Research Article

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Development of a deep learning survival model to predict the individual risks of peritoneal metastasis of colorectal cancer.

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Running Head : A Deep Learning Survival Model in PM

Highlight : We have applied deep learning techniques to construct an artificial intelligent model that can automatically predict survival of colorectal cancer patients with peritoneal metastasis. It focused more on the prediction of individual patients that can help design personalized treatments. With the combination of deep learning and statistical methods, our study provided a new perspective while dealing with complex survival analysis.

ABSTRACT

Background : Peritoneal metastasis (PM) has been considered to be the terminal stage of colorectal cancer (CRC) due to poor prognosis. We purposed to construct an AI model of clinicopathological parameters to predict the survival prognosis of PM in CRC.

Methods : Our model was constructed through modifying a classic neural network with COX proportional hazards as loss function in the training cohort. It is able to predict the overall survival (OS) of each individual patient with clinicopathological parameters. Multivariate analysis was conducted to identify independent risk factors for the prognosis of PM patients.

Results and Conclusion : In the testing cohort, the deep learning model show good performance with the c-index of 0.76 and brier score of 0.20.

Conclusions : We have developed a deep learning model to predict the survival of individual patients precisely. It can provide evidence to apply personalized treatments and assisted surgeon to select optical treatments for CRC patients with PM.

Keywords
Artificial Intelligent, Deep Learning, Colorectal Cancer, Peritoneal Metastasis, Survival.

INTRODUCTION

The incidence of colorectal cancer (CRC) has increased rapidly around the world. There were approximately 1.85 million new cases of colorectal cancer worldwide per year, ranking the third amongst the spectrum of malignant tumors. The CRC-related deaths were 900,000 each year, ranking second position in the spectrum of malignant tumor death[1]. The metastasis of tumor cells is the main cause of death, including liver, lung, and peritoneum cavity[2]. Among these organs, the incidence of simultaneous peritoneal metastasis (S-PM) is from 12% to 20%, and the incidence of metachronous PM S-(M-PM) reach 44% to 50%[3]. PM has been considered to be the terminal stage of CRC (IVc stage) because poor prognosis of PM according to TNM staging[4]. Since the 1990s, studies reported that cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is the recommended therapy for CRC patients with PM, which significantly improved

the prognosis and even achieve long-term survival in some cases[5]. The median overall survival (OS) of CRC patients with PM underwent CRS+HIPEC was 22-42 months, while palliative chemotherapy obtained median OS of only 13 months[6].

However, main challenge is the selection of optical patients who can achieve benefit from CRS. Some studies provide clinicians and researchers with a prognostic survival prediction tool. Pelz developed the peritoneal surface disease severity score (PSDSS). It includes prognostic factors such as the extent of PM (peritoneal cancer index, PCI), presence of clinical symptoms, and histopathological features of the primary tumor. At the same time, various nomograms have been used to predict the prognosis of PM patients. However, the risk factors of survival outcomes are based on the previous literature, and only a few parameters are included in one study due to traditional analyses with cox proportional risk regression, which need specified fixed weights, and missing data were not allowed. For PM patients, not all patients undergo systematic treatment due to treatment decisions and personal financial reasons. Due to incomplete clinical data, these patients can't opt for previous prognostic models. All these prediction models were outdated and rigid tools. Therefore, new approaches to better personalize treatment strategy are urgent.

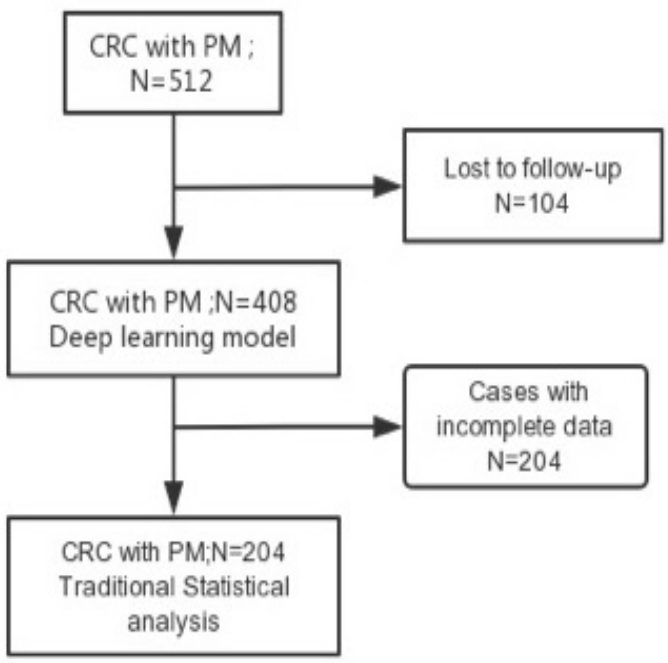
Recently, artificial intelligence (AI) has obtained big advances in tumor diagnosis, treatment response and survival prediction in many cancers[13, 14]. AI is a form of new technological sciences that simulates and extends human intelligence. Deep learning is a branch of artificial intelligence that uses algorithmic approaches to learn from large, heterogeneous sets of data and perform specific tasks without predetermined rules. DL reveals huge advantages in the field of medical big data and imaging mining compared to human brain. However, many current machine learning algorithms are essentially "black boxes" in which the model cannot explain the results of the model, leading to doctors' inability to trust the predictive power of the model. Therefore, in this study, we aimed to construct a DL model that can predict the individual survival prognosis curve of CRC patients with PM, thus made possible explanation for factors of clinical concerns. Utilizing this model to provide guidance for individualized treatments based on the result of individual survival prognosis curve.

METHODS

Patients

In this study, both S-PM and P-PM of CRC patients were included. The criteria of inclusion were as follows: (1) Pathological diagnosis of PM in the Sixth Affiliated Hospital of Sun Yat-sen University between March 2012 to August 2019; (2) Patients with complete follow-up data. Patients were identified from one prospective maintained database of colorectal cancers by professionals. Informed consent was obtained when they were enrolled into this database. The last follow-up time of enrolled patients was August 31, 2019. The inclusion and exclusion criterions were visualized in a flowchart (Figure 1)

Figure 1: Flow chart of patient selection.



Clinicopathological parameters

Clinicopathological parameters that were included to construct AI model were as follows: gender, age, body mass index (BMI); tumor location, carcinoembryonic antigen (CEA), cancer cell surface antigen (CA) 125, CA15-3 and 19-9, AFP; bowel obstruction, bowel fistula, CRS, HIPEC, chemotherapy; pT stage, pN stage, lymph node metastasis, number of positive lymph nodes, vascular nerve bundle invasion, differentiation, pathological type, and KRAS/BRAF/PIK gene mutational status.

Construction and Validation of the Deep Learning Model

The construction of deep learning model in this study were performed through Python (Version 3.8). We have applied a model called DeepSurv [15], which is a deep neural network with negative logarithm of Cox proportional likelihood as loss function. It is a survival method to find the survival duration of patients with features selected from clinicopathological parameters. The DeepSurv model is constructed through modifying a classic neural network called Multi-layer Perceptron (MLP), which is consisted of three layers: input layer, three hidden layers and output layer (Figure 2).

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Figure 2

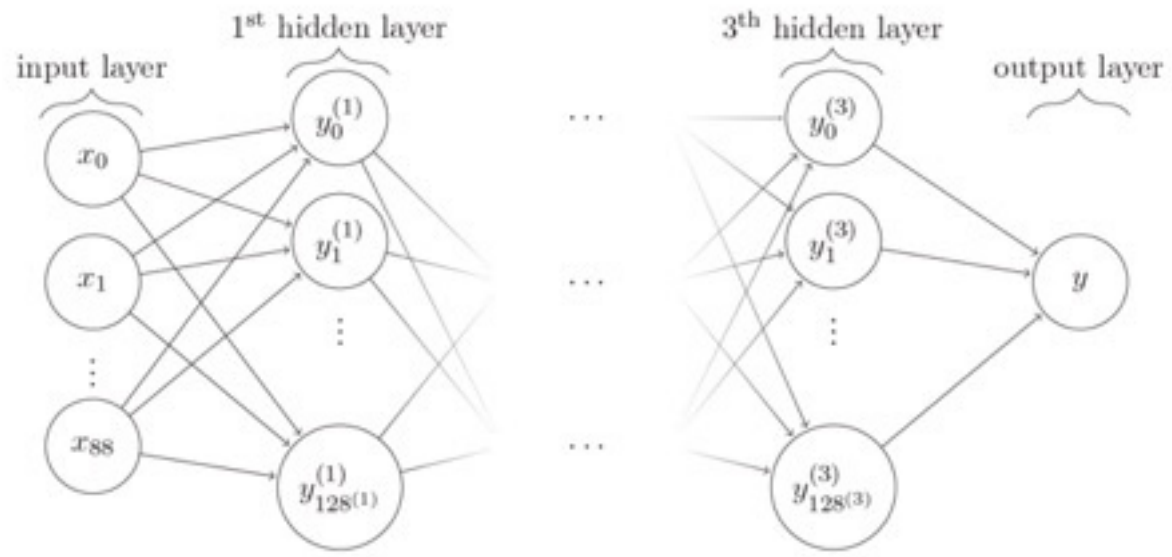

Figure 2 : Network graph of a Multilayer Perceptron. It contained three hidden layers in the middle of input layer and output layer. This perceptron had 88 input units and 1 output unit. Each hidden layer contains 128 hidden units.

The output of the network is a single node, which estimates the risk function h_θ (x) parameterized by the weights of the network θ. Since the loss function measures how far an estimated value is from its true value, we have chosen the negative log of Cox partial likelihood, which is the product of the probability at each event time T_i that the event has occurred to individual i, given the set of individuals still at risk at time T_i.

$$l(\theta) = -\sum\left(\bar{h}_\theta(x_i) - \log\sum\exp\left(h_\theta(x_i)\right)\right)$$

Moreover, some advanced DL methods have been applied in order to tune the hyper-parameters in this model, including the rectified linear activation function (ReLU), Adaptive Moment Estimation (Adam) as the gradient descent algorithm, learning rate scheduling, random hyper-parameter optimization search, and batch norm and dropout. Early Stopping callback to stop training were also included when the validation loss stops improving. After training, this callback will also load the best performing model in terms of validation loss.

Training, validation and testing sets were divided from a registry of patients. Testing set accounted for 20% of the whole dataset; Training set was accounting for 80%× 80%=64% of the total patients, while validation cohort had the remaining 16% of patients. We aimed to construct the survival model for each patient and then evaluated the performance of DL model. As cox proportional hazards regression is semi-parametric method, we have calculated the non-parametric baseline hazard estimates. Moreover, the concordance (C-index), brier score and binomial log-likelihood were used to further estimate the goodness-of-fit and censoring distribution by Kaplan-Meier curve on the test set. The C-index shows the probability that, for a random pair of individuals, the predicted survival times of the two individuals have the same ordering as their true survival times. The brier score is used to evaluate the accuracy of a predicted survival function at a given time t; it represents the average squared distances between the observed survival status and the predicted survival probability and is always a number between 0 and 1, with 0 being the best possible value.

Missing Data Imputation

In this study, the clinical data of some patients was incomplete due to the respective study. Since the deep learning model is unable to handle missing data and was very sensitive to inaccurate alteration, data imputation was necessary. For continuous variables such as CEA, CA199, CA125, CA153, AFP and BMI, median 10.51 ng/ml, 34.98 U/ml, 57.65 U/ml, 9.00 U/ml, 2.52 ng/ml and 20.96 kg/m was applied to replace missing values respectfully. The average of these features was influenced by extremums and was too large to be used as data imputation. For other dummy variables, missing data was separated as an individual column indicating by 0/1.

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RESULTS

Patient demographics

A total of 408 CRC patients with PM were included in the AI model for training set. The clinicopathologic factors and treatment details of the patients were shown in Table 1. Among them, 349 (85.54%) patients received CRS and 175 (42.89%) patients of them reached CCR0-1, which indicates that most of tumors were removed. 174 (42.65%) patients received only CCR2-3, which shows the diameters of residual tumors were > 2.5mm. In addition, 155 patients (37.99%) received HIPEC and 210 patients (51.47%) received chemotherapy.

DL Model performance

A total of 408 PM patients were enrolled to construct the deep learning model. Based on the proportion of 8:2, we first divided the dataset into two parts: 326 patients were used as the training set, while the remaining 82 were classified as testing set. Within the training set, we then performed the division again based on the proportion of 80% as training group and 20% as validation group. Finally, we had 261 patients in training set; 65 in validation set and 82 in prediction set. After construction of the DeepSurv model in training set and finetuned it with validation set, we evaluate the prediction power in the testing set. In the testing set, the survival analysis indicated that the c-index was 0.76 and the average brier score was 0.20. These results demonstrated the wellness-of-fit of our deep learning model towards the results. For further evaluation in individuals, we obtained survival estimates of two patients in the testing set, patient 1 had an accurate survival of 58.7 months, while patient 2 had survival of 21.0 months. The model predicted patient 1 with a median survival of 47.5 months and patient 2 of 12.5 months. The demonstration of individual survival curve of these two patients predicted by the deep learning model is in Figure3.

Figure 3

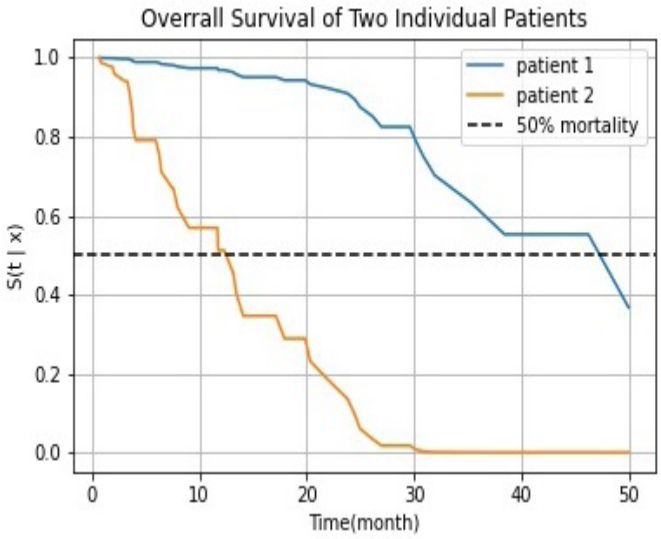

Figure 3. The overall survival of two CRC patients with PM. The model predicted patient 1 with a median survival of 47.5 months and patient 2 of 12.5 months, while patient 1 had an accurate survival of 58.7 months, while patient 2 had survival of 21.0 months.

DISCUSSION

For a long time, PM of colorectal cancer has been regarded as an end-stage disease, and most patients only receive supportive treatment or palliative treatment[4, 6]. However, it is currently believed that PM patients are not extensive metastases, the prognosis of a local and regional metastasis (PCI <20) can be significantly improved with active treatment[16]. The plots demonstrated that there is great discrimination on prognosis between patients of whether being conducted CRS + HIPEC or not (Figure 4ab).

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Figure 4ab

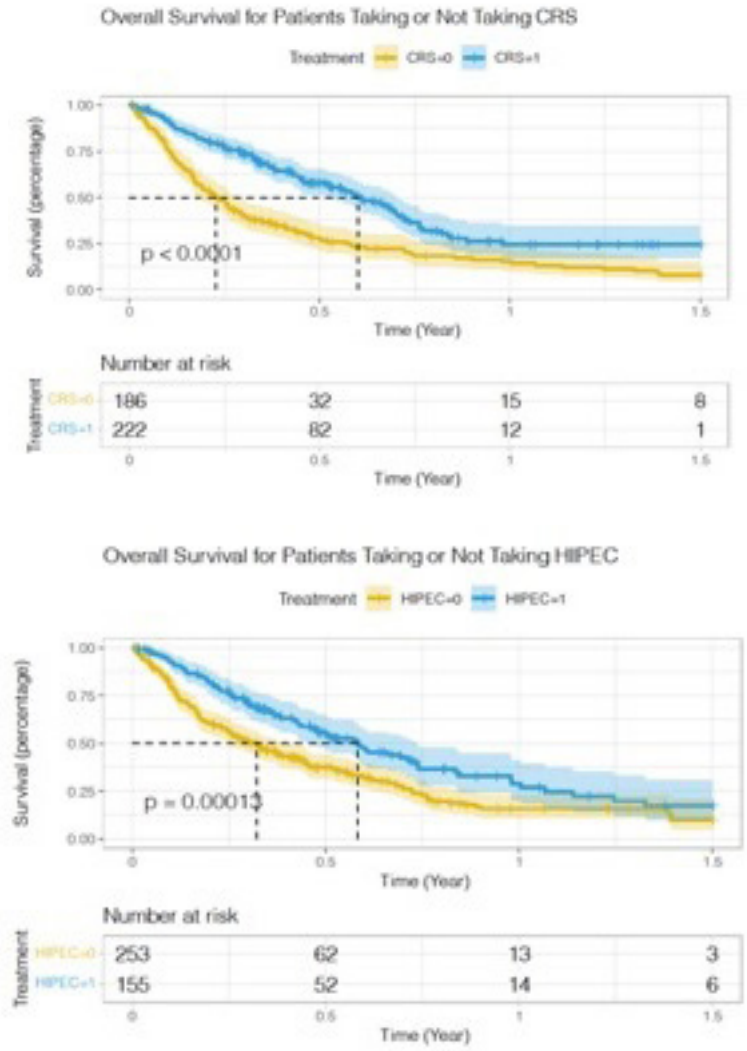

Figure 4 : a. Overall survival for CRC patients with PM taking CRS vs not taking CRS. b. Overall survival for CRC patients with PM conducting HIPEC vs not conducting HIPEC. The plots demonstrated discrimination on prognosis between patients of whether being conducted surgery (CRS or HIPEC). The p value showed how distance two curves are, that is, the smaller the p value is, the larger distance two curves have. From these two plots, both CRS and HIPEC treatment received higher survival rate compared to not conducting surgery, along with p values that are both far smaller than 0.05.

CRS combined with HIPEC is currently an effective treatment for PM patients. Along with systematic chemotherapy, the median OS increased from 13 months of palliative chemotherapy to 22-42 months of CRS combined with HIPEC, which can significantly prolong the prognosis of PM patients. However, the prognosis is still poor compared with other locally advanced colorectal cancers. Therefore, the researchers developed and established models to predict the individual prognosis of PM patients. Current prediction models only contain a few of perioperative features, which cannot include all risk factors of survival for incomplete data in most retrospective studies. The most used prognostic scoring for patients with peritoneal metastasis is PSDSS, but the development of the model was created in a small cohort and the validation was not performed.

With the advantage on processing big data and incomplete data, this study applied deep learning model to develop a clinical prediction model for PM patients to predict the survival rate by incorporating factors such as preoperative biomarkers, intraoperative treatment, postoperative pathology and genetic status. The model's C-index reaches 0.76 with a good predictive performance and yielded even high accuracy. The model firstly only included one hidden layer to iterate data, the more layers the more sufficient, if there is no overfitting. We have finally selected three hidden layers since it had the highest outcome. Deep learning model is able to include a much larger number of features compared to traditional statistical methods, which construct a cox regression that is more comprehensive. Although deep learning model requires larger data size, it is more stable and accurate when processing missing data. It is a reasonably ideal and viable tool for analyzing real-life data which

are not always sufficient for traditional statistical modelling methods.

This deep learning model included 23 factors and most of them are perioperative. However, when analyzing these factors with statistical method, the performance of COX regression went down due to the collinearity. For example, N stage is defined based on the number of positive lymph nodes. Traditional statistical method avoids this by performing selection before regression, on the contrary, AI model could include these factors altogether. Categorical variables have been divided into multiple dummy variables indicating by 0/1. For example, N stage was a categorical variable ranging from 0 to 3, then it will be separated into 4 columns, and each indicates whether that patient was classified to this stage. This enabled AI model to digest different features even though they were in different units and the collinearity was also solved by separating continuous variables and categorical variables.

In our study, we creatively applied artificial intelligent on survival analysis to better deal with larger data group and more related risk factors. Moreover, it focused more on the prediction of individual patients which can help design personalized treatments for them. Traditional cox regression analysis served as a supplement that filtered the most critical factors related to prognosis. This model provided a survival prognostic curve for individual patients with CRC for targeted treatment. However, some limitations are still existing. First, the training cohort is retrospective and from a single center. Although we have applied data imputation method, training with incomplete data may impact the accuracy of the model prediction. Secondly, we only included risk factors of the perioperative period. This model ignored factors such as postoperative rehabilitation and family economy, which might also affect the prognosis of the patient. Finally, since the AI model can only draw a personal prognostic survival curve, it cannot distinguish the specific factors that affect the patient's prognosis.

CONCLUSIONS

We have developed a deep learning model to predict the survival of individual patients precisely. It can provide evidence to apply personalized treatments and assisted surgeon to select optical treatments for CRC patients with PM.

Declarations

Ethics approval and consent to participate: The experimental protocols mentioned in the article were approved by the Sixth Affiliated Hospital of Sun Yat-sen University and all methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained when participants were enrolled into this database of the Sixth Affiliated Hospital of Sun Yat-sen University.

Consent for publication: The authors of this manuscript agree to publish.

Availability of data and material: The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request. The materials used are described in the article.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: The authors confirm contribution to the paper as follows: study conception and design: Ruwen Zhou, Zhijie Wu, Zixu Yuan, Jing Lu, Hui Wang; data collection: Jian Cai, Yang Li, Yebiao Zhao, Wenle Chen, Duo Liu; analysis and interpretation of results: Ruwen Zhou, Zhijie Wu, Tingyang Xu; draft manuscript preparation: Ruwen Zhou, Zhijie Wu. All authors reviewed the results and approved the final version of the manuscript.

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Abbreviations

Adaptive Moment Estimation, Adam
artificial intelligence, AI
body mass index, BMI
cancer cell surface antigen, CA
carcinoembryonic antigen, CEA
COlo-REctal-Pc, COREP
Colorectal cancer, CRC
Concordance, C-index
cytoreductive surgery, CRS
Deep learning, DL
hyperthermic intraperitoneal chemotherapy, HIPEC
metachronous peritoneal metastasis, M-PM
Multi-layer Perceptron, MLP
overall survival, OS
peritoneal carcinomatosis score, PCI
peritoneal metastasis, PM
Peritoneal Surface Disease Severity Score, PSDSS
rectified linear activation function, ReLU
simultaneous peritoneal metastasis, S-PM

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