. 콕스 회귀 모델은 암 연구에서 널리 채택되고 있는 주요 모델이지만, 비선형 연관성의 존재를 고려하면 선형 가정으로 인해 한계에 부딪힌다. 이러한 문제를 해결하기 위해, 본 논문에서는 ResNet의 잔여 학습 프레임워크를 활용하여 자궁경부암 사망률 예측의 정확성을 개선한 새로운 모델인 ResSurvNet을 제안한다. 이 모델은 본 연구에서 비교한 DNN, CPH, CoxLasso, Cox Gradient Boost, RSF 모델들을 능가하는 정확도를 보여주었기에 이러한 우수한 예측 성능은 자궁경부암 환자 관리에 있어 조기 진단 및 치료 전략 수립에 기여할 수 있고 임상적으로 적용할 때 큰 가치가 있음을 입증하며, 생존 분석 분야에서도 의미 있는 진전을 나타낸다.

키워드 : 자궁경부암, 생존 예측 모델, 콕스 비례 위험, 기계 학습, 심층 신경망, ResNet

1. Introduction

According to the World Cancer Research Fund Interna-

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tional, cervical cancer is the fourth most common cancer among women worldwide. In 2020, there were over 604,000 new cases of cervical cancer diagnosed globally, with approximately 341,831 women dying from the disease [1]. While cervical cancer incidence rates remain high in many regions worldwide, they have been gradually decreasing in South Korea but still maintain a relatively high level compared to the United States. Early detection of cervical cancer is crucial as survival rates are significantly higher when detected early, emphasizing the importance of prevention and early detection [2].

Early detection of cancer is closely associated with sur-

vival, making more accurate predictions vital in increasing patients' chances of survival. In the medical field, researchers have primarily used the Cox proportional hazard model as the basic statistical approach to predict survival rates for comparing differences among groups. However, this model often fails to capture the complexity of real-world environments and struggles to account for nonlinear relationships due to its linear assumptions. As a solution, new approaches are being proposed to consider more suitable nonlinear variables for complex and extensive real-world data. Optimization-based hybrid approaches combining multiple modalities, such as EEG and fNIRS, have been explored for brain-computer interfaces [3], suggesting the potential of integrating diverse data sources and optimization techniques in neural network models. Multistage, multiclass transfer learning frameworks using convolutional neural networks (CNNs) have been developed for chest infection diagnosis [4], highlighting the effectiveness of transfer learning and CNNs in medical image classification tasks.

Recently, survival analysis-based research using not only statistical approaches but also various artificial intelligence models has been actively conducted in the medical field. For instance, in predicting cancer incidence rates, models such as the Random Survival Forest, an extension of the Random Forest algorithm, are utilized [5]. Moreover, recent advancements in self-supervised learning (SSL) techniques have shown promising results in various deep learning contexts motivating their potential application in survival analysis tasks [6]. Deep learning has also been applied to assist in human embryo viability assessment for in vitro fertilization [7], showcasing the wide-ranging potential of deep learning techniques in various medical domains beyond survival analysis.

In this study, we compare the survival prediction accuracy of Cox proportional hazard (CPH) models, deep learning neural network models, and machine learning models for newly diagnosed cervical cancer patients. We aim to derive the most performant model and propose a novel model, "ResSurvNet," which is more efficient than the best-performing model identified.

2. Issue and Related Works

Traditional statistical approaches such as Cox Proportional Hazard (CPH) regression models tend to yield lower performance as the complexity and volume of data in-

crease, making statistical inference more challenging. In contrast, machine learning and deep learning approaches enable relatively accurate result predictions through automated learning and algorithms. To address the problem of deteriorating performance when using conventional statistical models, a new approach is proposed by combining the ResNet model, commonly used in the computer vision field, with the Cox model [8,9].

2.1 Trends

Recent research on prognosis prediction of cervical cancer using machine learning and deep learning techniques has been actively conducted. In particular, in studies utilizing large-scale patient data, survival prediction of cervical cancer is being performed based on numerous patient information. In these studies, machine learning algorithms such as random forest, logistic regression, and support vector machine are used to analyze patient characteristics and tumor properties, and to build models predicting prognosis [10].

Furthermore, with the increasing incorporation of deep learning technology, recent studies on predicting the prognosis of cervical cancer have applied deep learning algorithms using large-scale datasets. Especially, in retrospective studies based on the SEER database, the complex patterns of patient data are being investigated by comparing conventional statistical models with deep learning approaches. These research findings are promoting the development of new methodologies to improve prognosis prediction of cervical cancer. Therefore, the utilization of machine learning and deep learning technologies is expected to play a crucial role in the treatment and management of patients [11].

2.2 Healthcare Prediction Research Scalability

The optimization of deep learning network architectures and the effective integration of diverse information sources are pivotal in enhancing performance in medical prediction tasks. Selecting optimal deep learning network architectures and fusing information from multiple sources has been shown to enhance COVID-19 detection performance [12], suggesting the importance of model selection and information integration in medical prediction tasks. Various optimization techniques, such as Adadelta, RMSProp, and AdaMax, have been employed with multi-layer perceptrons to enhance brain stroke detection accuracy [13], highlighting the significance of optimizer

choice in deep learning models for medical applications. Deep learning-based classification models have been successfully applied to diagnose abrasion and ischemic diabetic foot sores using camera-captured images [14], demonstrating the versatility of deep learning in analyzing diverse medical image data. Network selection and feature optimization techniques have been utilized in deep learning models for breast cancer detection from ultrasonography images [15], emphasizing the importance of model architecture and feature engineering in medical image analysis tasks. This underscores the relevance to previous research and the critical role of deep learning in driving innovation in healthcare settings.

2.3 Data Source

The study was conducted based on the National Cancer Center database. The internal patient database of the National Cancer Center contains structured data such as cancer registration, diagnosis, death, test results, treatment information, as well as unstructured electronic medical record (EMR) data. These data were provided upon request after approval from the National Cancer Center Data Management Committee, and all patient data were anonymized before distribution to maintain confidentiality.

2.4 Model

The main objective of this study was to perform a survival analysis of patients with cervical cancer and compare the performance of various models. For this purpose, we employed the most traditional CPH regression model along with three machine learning methods—RSF, Cox Lasso, and Cox Gradient Boost—and a DNN model. Experiments were conducted using a 10-fold cross-validation to evaluate and compare the performance of each model [16].

The second objective of this study was to select the best-performing model among the compared models and further enhance its performance. Through this process, we aimed to identify the key factors related to survival prediction in patients with cervical cancer and to improve prediction accuracy. Death events were defined as overall survival (OS) and disease-specific survival (DSS), representing the time interval from the initial diagnosis to death from all causes and death specifically due to cervical cancer, respectively [17,18].

In this study, we applied a total of 5 models using vari-

ous approaches. The first approach utilized a statistical Cox Proportional Hazards regression model. This model is widely used in survival analysis and can evaluate the influence of various variables by considering changes in the hazard rate over time.

Secondly, machine learning methods were employed, applying Random Survival Forest (RSF), Cox Lasso, and Cox Gradient Boost models. RSF is an ensemble method specialized for survival analysis, providing high accuracy for complex survival data. Cox Lasso selects important explanatory variables and simplifies the model, useful for high-dimensional data. Cox Gradient Boost captures complex patterns in survival analysis data using the Gradient Boost technique and optimizes the ensemble [19].

Lastly, a deep learning approach was employed to estimate patients' survival risks using a subnetwork of deep neural networks with a single output node. This model combines the Cox Proportional Hazards model with a regression model to predict survival times. Constructed by optimizing the negative logarithm of the partial likelihood function, this model features a hierarchical structure comprising multiple hidden layers. Each layer transforms inputs through linear transformations and ReLU activation functions, with dropout applied to prevent overfitting. The hidden layers are set to 32, with a dropout rate of 0.1. The learning rate is set to 0.001.

Additionally, the model consists of two sub-networks: the first sub-network serves as a regression model to predict survival times, while the second sub-network evaluates the risk of death based on the Cox Proportional Hazards model. Each sub-network is trained using an appropriate loss function tailored to its objective [20].

Additionally, this study introduces the newly proposed ResSurvNet model, which extends ResNet tailored for survival analysis tasks. It performs optimized learning through deep layers using ResNet's residual learning framework. While ResNet is primarily used in image recognition, in this study, it is applied to survival analysis to handle complex data and modeling.

2.5 Evaluation Method

To analyze the research findings, the evaluation metrics used are the Concordance Index (C-Index) and Mean Absolute Error (MAE). The C-Index is commonly used in survival analysis, comparing the predicted hazard ratio order with the actual event occurrence order to assess

model accuracy. A value closer to 1 indicates better predictive ability. Additionally, the MAE metric represents the average error between predicted and actual survival times. These evaluation metrics play a crucial role in quantitatively assessing model performance [21].

3. Study Scheme

3.1 Study Population

The present study utilized data from patients within the National Cancer Center. This data was obtained through customized applications and received approval from the Data Review Board after undergoing review by the Institutional Review Board. Data with a high degree of missing values were excluded, and clinically significant variables, such as Lymph node, Metastasis, and Recurrence, were preprocessed from the National Cancer Center's EMR unstructured data, then incorporated into the analysis.

The study population consisted of patients registered in cancer registration data as having uterine cancer (based on ICD-10 codes: 'C53', 'C54', 'C55', 'D06') from 2001 to 2020. Among them, patients diagnosed with cervical cancer were defined based on oncology ICD-O and ICD-10 codes as "C53". Specific exclusion criteria corresponding to "FIGURE 1" were as follows: 1) Patients diagnosed with cervical cancer from 2002 to 2019, 2) Patients under the age of 20 at the time of initial diagnosis, 3) Patients diagnosed with other cancers before or at the time of cervical cancer diagnosis, 4) Patients with unspecified STAGE 1-4, and 5) Patients with a follow-up period of less than 1 year. A total of 3,498 subjects meeting these exclusion criteria were excluded, resulting in a final analysis cohort of 2,283 subjects [22].

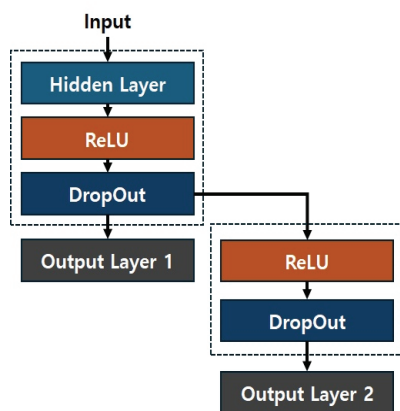


Fig. 1. DNN(Deep Neural Network) Architecture

3.2 Research Methodology

The main objective of this study is to perform survival analysis on cervical cancer patients and compare the performance of various models. For this purpose, we employ the most traditional Cox Proportional Hazards (CPH) regression model along with three machine learning methods: Random Survival Forest (RSF), Cox Lasso, Cox Gradient Boost, and a deep neural network model. The experiments are conducted using 10-fold cross-validation to evaluate and compare the performance of each model.

Additionally, the second goal of the study is to select the best-performing model among the compared models and further enhance its performance. Through this process, we aim to identify key factors related to predicting survival in cervical cancer patients and improve the accuracy of predictions. The events of death are defined as Overall Survival (OS) and Disease Specific Survival (DSS), representing the time interval from initial diagnosis to death from all causes and death specifically due to cervical cancer, respectively.

3.3 Characteristics of Study Population

In this study, the main variables for predicting cervical cancer survival were selected based on the cancer stage, histology, treatment method, and tumor-related informa-

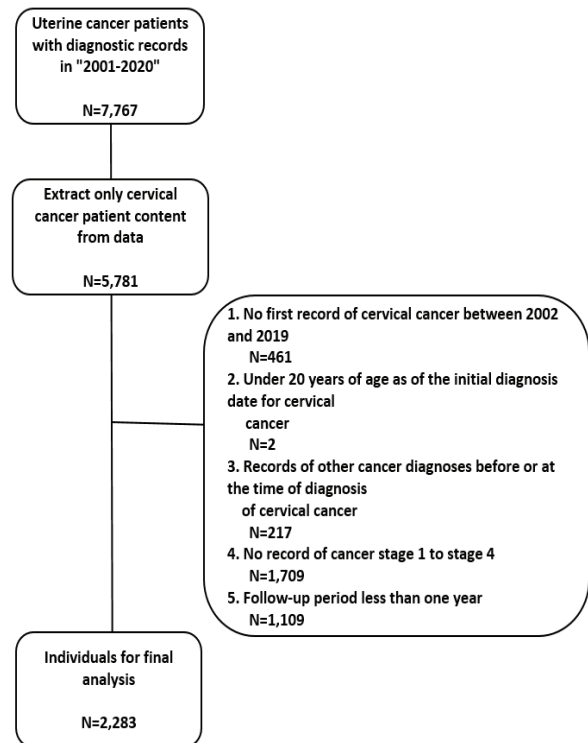


Fig. 2. Data Preprocessing Process for Research

Table 1. Baseline Characteristics of the Study Population

Features	Total Patient N = 2,283	
	N	%
Age		
mean,std	51.046(12.99)	
20-30	55	2.41%
30-40	411	18.00%
40-50	667	29.22%
50-60	552	24.18%
60-70	369	16.16%
70-80	188	8.23%
>=80	41	1.80%
Stage		
stage I	1,137	49.80%
stage II	678	29.70%
stage III	244	10.69%
stage IV	224	9.81%
Histologic condition		
Squamous cell	1,716	75.16%
Adenocarcinoma	385	16.86%
Adenosquamous	87	3.81%
Other	95	4.16%
Surgery		
NO	785	34.38%
YES	1,498	65.62%
Radiotherapy		
NO	1,060	46.43%
YES	1,223	53.57%
Chemotherapy		
NO	1,382	60.53%
YES	901	39.47%
lymph node		
NO	1,602	70.17%
YES	681	29.83%
Metastasis		
NO	1,300	56.94%
YES	983	43.06%
Recurrence		
NO	1,848	80.95%
YES	435	19.05%
Diagnosis of other cancers after cervical cancer diagnosis		
NO	2,176	95.31%
YES	107	4.69%

tion. These variables have significant impacts on the survival prediction model and were systematically extracted from clinical and image-based data. Drawing from various research findings in previous studies¹¹, it was confirmed that the selected variables play an important role in predicting cervical cancer survival.

This study analyzed a total of 2,283 patients. The average age of the study participants was measured at 51.046 ± 12.99 years old, with the majority being at stage 1 of the disease. Regarding histological characteristics, the analysis revealed that the majority of patients had "Squamous cell" type. Therapeutically, most patients underwent surgery and radiation therapy, while only approximately 30% received chemotherapy. Metastasis accounted for the highest proportion in tumor progression, and patients diagnosed with cancers other than cervical cancer comprised approximately 4% of the total.

In EMR data, among patients with positive records of cervical cancer tumors, a variable named "metastasis" was created based on the record of metastasis. Subsequently, a variable named "recurrence" was generated based on the record of recurrence. Additionally, among patients with previous records of "metastasis," the lymph node variable was established based on the record of lymph node. Furthermore, the variable "Diagnosis of other cancers after cervical cancer diagnosis" was defined using structured data, specifically based on newly diagnosed cancer codes (ICD codes starting with "C") following the diagnosis of cervical cancer.

4. Results and Performance Analysis

4.1 Survival Analysis models comparison

Upon summarizing the results from Fig. 2, it is observed that when considering the average outcomes of Overall Survival (OS) and Disease-Specific Survival (DSS), Random Survival Forest (RSF) exhibits superior performance compared to Cox Proportional Hazards (CPH). However, Deep Neural Networks (DNN) also demonstrate a high level of performance, which is comparable to RSF. Therefore, the performance of the models can be ranked as follows: Random Survival Forest (0.794/0.808), Deep Neural Networks (0.787/0.804), Cox Gradient Boosting (0.785/0.795), Cox Lasso (0.771/0.794), Cox PH (0.770/0.792).

According to the analysis of Mean Absolute Error (MAE), Deep Neural Networks (DNN) exhibited significantly lower values compared to other models, indicating better performance. Additionally, considering the average performance across OS and DSS, the performance of the models is ranked as follows: Deep Neural Networks (50.227/51.369), Random Survival Forest (89.924/99.422), Cox Lasso (109.434/113.978), Cox Gradient Boosting (109.438/113.989), Cox PH (109.444/113.988).

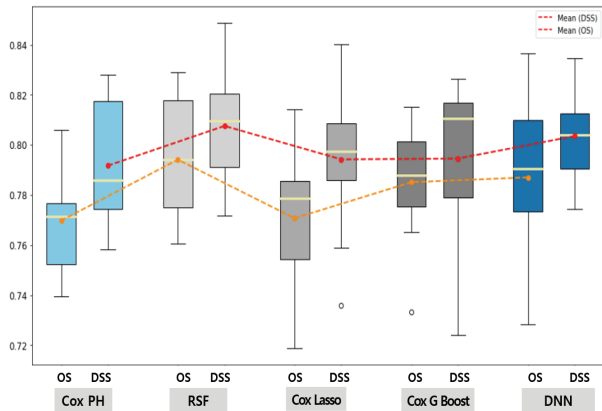


Fig. 3. Comparison of the Survival Analysis Models c-index

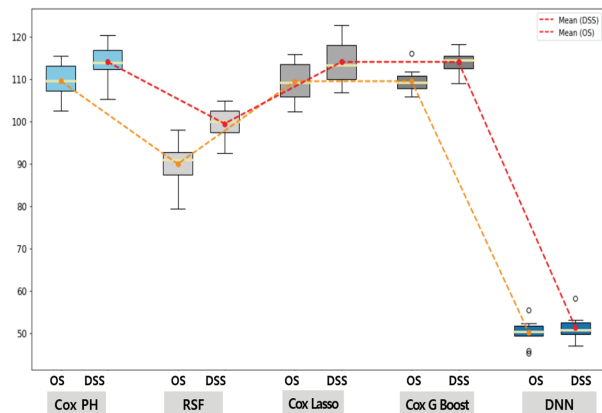


Fig. 4. Comparison of the Survival Analysis Models Mean Absolute Error

In summary, Random Survival Forest and Deep Neural Networks exhibited the highest values in Concordance Index (C-Index). However, considering other metrics such as Mean absolute error(MAE), Deep Neural Networks showed significantly superior performance, indicating it as the outstanding model among the compared models. Taking these results into account, we aim to implement a deep neural network model to achieve better performance than Cox analysis. Therefore, leveraging the advantages of deep neural network models, we seek to develop a model suitable for survival analysis.

4.2 ResSurvNet performance

The structure of ResSurvNet proposed in this study is similar to the existing deep learning architectures with Residual Blocks and FC Layers added, as depicted in Figure 4. ResSurvNet aims to increase accuracy during model architecture design by incorporating residual connections (Residual Blocks) and deepening the neural network. Additionally, an Output Layer is included to pre-

dict various events. Each linear layer has doubled in size to [64, 64] compared to the previous model structure, with Dropout Layers added to prevent overfitting. Furthermore, a Fully connected Layer with up to 2048 units before the output layer is utilized. ReLU activation function is employed to increase learning speed and address the vanishing gradient problem.

The Residual Blocks in ResSurvNet effectively address the vanishing gradient problem that arises as the network deepens. This structure operates by adding the result of the previous layer to the next layer instead of directly feeding into the next layer. This approach mitigates the vanishing gradient problem as the network deepens, enhancing learning stability. It has been demonstrated to be useful when training on larger amounts of numerical data, and it achieves superior prediction performance compared to Cox models [23]. Consequently, leveraging these characteristics, a new model development analysis was conducted to achieve superior prediction performance compared to Cox models.

Table 2 shows the comparison of survival analysis models, wherein when comparing Survival Analysis models in figure 2 and 3, Random Survival Forest and Cox Gradient Boosting showed the best performance. Therefore, we performed comparisons with RSF and Cox Gradient Boosting to evaluate the performance of ResSurvNet. In the C-index for Overall Survival (OS), ResSurvNet exhibited the highest average and maximum values. However, for Disease-Specific Survival (DSS), Random Survival Forest showed the highest average value at 0.808, while

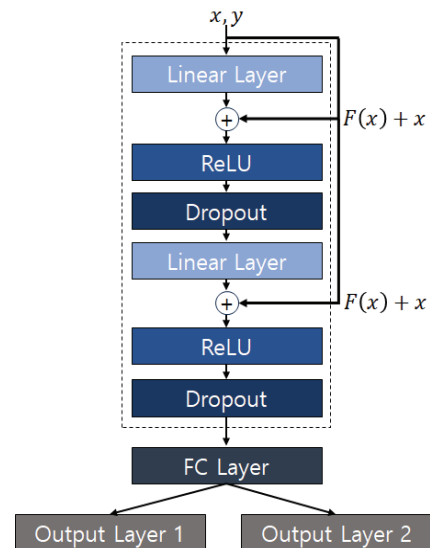


Fig. 5. ResSurvNet Architecture

Table 2. Comparison Survival Analysis Models and ResSurvNet

Model	Concordance index	Mean Absolute Error
	mean (min-25%-75%-max)	
overall survival		
Random Survival Forest	0.794 (0.761-0.755-0.818-0.829)	89.924 (79.420-87.338-92.667-97.917)
Cox Gandient Boosting	0.785 (0.733-0.776-0.801-0.815)	109.438 (105.897-107.850-110.774-116.041)
ResSurvNet	0.796 (0.763-0.784-0.811-0.825)	49.219 (45.344-47.017-50.091-56.182)
Disease specitic survival		
Random Survival Forest	0.808 (0.722-0.791-0.820-0.849)	99.422 (92.418-97.439-102.414-104.847)
Cox Gandient Boosting	0.795 (0.734-0.787-0.822-0.826)	113.989 (109.004-1120478-115.357-118.167)
ResSurvNet	0.800 (0.764-0.779-0.814-0.857)	49.026 (45.382-47.338-50.845-52.170)

ResSurvNet achieved the highest maximum value at 0.857. These results suggest that ResSurvNet can offer robust performance across various survival analysis tasks.

ResSurvNet exhibits excellent performance in Mean Absolute Error (MAE), recording the lowest MAE values of 49.219 and 49.026 for Overall Survival (OS) and Disease-Specific Survival (DSS) respectively. Additionally, ResSurvNet's maximum and minimum values outperform those of other models. Consequently, ResSurvNet demonstrates a performance difference of over 40 compared to other models, showcasing superiority in prediction consistency and accuracy.

In summary, ResSurvNet demonstrates notable performance in survival analysis. Compared to other models, it achieves the highest C-index for Overall Survival (OS) and also performs well in Disease-Specific Survival (DSS). These results indicate that ResSurvNet sets a new standard in survival prediction, showcasing superior consistency and accuracy, as evidenced by its impressive performance in MAE as well. Overall, ResSurvNet is poised to drive significant advancements in the field of survival analysis.

5. Conclusion

The study compared CPH, Cox Lasso, Cox Gradient Boost, Random Survival Forest, and DNN models for OS and DSS mortality events, respectively. Ultimately, the DNN model exhibited the best performance. This highlights the superior performance of artificial intelligence techniques over traditional statistical methods in predicting various mortality events. Consequently, the researchers proposed ResSurvNet, which incorporates a Residual Block structure into the DNN model. ResSurvNet demonstrated higher maximum C-index values and lower MAE values compared to the baseline DNN model, con-

firming its superiority.

Currently, the researchers are conducting Hyperparameter tuning to further enhance the performance of ResSurvNet and plan to collect additional datasets to better leverage the strengths of deep learning models. Through these efforts, the study aims to propose more advanced deep learning network structures for future survival analysis research. ResSurvNet, as presented in this study, serves as a form of predictive model for survival analysis, applicable to various studies including survival rate prediction for different types of cancer such as cervical cancer. This model is expected to be effectively applied not only in medical but also in other fields, supporting personalized treatment strategies and decision-making processes.

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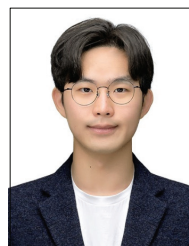


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