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Review on Ovarian Cancer Detection Using Artificial Intelligence & Machine Learning.

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Abstract: Science and technology have changed almost everything. There is nothing left that we can say that is unachievable by making use of science technology. The imaging process is showed in this paper is the reviewed work that describes ovarian cancer. Right now ovarian cancer is very much spread and become the common disease that is used to be seen in most people women who needed early diagnosis.
Artificial intelligence is a different kind of technical science that can pretend, lengthen and develop human intelligence by developing respective theories, methods and application systems.
In the past five years, the utilization of AI based tools in medical research is considered to be the high lightened topic in modern science and technology. AI plays a great role in Gynecological malignant tumors. This includes medical image recognition, auxiliary diagnosis, drug research and development, formulation of treatment schemes, and other fields.
The main aim of this paper is to give essential knowledge of the AI implementation in ovarian cancer detection. AI is believed to improve diagnostic efficiency, reduce the burden on the doctor, and then improve the effect of treatment and prognosis.
Ovarian cancer is often describe as most common type of gynecological cancers. Correct classification of ovarian carcinoma is an important element in various diagnoses. Computer-aided diagnosis (CAD) can provide the pathologist with useful guidance in making the correct diagnosis. The presented paper gives idea about various types of ovarian cancer and tools used to diagnose ovarian cancer.
The proposed method uses ovarian cancer detection with machine learning algorithms.
***Keywords*:** Artificial Intelligence, Gynecological Malignant Tumor, Diagnosis, Treatment, Prognosis

Introduction

Ovarian Cancer may affect body in various ways. It may also affect all the body parts that are closest to the ovaries, most likely the uterus & ovaries fallopian tube.
Artificial intelligence is having considerable ability to make desired changes in the healthcare system by offering automatic tools implementation [1]. As the world's population is increasing, the pressure on the health care system will also increase and so far the workload will also increase. New technologies which are most implemented by using artificial intelligence have the potential to disrupt existing practices, primarily by enhancing rather than replacing the skills of professionals [4,5].
Artificial intelligence may be considered as the ability of systems to "copy" human intelligence by executing code using number of algorithms. Machine learning is also a big portion of Artificial intelligence, where the statistical methods has been used to develop and implement algorithms. Also, Deep learning, is also considered as a subset of Machine learning depending on a neural network layer that allows computers to train specific tasks. Although AI has generated eagerness in life sciences and healthcare, therefore, key challenges remain related to data availability, quality, and modeling. Conveying these issues, as well as other limitations, will be critical to reaping the benefits of these technologies to advance health. Important applications of AI will be in the area of cancer biomarker discovery. Artificial intelligence is used to be defined as the ability of systems to "copy" human intelligence by running code that includes in large number of algorithms. Machine learning is considered to be large portion of AI, in which statistical methods are used for developing and improving algorithms. Whereas, Deep learning, is a major part of ML based on a neural network layer which allows computer systems to train specific tasks.
Ovarian cancer is considered to be the most common and dangerous gynecological cancer [6]. Primary epithelial ovarian carcinoma can be divided into serous, endometriosis, mucinous and clear cell subtypes [7]. The four subtypes of cytological images are often difficult to distinguish accurately by the pathologist's eye and mind, especially when a large number of images need to be analyzed and diagnosed, and errors can easily occur. To improve diagnostic accuracy and reduce the burden on pathologists, we tried to use computer technology in pathological diagnosis. Computer-aided diagnosis (CAD) makes differential diagnosis more accurate and less dependent on the skills of the

observer. [8]. CAD technology has come a long way in recent years with the advent of Whole-Side imaging (WSI) and machine learning algorithms. Several studies have been conducted to apply CAD techniques to medical imaging (X-ray, CT, MRI, etc.). [9].

Literature Review

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Purpose of Machine learning for Ovarian Cancer diagnoses.

Machine learning concept are greatly used in Computer Aided Diagnosis. Deep learning, which is included in machine learning, is based on the concept of processing and representing data for any job-based algorithm. The concept of deep learning starts in 2012, where a completely convolutional neural network (CNN) approach to deep learning won a big win in the world's most famous computer vision competition.[12]. Having been compared to older outlooks like the medical imaging processing system approach and also deep learning that directly uses image pixel values due to received data rather than computed image resources from segmented objects. This makes all simple and convenient. After reviewing a large number of relevant studies, we found that so far no one has so far applied deep learning to the classification of ovarian cancer.

Ovarian cancer

Ovarian cancer is considered to be the most usual disease often occurs in women. The Cancer which is used to forms in the ovary where the ovaries are part of the female body. The main work and aim of the ovaries is creating the eggs for reproduction. Ovarian tumor is by far the largest malignant tumor in women.

The ovaries are oval in shape and large in size and are placed on both sides of the uterus and consist of two numbers. It give rise to the two sets of hormones like progesterone and estrogen. The ovary can be categorized into three categories: normal, cystic and polycystic ovary.

Ovary growth averages 8mm to 10mm [6]. Ovarian cancer affects the entire body and can be classified in three ways, such as attachment, enlargement and dissemination. It tends to affect the entire organ closest to the ovary, such as the uterus and fallopian tubes. Enlargement is the other effect that divides cancer cells and these cells move to the abdomen and give rise to the new tumors. The spread is the central cancer that has dispersed the lymphatic system to the pelvis and chest. It also has large effect on lungs & liver.

Detection and Prevention Techniques: Ovarian cancer screening and diagnosis are performed using several techniques described in the following:

Description DWT (Discrete wavelet transform):

It converts the image into certain sub-bands that consist of a lot of orientation and documentation data. It was used to minimize image noise.

SF (Statistical Features) method:

For ovarian cancer, the data set is expressed as mean and standard deviation. The statistical characteristics for the detection of cancerous diseases show the four concepts and are as follows: true positive, false positive, true negative and false negative.

Morphologic tumor indexing featuring (MF):

MF has found an effective approach that easily reduces observation variances and false positive output [3].

Fuzzy Technique (FT):

In this method, fuzzy operators, math, & rules are used to deal with problem uncertainty due to ambiguity. Its membership function helps to describe linguistic properties.

Computer Aided Diagnostic:

These are image-based spectra used for feature extraction, decision classifiers. Online data analysis went well, but required more storage space for offline data analysis [5].

Overview of Ovarian cancer

Biomarkers play a great role in medicine and are urgently needed for the early diagnosis of ovarian cancers, particularly in CEOs, due to the lack of a standard screening assessment and the high relapse rate.

In particular, these are not the allowed for screening tests for early detection, but rather predictive algorithms for determining the likelihood of malignancy and the need for referral to a gynecological oncologist.

Materials and methods

Study population

We screened the data of 443 patients confirmed EOC from Jan.2010 to Dec.2020 from our institution. Then, patients were excluded referring to the following criteria : (1) without incomplete clinical stage and histologic type (n=10), (2) with cancer coexistence or past medical history within 5 years(n=14). Finally, a total of 419 EOC patients were randomly matched with 113 benign gynecological diseases patients *via* age feature between Jun.2018 and Jun.2020 from our institution, approximately at the ratio of 4:1. Moreover, the external validation cohort that included 102 EOC patients and 31 benign gynecological diseases patients were enrolled from Obstetrics and Gynecology Hospital Affiliated to Fudan University from Jan, 2010, to Dec. 2020 to assess the performance of models. The analysis was approved by the Ethics Committee of Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, as well as the Ethics Committee of Obstetrics and Gynecology Hospital Affiliated to Fudan University.

Model development and validation

In this study, the derivation cohort was randomly and repeatedly split into a training cohort (70%) which was used for developing the 9 ML models and tuning the parameter, and an internal validation cohort (30%) which was used for testing the models on unseen data to fine-tune the hyper parameters.

Supervised ML classifiers and unsupervised clustering

We applied nine types of supervised ML classifiers to model our cohorts: LR, DT, RF, GBM, XGBoost, AdaBoost, NB, SVM, and NNET. Classifiers were trained using k-fold cross-validation (k=5) to avoid over fitting and ensure the best hyper-parameter to evaluate the predictive result in the validation cohort. The final ML models were estimated by the confusion matrix metrics with the area under receiver operating characteristic (ROC) curve (AUC), accuracy, sensitivity, specificity and so on. In the performance comparison of ML algorithms, the closer the AUC is to 1, the better the classification model performs. All algorithms were implemented using R software (version 3.6.3) and the R package carets "e1071," "rpart," "randomForest," "nnet," "gbm," "adabag," "xgboost," "Matrix," "caret," "tidyverse". Multidimensional scaling (MDS) provides a set of datasets with the visible representation of the positional relationship. Subsequently, K-means unsupervised clustering algorithm was applied on the two scaling coordinates of MDS.

XGBoost classifier and interpreting the model predictions

XGBoost algorithm, an integrated lifting algorithm, is implemented based on gradient tree boosting which has been proven to give many standard classification benchmarks with progressive achievements (14). The idea of Boosting algorithm is to continuously improve and upgrade the weak classifiers, and integrate these classifiers to form a strong classifier. However, ML classifiers usually have distinctive black boxes and uninterpretable features, which means that the functions between the features and the responses are invisible to researchers (15–18). Here, SHapley Additive exPlanations (SHAP) method, evolved from cooperative game theory, was adopted to highlight the most contributing and important features, allowing the classifiers to generate global and individual interpretation of predicted outcome (19). SHAP analysis was implemented using R package "SHAPforxgboost" (https://CRAN.R-project.org/package=SHAPforxgboost).

Image Dataset [aa]

Eighty-five (85 specimens in all, 24 serous carcinoma, 22 mucinous carcinoma, 21 endometrioid and 18 clear cell carcinoma.) qualified hematoxylin-eosin(H&E) stained tissue sections of ovarian cancer were obtained from First Affiliated Hospital of Xinjiang Medical University. And the time of making specimens varied from 2003-2016 years. Each tissue section was clearly marked the subtype which was confirmed by at least 2 pathologists. All the H&E stained tissue sections were partly digitized to images in JPG format by a microscope with×40 objective lens (Model:PH100-DB500U-IPL, Brand: Phenix, Place of origin: China) and a digital still camera(Model:Phenix, Brand: MC-D200UVA, Place of origin: China). There are about 20-27 qualified images captured from different parts of every H&E tissue section while keeping their orientation invariable. Thus, we finally got 1848 ovarian cancer cytological images, which have uniform matrix size - 1360*1024 pixels. For the requirements of follow-up research, we cropped all the images into 1024*1024 pixels from the center part, each of which was divided into 4 small images from the center point with the same size of 512*512 pixels, and then resized them to the 227*227 pixels. At last we got 7392 original images with the uniform size of 227*227 pixels. Fig.1. showed the image process.

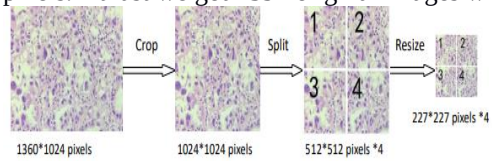


Fig.1. Cytological Images Preprocessing for Automatic Classification of Ovarian Cancer by DCNN Our study was approved by an established ethics committee and institutional review board. All the tissue sections and other data related to the patients were anonymous. 2.2 Data Augmentation A deep neural network model typically requires a large amount of training data [22]. Insufficient size of training

sample can directly lead to overfitting and other mistakes happen. In our study, we increased the sample size by image manipulation in order to improve the accuracy of classification [23,24]. Image manipulation includes image enhancement and image rotation.A Gaussian High Pass-filter with kernel size =3*3 and Laplass filter were apply to the image to improve the image clarity and edge sharpness. The direction of H&E stained tissue sections was invariable during the image acquisition by the microscope and camera. Thus, we rotated the original images (size of 227*227) from 0°to 270°in 90° steps around their center point to increase the sample sizes. Fig.2 and Fig.3 show the process of image enhancement and rotation. Two independent recognition models were made by our 2 group data, one group used original image dataset as training data without image augmentation, and the other one used image dataset augmented as training data , whose sample size is 11 times(81312) bigger than original image sets(7392).

Fig.2. Image enhancement

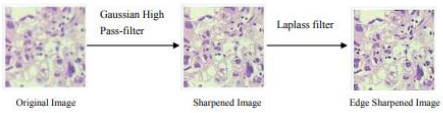
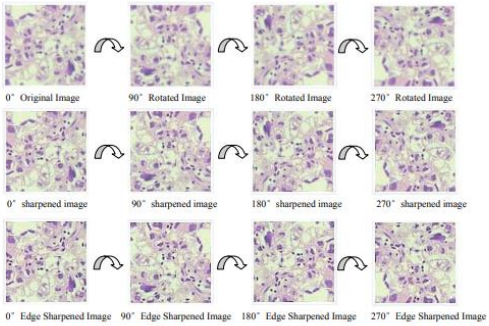


Fig.3. Image rotation



Machine learning using unsupervised clustering analysis associated with prognosis

In the derivation datasets, 332 EOC patients had survival time follow-up information, of which 87 died, accounting for 26.2%. 301 cases knew whether there was recurrence information accurately, and 142 cases recurred, accounting for 47.2%. Data-driven groups were created using unsupervised machine learning. We initially applied MDS technique to reduce dimension to show a low-dimension (MDS1, MDS2) projection which could reserve as much as possible the distance among features in the original high-dimension datasets space, and generated MDS plot (Figure 4A). Then, K-means clustering analysis with K = 2 showed distinct clusters on the MDS data (Figure 4B). We found that most of the early-stage EOC were included in cluster 1, whereas late-stage EOC patients were widely distributed between clusters 1 and 2. Moreover, we also found a significant difference in OS (Figure 4C, $p<0.0001$) and RFS (Figure 4D, $p<0.0001$) between the clusters.
Figure 4

FIGURE 4 Machine learning using unsupervised clustering analysis associated with prognosis. **(A)**, Applied MDS technique to reduce dimension and generated MDS plot. **(B)**, EOC patients clustered into two groups using K-means method. **(C, D)** Kaplan–Meier curves showed OS **(C)** and RFS **(D)** of each cluster in all EOC. **(E)**, Box plots representing distribution of top seven differential blood markers between the cluster 1 and cluster 2. **(F)**, Correlation between top seven differential predictors evaluated using Spearman rank coefficient. **(G)**, Comparing the AUCs of CA-125, ALB and score. **(H–J)** Performing Kaplan–Meier method on the traditional CA-125 **(H)**, Alb **(I)**, and comprehensive score **(J)**. **(K)** Sankey plot showed the transition of the values of new CA-125, Alb, and score, and the proportions of clusters. Multiple blood markers including CA-125, Lym, PA, Alb, Fb, Hb and Hct were significantly different in the two clusters (Figure 4E). To investigate the impact of these variables on prognosis, we initially performed Spearman correlation analysis, and we found there were strong positive correlations between Hb and Hct, and moderate positive correlations between PA and Alb (Figure 4F). Next, the AUC value of single significant variable in predicting 5-year survival was assessed by ROC analysis. We selected two variables CA-125 (AUC = 0.67) and ALB (AUC = 0.66) with AUC greater than 0.6 and without strong correlation. According to the ROC method, CA-125 = 510 U/mL and Alb=41.9 g/L were identified as the best cutoff value. We set CA-125 value greater than 510 U/ml as worth 1 score, for Alb, values greater than the cutoff point was considered 0 score, and vice versa, then, calculating their total scores. We compared the AUCs of CA-125, ALB and score, and found that the AUC value of comprehensive consideration of CA-125 and ALB was higher than that of single feature analysis (Figure 4G). We performed KM method on the traditional CA-125 with a normal value less than 35 U/ml (Figure 4H) and Alb with a normal value between 35 g/L and 55 g/L (Figure 4I), and the comprehensive score of CA-125 and Alb with 0, 1 and 2 points (Figure 4J). For EOC dataset, the comprehensive score achieved significantly different ($p<0.0001$). Sankey diagram directly shows the transition between the value including new CA-125, Alb and score and the two clusters (Figure 4K). As can be seen, 2 scores accounted for the highest proportion in cluster 2, which can help identify EOC patients at high risk of progressing to clusters with worse prognosis.

Results [aa]

3. Results We finally got 2 independent models of ovarian cancer type classification by training original images (1848 samples) and augmented images (20328 samples) separately. The 10-folder cross-validation was applied to calculate the classification accuracy of the models. The random number of original and augmented images for each data set is listed in table1.

	Serous		Mucinous		Endometrioid		Clear cell	
	O	A	O	A	O	A	O	A
DataSet1	42	462	48	528	42	462	41	451
DataSet2	41	451	50	550	45	495	40	440
DataSet3	54	594	41	451	47	517	40	440
DataSet4	52	572	40	440	54	594	52	572
DataSet5	51	561	44	484	46	506	46	506
DataSet6	52	572	50	550	50	550	42	462
DataSet7	47	517	46	506	47	517	40	440
DataSet8	46	506	41	451	53	583	40	440
DataSet9	48	528	51	561	53	583	45	495
DataSet10	48	528	42	462	47	517	44	484

Discussion

AI has gradually been accepted by medical workers and used in decision-making assistance for some diseases (20–22). In gynecological tumors, the application of AI is also becoming increasingly prevalent (13, 23). We can now use machine learning to improve the accuracy of ovarian cancer prediction by existing screening methods and help manual decision-making, to reduce the occurrence of false-positive events and avoid unnecessary losses.

In this article, we have demonstrated the feasibility of using machine learning to develop a predictive model for EOC, using age and 33 peripheral blood parameters to analyze the diagnosis, clinical features (including pathological subtypes, pathological grade, and clinical stage) by supervised ML classifiers, as well as prognosis of patients *via* unsupervised clustering. In a previous study, AI system was used for diagnosis assessment of patients with EOC based on blood features through RF method (26, 27).

However, the major issues in the use of ML in predicting response in the "black box" were complexity and opacity of algorithms, which limited their mainstream acceptance by the medical communities (28). Therefore, it is necessary to understand the clinical efficacies of the different models to generate clinical settings that help doctors make clinical decisions and develop optimal interpretation of ML model outcomes. Here, we utilized the model explanation algorithm, SHAP method, to determine the most important features for prediction. Research workers often use partial correlation diagrams or feature importance to explicate ML models before SHAP method was widely used. Through SHAP value, we can not only know the contribution of variables to prediction ability but also know the positive and negative correlation.

It is hoped that more models and their interpretation algorithms will appear in the future, which can not only process high-throughput clinical data at the same time but also better improve the accuracy and interpretability of data prediction.

Machine learning can identify more biological indicators related to diagnosis and prognosis, to improve the accuracy and sensitivity of ovarian cancer screening.

This study, however, also has some limitations. Firstly, the study was based on two-center databases, involving a relatively small number of patients. So, patients from more multiple sources are needed to verify the universal property of the model. Secondly, the retrospective nature of the study increased the possible risk for selection bias. In addition, although this study showed that machine learning can promote medical accurate decision-making to a certain extent, its clinical application and the responsibility of auxiliary medical decision-making still need to be further discussed.

Conclusion:

In conclusion, we developed machine learning models to predict diagnosis and prognosis for EOC patients. ML can achieve more accurate preoperative evaluation, help doctors make decisions, avoid unnecessary surgery, guide the choice of different treatment schemes, and adapt to the development trend of contemporary precision medicine. We believe that future research can use AI by combining image data with serum biological indicators to develop new models and promote the diagnosis and treatment of ovarian cancer.

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