

Role Of Artificial Intelligence In Gynaecologic Oncology

Review

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Abstract – With the improvement of machine learning and deep learning models, artificial intelligence is now being utilized to the subject of medicine. In oncology, the use of artificial intelligence for the diagnostic comparison of medical images such as radiographic images, omics evaluation using genome data, and clinical data has been growing in latest years. There have been growing numbers of reviews on the use of artificial intelligence in the subject of gynaecologic malignancies, and we introduce a review of these studies. For cervical and endometrial cancers, the contrast of medical images, such as colposcopy, hysteroscopy, and magnetic resonance images, the usage of artificial intelligence is frequently reported. In ovarian cancer, many reviews mix the evaluation of medical images with the multi-omics evaluation of medical and genomic data using artificial intelligence. However, few find out about consequences can be applied in clinical practice, and further research is wished on the future.

Keywords – artificial intelligence, deep learning, gynaecologic oncology, machine learning, neural network.

I. INTRODUCTION

Although there is no clear definition of the time period of artificial intelligence (AI), its use has unfold in the feel of “human-like information processing by means of a computer,” and the important points have been described from a number views relying on researchers and times . In the history of AI, its first growth came about in the 1950s. [1] This used to be a growth of the “inference and search” technology when the term AI was once coined. However, with this science alone, the quantity of occasions that ought to be dealt with used to be so constrained that this increase was once quickly over.[2] Then, in the 1998s and 1990s, as home computer systems grew to become extra common, the 2d AI growth began. This phase of the AI growth is characterised through the upward push of the “expert system.” An expert system is one in which, the understanding of an specialist is programmed into a computer, and the trouble is solved by means of the computer, on behalf of the expert, primarily based on the programmed knowledge.[3,4] At first, AI scientists have been positive that AI would quickly substitute humans. However, due to the complexities of translating specialist understanding into algorithms and the difficulties of flexibly adapting exceptions and conflicting rules, obstacles quickly grew to be apparent. Consequently, this 2d AI growth was once hampered via the gap between expectations that “artificial intelligence can be utilized to everything” and the disappointment that “artificial intelligence can't do something without detailed instructions.”

1. Machine learning

Machine learning refers to analytical methods concerned in the technological know-how that learns regularity and derives standards from records to predict and categorize unknown objects based totally on these standards. [5] There are three major sorts of machine learning: supervised learning, unsupervised learning, and reinforcement learning. Supervised learning of machine learning that presents an end result or reply based totally on training data and is mostly used for regression and classification.[6] In supervised learning, training data are used as recognised data for learning, and a regression or classification model is built that

can reply to unknown information. A representative method is an evaluation approach using decision tree such as the random forest approach and regression analysis.[5] Unsupervised mastering is the kind that does not require education information to decide the right answer. Unsupervised learning is used to group data and summarize information. A regular unsupervised studying algorithm is clustering. Reinforcement studying makes use of trial and error to create algorithms that research the most beneficial behaviours and choices.[5]

2. Deep learning

Deep learning, which has driven the modern AI boom, is a structure of machine learning with extra than 90% supervised learning.[6] Deep learning is characterised via an evaluation approach that makes use of neural networks, which appoint mathematical models to imitate neurons in the human intelligence . The neural network consists of three sorts of layer categories, every of which might also consist of countless layers: the input, intermediate, and output layer categories. [5,6]. The output of the neural network is in contrast with the training data, and the weighting of the data is adjusted so that the rate of the correct output increases. The introduction of deep mastering has made it viable to function picture and speech recognition, natural language processing, and anomaly detection.[6]

3. Application of AI in cancer

As described above, machine learning, specifically deep learning techniques, is appropriate for extracting image characteristic quantities and is right at detecting, classifying, and figuring out tasks. Therefore, in current years, efforts have been made to observe deep learning technology to medical images. Image cognizance the usage of AI technology can be roughly divided into classification and detection. In medical imaging, tries have been frequently made to introduce AI into endoscopic, magnetic resonance (MR), computed tomography (CT), ultrasound imaging, and pathological imaging. Yanagawa et al. [7] generated an algorithm that was once skilled to analyse CT photographs primarily based on the images of 285 patients with lung cancer. When the images had been interpreted via inexperienced radiologists, the accuracy of lung cancers prognosis used to be greater in the group that used the deep learning support than in the group that did not.[7] Regarding the use of AI for MR images, Chang et al.[8] examined whether or not IDH mutations can be envisioned via examining the facets of MR images of glioma, a kind of brain tumour, the usage of deep learning. Their strategy accomplished an accuracy of at least 87%.[8] In a report on AI-assessed ultrasound images, 4828 ultrasound images of 1275 patients with breast cancers have been analysed via a deep learning of neural network, and the best fine predictive value used to be 93.29%.[9] The utility of AI has additionally been tried the use of pathological images. Yamamoto et al. [10] analysed 13 188 pathological images of prostate cancers using machine learning. They observed the accuracy of this method to predict tumour recurrence inside 1 year to be 0.820, suggesting that AI may also be an integral tool for pathological image diagnosis in the future.[11] AI has begun to be utilized now not solely to medical images however additionally to omics data, such as genome data. For example, the use of AI to analyse RNA expression, DNA methylation, point mutations, and omics records of the copy number variant posted in The Cancer Genome Atlas (TCGA), Ramazzotti et al. succeeded in predicting the prognosis of 27 out of 36 cancers.[11] Chaudhary et al. used DNA methylation, mRNA, and miRNA omics facts of liver cancers with AI to perform dimensional compression and then used the Cox proportional risks models to identify 37 prognostic features.[12] As stated above, AI has been utilized to a various cancer, such as gynaecologic malignancies. This evaluate describes the use of AI for the three most important gynaecologic forms of cancers: cervical, endometrial, and ovarian cancers.

3.1 Application of AI in Cervical Cancer and Cervical Intraepithelial Neoplasia

Many researches on cervical cancers and cervical intraepithelial neoplasia (CIN) have pronounced the utilization of AI, which can be in general divided into the evaluation of colposcopy, MR imaging (MRI), CT, cytology, and human papillomavirus (HPV) data.

3.1.1 Colposcopy

Sato et al. [13] analysed 485 colposcopy images the usage of deep learning to predict high-risk CIN. The diagnostic accuracy of the validation set used to be ~50%.¹⁴ Another report used colposcopy images of 19 435 patients from six centres to boost Colposcopic Artificial Intelligence Auxiliary Diagnostic System, a deep learning colposcopy diagnostic and biopsy guide system. The outcomes of biopsy analyses assisted by using this system have been greater accuracy than these received via gynaecologists alone (82.2% vs. 65.9%, 0.750 vs. 0.516, respectively; $p < 0.001$).^[14] Attempts have been made to enhance

accuracy when solely a restrained number of images are available. In deep learning, transfer learning is an approach that makes use of what has been realized in one region, to another, beforehand unknown region, to expand gaining knowledge of efficiency. Kudva et al. developed a new gaining knowledge of approach known as hybrid transfer studying and increased the accuracy of colposcopy image diagnosis by means of their deep learning system to 91%.[15] New cervical imaging tools specialised for AI-based diagnosis have additionally been developed. Hu et al. [16] developed an approach known as cervicography in which a digital camera focuses on cervical lesions and analyses the image using deep learning. The effects established an accuracy of 91%. This opens the opportunity that cervicography turns into a new tool for cervical cancers detection survey.[16] In addition to AI application using of colposcopy images, deep learning techniques additionally included HPV typing data. Miyagi et al. [18] mixed 253 colposcopy images containing CIN with HPV-typing data and developed a CIN lesion analysis algorithm using deep learning. The diagnostic accuracy of gynaecologic oncologists was 0.843, whereas the accuracy of the deep learning algorithm was 0.941.[17]

3.1.2 Pap smear and HPV testing

Several researches of deep learning involving pathological images of cervical cancers or CIN involve cytology (Pap smear). For example, Sanyal et al. [18] developed a model that used deep learning 1838 cervical cytology images to discover normal and abnormal findings (normal 1301, atypical findings 537 images). The results confirmed an accuracy of 94%, sensitivity of 96%, and specificity of 91%.[18] In other report, they used deep learning to analyse cytologic images from 700000 patients and developed a model to discover lesions with a CIN ≥ 2 . The diagnostic accuracy with AI guide was once greater than that without.[19] AI researches have additionally categorized the degree of CIN and carcinoma in situ. Bao et al. [20] used deep learning to analyse 188 542 cervical cytology images to increase a diagnostic system that can distinguish carcinoma in situ from cervical dysplasia. The diagnostic accuracies of CIN 2 and CIN 3 have been 92.6% and 96.1%, respectively. In HPV-positive patients, this AI-assisted prognosis tool increased the specificity without lowering sensitivity.[20] Shanti et al. [21] set up a deep learning model focusing on the morphology of single cells in the cervical cytology. The accuracy for the 5 categories—normal, mild dysplasia, moderate dysplasia, severe dysplasia, and cancer—was 94.1%.[21] Machine learning the using data from HPV typing has additionally been studied. Tian et al. [22] used HPV typing information collectively with data about 522 cervical cancer associated mutant genes in HPV infection, the degree of CIN, and cervical cancers samples to perceive novel biomarkers that predict CIN 2 or greater based totally on the random woodland method. The CIN 2 + enriched biomarker alongside with HPV information, gene mutation information, and mitochondrial change, predicted CIN 2 or greater with an accuracy of 0.814.[22]

3.1.3 MRI and CT

Because MRI is a frequently employed imaging modality in the diagnosis of localized cervical cancer, there are some reviews of lookup using AI. Urushibara et al. studied sagittal and T2-weighted MR images of the uterus of 177 patients with cervical cancers and 241 patients without cancers using deep learning and determined that the diagnostic accuracy of this system was similar to that of radiologists.[23] In addition to AI-based diagnosis, there have been reviews of metastasis prediction using MRI. Wu et al. [24] developed a model for predicting lymph node metastasis based totally on deep learning analysis of preoperative MR images in 894 patients undergoing radical hysterectomy for stage IB–IIB cervical cancer. Following the learning process technique involving tumour lesion and circumference in T1-weighted images, the accuracy was 75%, sensitivity 88%, and specificity 71%.[24]. The adaptation of AI to CT images of cervical cancers has additionally been reported. A model for predicting chemosensitivity in cervical cancers was developed by using analysis of CT image features and chemosensitivity data of 221 patients with locally advanced cervical cancers the use of the random forest method. The area underneath the curve (AUC) value of this method used to be 0.821.[25] Shen et al. used deep learning to analyse 142 pre-treatment positron emission tomography with 2-deoxy-2- [fluorine-18] fluoro-D-glucose integrated with CT (18F-FDG PET/CT) images of patients with cervical cancers and developed a model for predicting local and distant recurrence after concurrent chemoradiotherapy. The sensitivity and specificity for predicting local recurrence have been 71% and 93%, respectively, and the sensitivity and specificity for predicting distant recurrence have been 77% and 90%, respectively.[26]

3.2 Application of AI in Endometrial Cancer

Compared to cervical cancers and ovarian cancer, there are solely a few researches on endometrial cancers that used AI. These researches are divided into reviews on database (clinical information and omics database) and reviews on medical imaging (MRI, pathological imaging, and hysteroscopy) amongst endometrial cancers patients.

3.2.1 Medical images

MRI is a crucial tool in the preoperative diagnosis of endometrial cancer, and there are some reviews on its use with deep learning approaches. Deep muscle invasion is an important factor that impacts the prognosis of uterine cancer. Dong et al. [27] developed a deep learning model primarily based on 4896 MR images from 72 endometrial cancers patients to predict deep muscle invasion and compared the model prediction with readings of radiologists. The accuracy rate was 75% or greater in both groups; this distinction was once not statistically significant.[27] In a similar study, Chen et al.[28] used 530 MR images from 4806 patients with endometrial cancers to enhance a deep learning-based model that can predict deep muscle invasion. The results confirmed an accuracy of 84%, a sensitivity of 66.7%, and a specificity of 87.5%.[28] Preoperative diagnostic imaging is very essential for endometrial cancers due to the fact lymph node metastasis determines the remedy plan and is associated to patient prognosis. Xu et al. used MR images and CA 125 values from 200 patients with endometrial cancers to increase a prediction model for lymph node metastasis of normal size and determined that the right diagnosis rate was about 85%.[29] A prior study aimed to strengthen an automated diagnosis system by examining endometrial cytology images the use of deep learning. In this study 416 members (168 normal, 152 malignant, 52 endometrial hyperplasia without atypia, 20 endometrial hyperplasia with atypia, and 90 endometrial polyps), the deep learning was skilled to analyse images of liquid endometrial cytology, and a predictive model with an accuracy rate of 90% or larger was developed.[30] Hysteroscopy is an endoscopic examination of the endometrium and is used to differentiate uterine body tumours, such as endometrial polyps and endometrial cancer. We divided hysteroscopic images of 177 patients (60 with normal endometrium, 60 with endometrial polyps, 21 with uterine myoma, 15 with atypical endometrial hyperplasia, and 21 with endometrial cancer) into two groups (malignant and non-malignant groups) and used deep learning. In the traditional assessment method, the common accuracy rate developed, extended the common accuracy rate to 85% and 90% or more, respectively. These effects endorse that the system we have developed might also lead to a new technique of endometrial cancers screening on the future.[31]

3.2.3 Databases of endometrial cancer

There are some reviews involving lookup on deep learning using endometrial cancers databases. Günakan et al. [32] developed a predictive model for lymph node metastasis using machine learning using pathologic data (tissue type, vascular invasion, tumour diameter, deep muscle invasion, cervical invasion, adnexal metastasis, etc.) from 762 patients with endometrial cancer. The predictive accuracy for lymph node metastasis used to be about 85%.[32] Another study compared machine learning of artificial neural networks (ANNs) with that of classification and regression trees (CARTs). This study included 106 women with endometrial cancers and 72 healthy women, with a total of 178 postmenopausal women, and the analysed parameters included age, presence or absence of menopause, presence or absence of diabetes mellitus, presence or absence of hypertension, smoking, and obesity. The correct diagnosis of ANNs and CARTs had been 85.4% and 77.5%, respectively.[33] Since endometrial cancers is associated with lifestyle-related diseases, other study aimed to discover endometrial cancers through inspecting metabolic records in the blood. In this study, machine learning to know of metabolome statistics derived from blood samples of 1550 postmenopausal female consisting of 16 women with endometrial cancers resulted in an algorithm that used to be greater than 99% correct in diagnosing endometrial cancer.[34] Endometrial cancers is divided into 4 prognostic subgroups (Polymerase E, microsatellite instability [MSI], copy number low, copy number high) in the TCGA database. Raquel et al. [35] carried out random forest classification on 13 next-generation sequencing gene panels and MSI tests and examined whether or not this method should be used to classify patients into the 4 subtypes. The correct prognosis rate of this system was 0.9753. These results recommend that clinical genetic panel testing may permit the classification into the 4 prognostic subtypes.[35]

3.3 AI and ovarian malignancy

3.3.1 Medical images

MRI is a necessary imaging approach in the preoperative prognosis of benign and malignant ovarian tumours. Wang et al. [36] used deep learning to examine MR images of 451 patients with ovarian tumours (379 benign, 166 malignant), developed an algorithm for diagnosing them as benign or malignant tumours, and in contrast the algorithm outcomes with readings via radiologists. The established diagnostic model combining MR images with medical data had greater accuracy (0.87 vs. 0.64, $P < 0.001$) and specificity (0.92 vs. 0.64, $p < 0.001$), as similar sensitivity (0.75 vs. 0.63, $p = 0.407$).[36] Ultrasonography is other treasured device for the differentiation between benign and malignant ovarian tumours, and deep learning has been used in quite a number studies. MartínezMas et al.[37] analysed ultrasound images of 348 ovarian tumours in a database the use of a number of

machine learning strategies such as k-nearest neighbour (KNN), linear discriminant (LD), support vector machine (SVM), and extreme learning machine (ELM) algorithms to enhance a predictive model for the discrimination of benign from malignant ovarian tumours. The correct diagnosis rate of the KNN model was as low as about 60%, whereas these of LD, SVM, and ELM had been above 85%.³⁸ Zhang et al.[38] developed a benign-malignant diagnostic model by way of making use of machine learning with a Google LeNet deep neural network and an eCost-sensitive random forest classifier to coloured echo graphic images of extra than 3000 malignant and extra than 500 benign ovarian tumours. The diagnostic accuracy was 96%, and the sensitivity and specificity have been 96% and 92%, respectively.[38] Similarly, deep learning utilized CT images. Wang et al. [39] developed a recurrence prediction model with the aid of examining 8917 CT images of 245 high grade serous carcinomas. Two cohorts have been used to decide the accuracy and to predict the recurrence at three years, with a precision (in terms of the AUC value) of 0.722 and 0.694, respectively.[39] Another document used cytologic images for deep layer learning. Wu et al. [40] expanded the ascitic cytology images of 1848 ovarian most cancer patients to 20 328 images, educated a deep learning of model with them, and developed a predictive model of the tissue type. The ensuing classification accuracy of the 4 foremost histologic types, that is, serous carcinoma, mucinous carcinoma, endometrioid carcinoma, and clear cell carcinoma, was about 80%.[40]

3.3.2 Database of clinical information

Several research in ovarian cancers have analysed machine learning processes that used clinical information databases. In ovarian most cancers treatment, it is necessary to predict the success of R0 surgical treatment preoperatively. In their report, Laios et al.[41] used clinical information (age, body mass index [BMI], CA125, Charlson comorbidity index, surgical complexity score, operative procedure, disease score, etc.) as parameters and the KNN classifier to boost a prediction model of the success rate of R0 surgery. The effects confirmed an accuracy of 66% and a negative predictive value of about 90%.[41] Akazawa et al.[42] analysed clinical information (age, menopause, endometriosis, BMI, white blood cell count, haemoglobin, C-reactive protein, CA 125, CA 19-9, etc.) and CT image data (tumour size, presence, or absence of ascites) from 202 patients with ovarian tumours (cancer 53, borderline malignancy 23, benign tumour 126) the usage of 5 machine learning strategies to increase a predictive model for benign or malignant potential. Among the 5 approaches, the suited prognosis rate was absolutely at 0.80 for the machine learning approach known as XGBoost.[42] Kawakami et al.[43] studied blood sampling data (albumin, C-reactive protein, CA 125, leukocytes, haemoglobin, lactate dehydrogenase, etc.) from 334 patients with ovarian cancers and a 101 patients with benign ovarian tumours the use of machine learning methods such as SVM and random forest classifier. They developed a benign/malignant analysis model for ovarian tumours and a tissue typing model for ovarian cancer. The correct analysis rate to classify ovarian cancers and benign ovarian tumour was 92.4%, and high-grade serous carcinoma and mucinous carcinoma ought to additionally be categorized based totally on the blood sampling data. Moreover, it was possible to classify ovarian cancers patients with proper prognosis and negative prognosis into two groups by means of combining the blood series data.[43] In recurrent ovarian cancer, secondary cytoreductive surgical procedure (SCS) may also enhance the prognosis, however the standards of SCS for a higher prognosis continue to be unclear. Bogani et al. [44] used ANNs to analyse which clinical information was a prognostic issue for SCS success. The size of the disease-free interval and the presence of a recurrent tumour in the retroperitoneum had been recognized as prognostic factors.[44]

4. Databases of omics

AI lookup in ovarian cancers has additionally been utilized to primary research datasets, such as omics analyses. Effective immunotherapy requires the proximity of cytotoxic T lymphocytes and tumour cells. However, the elements that manage the spatial distribution of T cells in the tumour microenvironment are now not nicely understood. Desbois et al. combined transcriptome data with pathological images to analyse a large ovarian cancers cohort and developed a machine learning strategy to molecularly classify and symbolize tumour immunophenotypes.[45] Lu et al. [46] extracted 657 quantitative mathematical descriptors from preoperative CT images of 364 patients with ovarian cancer. Using machine learning, they developed a radiomic prognostic vector (RPV) for ovarian cancers that reliably recognized 5% of patients with a median universal survival of much less than two years. Furthermore, genetic, transcriptomic, and proteomic analyses from two independent datasets revealed that stromal phenotypes and DNA damage response pathways have been activated in RPV-stratified patients with ovarian cancer.[46] Some reviews have additionally used the already referred to TCGA database. Dong and Xu [47] extracted miRNA expression levels from the ovarian cancers database of TCGA. Using these miRNA and clinical data, they developed a prognostic prediction model using an SVM approach. Their SVM-based model recognized 19 miRNAs that ought to predict tumour recurrence.[47] Other publications classify carcinoma using machine learning. Using machine learning procedures with microarray data, Jansi and

Devaraj [48] aimed to extract important gene mutation groups suitable for cancers classification of patients with ovarian, lung, and colorectal cancer. The accuracy of ovarian cancers classification the use of 10 genes extracted via machine learning was over 95%.[48] Another find out about utilized AI to the early detection of ovarian cancer. Tanabe et al. [49] transformed records on glycopeptide expression in the sera of patients with ovarian cancers and non-cancer patients into 2D barcode records that was analysed by using a deep learning model. Based on the assessment of CA 125 and HE4 values, the analysis rate of early ovarian most cancers reached 95%.[49]

II. THE VISION OF PERSONALISED MEDICINE

Hanahan and Weinberg mentioned the significance of the six integral hallmarks in most cancer biology. This has been the groundwork of the modern-day molecular oncology principles, and an imperative step to pursue the imaginative and prescient of being in a position to provide individualised method for each cancer patient [50]. Personalised medication can be described as the use of combined knowledge about a person (e.g. genetics, medical history) to predict disorder susceptibility, prognosis or remedy response [51]. Prognostic and predictive biomarkers can guide person management and forecast outcomes. Mutations of breast cancers gene 1 and two (BRCA1 and BRCA2) are a profitable instance of parameters for provision of customized remedy primarily based on character predictors or prognosis and response to remedy [52]. KRAS mutations in endometrial cancers and WNT signalling in ovarian, endometrial and cervical cancers are additionally potential future objectives primarily based on which prognosis of most cancers development would possibly be estimated on a woman groundwork and preliminary therapy alternatives consequently be stratified as a result [53,54]. Modern remedy has shifted from developing treatment after the fact, to preventing, personalising and handing over precision care. This requires great amounts of data to make increase available information on disease processes. Examples of processable information encompass proteomic, genomic and transcriptomic biomarkers, and baseline characteristics of patients. AI has been declared as the most important tool to synthesise data on complex cancers oncology and attain the imaginative and prescient of personalized medicine.

III. RESEARCH GAP

Currently, the most difficult concern that scientific staffs regularly face in gynaecologic practice is the differential diagnosis of malignant and benign adnexal masses using ultrasound images. The transvaginal ultrasound used to be the most really useful direction for figuring out variations and has been notion to be the first-line imaging system. Moreover, it has primarily relied on the skilled examiner, i.e., the foremost flaw of this tools is that its diagnostic enactment used to be mainly primarily based on the biased impression of investigative clinical sonographers [55]. Moreover, it has been pointed out that the AI was once extra probable to end result from misinterpretations in patients with coexisting polypoid tumours (or) benign leiomyomas [56]. With the person variants of cancer patients and the multidrug conflict development, numerous patients with gynaecological cancers have poor drug sensitivity follow-on unacceptable clinical cure [57].

IV. RECOMMENDATIONS

At present, large achievements have been executed in the software of AI in gynaecology, however the effectiveness and universality of a range of models nonetheless need similarly exploration. Additionally, with the modification and optimization of algorithms, the ideas and common sense in the back of these methods must be known, no longer solely through the algorithm builders however additionally with the aid of the clinical professionals. Thus, they ought to standardize or take away subjective bias to keep away from misdiagnosis for accomplishing fair, unified, and goal generalization standards. However, the science used to be proven to be beneficial in transnational consultation. Thus, this place wishes to be researched further. The detection model wishes to be extended similarly for evaluation with different medical images and counselled to try community optimization in cell structures [58]. Regardless of being an auspicious second for AI, some issues nevertheless want to be solved in the future. So far, AI is nevertheless immature, in its start-up stage, and is nonetheless no longer an individual procedure. Medical experts are nevertheless advised to function AI safely for engendering their optimization and speculation of AI utility in clinical practice.

V. CONCLUSION

AI is a hot subject and its utility in several specialities has been related with excellent expectations; a growing trend in funding AI research reflects this. AI looks to be a promising tool in gynaecologic oncology for resolving several longstanding challenges. Our review concludes that AI can augment knowledge and aid clinicians in decision making in a range of areas in gynaecologic oncology. AI can delineate the complexity of the molecular biology of gynaecological cancers and therefore serve

the imaginative and prescient of personalized medicine. Many studies record the application of AI to medical imaging such as CT, MRI, and cytopathological images, and the variety of AI studies assessing genome and clinical information is additionally increasing. However, few study findings can be carried out in clinical practice, and in further research is needed in the future.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

Authors have equally participated and shared every item of the work.

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