

Logistic models and artificial intelligence in the sonographic assessment of adnexal masses – a systematic review of the literature

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Abstract:

Adnexal masses are common, yet challenging, in gynecological practice. Making the differential diagnosis between their benign and malignant condition is essential for optimal surgical management, but reliable pre-surgical differentiation is sometimes difficult using clinical features, ultrasound examination, or tumor markers alone. A possible way to improve the diagnosis is using artificial intelligence (AI) or logistic models developed based on compiling and processing clinical, ultrasound, and tumor marker data together. Ample research has already been conducted in this regard that medical practitioners could benefit from. In this systematic review, we present logistic models and methods using AI, chosen based on their demonstrated high performance in clinical practice. Although some external validation of these models has been performed, further prospective studies are needed in order to select the best model or to create a new, more efficient, one for the pre-surgical evaluation of ovarian masses.

Keywords: artificial intelligence; deep learning; diagnosis; image interpretation; computer-assisted

Introduction

Ovarian tumors commonly present diagnostic challenges in gynecological practice. For instance, it is important to make the difference between a benign and a malignant ovarian tumor before surgery, especially in young patients who desire fertility. While benign masses can be treated conservatively [1] or by surgical removal thorough minimally invasive surgery [2], masses sus-

pected of being malignant should be referred to a tertiary care center which may already be dealing with high numbers of ovarian cancer cases [3]. Therefore, accurate diagnosis is essential for planning appropriate patient management [4].

The diagnostic performance is in direct correlation with the experience of the physician [5]. The first imagistic step in evaluating an adnexal mass is ultrasonography (US), but US reports are sometimes misleading and confusing for the clinician [6]. To distinguish between benign and malignant tumors by means of US examination is not always easy because, for example, the imagistic features of borderline tumors overlap significantly with those of invasive epithelial cancers. In order to overcome such a difficulty, simple rules [7] or scoring systems were introduced with reportedly good results [8]. However, their application is not superior to the subjective impression of an experienced examiner [9], so further alternatives to improve imagistic diagnosis are still required.

Received 01.04.2020 Accepted 22.05.2020

Med Ultrason

2020, Vol. 22, No 4, 469-475

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One possible way to improve the accuracy of US diagnoses of ovarian tumors is to use logistic models and artificial intelligence (AI) [10]. In the literature, there is ample research with regard to the development of algorithms or AI technologies.

In recent years, imagistic assessment practices have been enhanced by the introduction of new software based on automated identification (computer-aided detection) and characterization (computed-aided diagnosis -CAD) with the aim to assist physicians in the diagnostic process [11,12].

Logistic models apply mathematical methods to reported incidence of events in order to create an algorithm, which, may be used to predict further occurrences. Logistic models are the most common method used to predict dichotomous outcomes, e.g. benignity versus malignancy.

Artificial neural networks (ANN) are computing systems based on a collection of connected units or nodes called artificial neurons inspired by the biological neural networks that constitute animal brains [13,14].

Artificial intelligence (AI) is represented by several algorithm-based applications that can solve problems by simulating human mental processes and intellectual activity such as learning from the data and experience [10]. Several subset technologies have been developed recently under the umbrella of AI: machine learning (ML) and deep-learning (DL). They both can be applied to solve human problems in many different ways. **Machine learning** as one form of artificial intelligence uses algorithms that learn from given data and then teach themselves to adapt to new circumstances and perform certain tasks. In this way, computers can adapt and handle new scenarios by analysis, self-training, observation, and experience. Machine-learning artificial neural networks adapt and learn best when large amounts of data are available [15]. **Deep-learning** is a subfield of machine learning that uses algorithms inspired by the structure and function of the brain, called artificial neural networks. This technology is modeled after the human brain, and so, each time new data is added, it increases the capabilities of the system. Because it has the capacity to analyze massive amounts of data, these algorithms are able to quickly find correlations that the human mind cannot [16].

A glossary of all these terms is presented in Table I.

The aim of this review was to perform a systematic review of the literature and to provide up-to-date information regarding the application of logistic models and AI in the pre-surgical differentiation of adnexal tumors. With this review, we hope to increase the awareness and comprehension of clinical practitioners regarding

Table I. Glossary of terms used in artificial intelligence

Term	Definition
Artificial intelligence	Programs with the ability to learn and reason like humans
Machine learning	Algorithms with the ability to learn without being explicitly programmed
Deep learning	Subset of machine learning in which artificial neural networks adapt and learn from a large amount of data
ANN	Artificial neural networks inspired by biological neural networks.

the usefulness of logistic models and AI-related clinical practices in this particular field of imagistic assessment.

Material and methods

We systematically searched articles published between January 1990 and January 2020 in the following databases: Scopus, PubMed, Web of Science and Cochrane Library, and we also screened for relevant publications in the grey literature. We used the following search words and phrases: artificial intelligence, deep learning, diagnostic imaging, logistic regression analyses, logistic models, ovarian tumors and adnexal masses.

Results

Following the systematic search process, 153 citations were retrieved from the mentioned databases. Of these, 117 articles were excluded based on analyzing their titles and abstracts, resulting in 36 articles to be appraised in detail. We excluded general reviews and papers not related to our aim and, finally, 17 studies made the subject of this review.

For proposed logistic models, we analyzed 9 articles summarized in Table II.

For AI, deep and machine learning we analyzed 9 articles summarized in Table III.

Discussion

Logistic models and AI applications are being introduced in many medical fields and are marked demonstrable, valuable contributions in early detections, disease diagnoses, and therapeutic developments [10]. Several authors have proposed and published various logistic models to support less experienced sonographers predict adnexal malignancy. One of the first scoring systems, proposed in 1990 by Jacob et al, was the Risk of Malignancy Index (RMI) based on CA 125, ultrasound and menopausal status. The authors reported sensitivity for cancer of 85% and a specificity of 97%. Although MRI

Table II. Studies of logistic models in ovarian tumors

Author, year	No of patients	Variables analyzed	Performance
Jacobs, 1990 [17]	143	CA 125, ultrasound findings, menopausal status	Sn 85% Sp 97% for cut-off level of 200
Prompeler, 1997 [18]	754	Ascites, solid areas without acoustic shadows, masses with at least 30% solid area, tumor diameter, multilocular structures, surface of the cyst	For premenopausal women: Sn 86.5% Sp 92.6% For postmenopausal patients: Sn 93% Sp 82.7% Cut-off level of 10%
Taylor, 1997 [19]	67	Age, maximum tumor diameter, tumor volume, unilocularity, papillary projections, random echogenicity, highest peak systolic velocity, time-averaged maximum velocity, pulsatility index, resistance index	Sp 90.4% Sn 93.3% Cut-off value of 25 for malignancy
Alcazar, 1998 [20]	79	Menopausal status, color Doppler findings, ultrasound morphology	Sn 84.6% (95% CI, 59 to 98%); Sp 100% (95% CI, 92 to 100%); PPV 100% (95% CI, 92 to 100%); NPV 95.7% (95% CI, 85.5 to 99.5%)
Timmerman, 1999 [21]	191	Menopausal status, CA 125 level, the papillary growth (>3 mm in length), color score indicative of tumor vascularity blood flow	Sn 95.9% Sp 87.1%
Alcazar, 2001 [23]	377	Menopausal status, tumor blood flow location, papillary projections, CA 125, Lowest RI	Sn 96.9 (83.8–99.9) Sp 94.2 (87.7–93.8) PPV 83.8 (67.9–93.8) NPV 98.9 (94.4–99.9)
Maret, 2002 [24]	130	Gray scale, RI < 0.53, flow location	Sn 83% Sp 93%,
Timmerman, 2005 [7]	754	LR1 - 12 predictors: personal history of ovarian cancer, current hormonal therapy, age of the patient, maximum diameter of the lesion, pain during examination, ascites, blood flow within a solid papillary projection, a purely solid tumor, the maximum diameter of the solid component, irregular internal cyst walls, acoustic shadows, color score LR1 - 6 predictors: age (years), presence of ascites, presence of blood flow within a papillary projection, maximum diameter of the solid component, irregular internal cyst walls, presence of acoustic shadow	LR1 Sn 93% Sp 77% Cut-off 10% LR2 Sn 92% Sp 75% Cut-off 10%
Meys, 2017 [22]	851	Age, serum CA125 level, type of center (oncology center/ other hospital), diameter of the lesion (mm), proportion of solid tissue, papillary projections more than 10 cyst, locules, acoustic shadow, ascites	Sn 0.98 (95% CI, 0.93-1.00) Sp 0.62 (95% CI, 0.55-0.68) Cut-off of $\geq 10\%$

Sp - specificity, Sn - Sensitivity, PPV - positive predictive value, NPN - negative predictive value

was recommended by many national guidelines, the external validation of this model yielded poor performance results [34].

Several years later, Taylor et al [19], Alcazar et al [20] and Timmerman et al [21] developed and put forth new logistic models to classify adnexal masses based on different ultrasound parameters, demographic data and markers (Table II). Unfortunately, most of these logistic regression models, when subjected to external validation, did not retain their original performance [35]. The key weakness of all these logistic models was the number of

cases used to obtain the results. Hsieh FY et al. stated that a logistic model should be developed on the basis of several hundreds of cases and none of the mentioned studies fulfilled this requirement [36].

The International Ovarian Tumor Analysis (IOTA) study was established to develop robust rules and prediction models that can be used by different examiners in various clinical settings. The IOTA authors developed simple ultrasound-based rules ('simple rules') and IOTA Logistic Regression models (LR) for ovarian tumors. The simple rules consist of five ultrasound features of

Table III. Studies with AI algorithms used in differentiating ovarian pathology

Authorship	No of patients	Methods used	Performance
Timmerman, 1999 [21]	191	ANN	Sp 93.5% Sn 95.9%
Biagiotti, 1999 [25]	226	Three-layer back-propagation networks	Sn 96% Sp 97.7%
Acharya et al., 2012 [26]	20	CAD technique	ACC of 95.1%, Sn of 92.5% Sp of 97.7%.
Acharya, 2012 [27]	20	SVM classifier	ACC of 99.9%
Acharya, 2014 [28]	20	Automatic CAD	ACC of 99.8%
Khazendar, 2015 [29,30]	177	SVM	Classification decisions of high, medium and low confidence, respectively, provided ACC of 90%, 81% and 69%.
Lu., 2003 [31]	425	Bayesian MLPs, Bayesian LS-SVMs, RVMs	Sp 85% Sn 81.48%
Aramendia-Vidaurreta, 2015 [32]	145	CAD technique	ACC 98.78%, Sn 98.50%, Sp of 98.90% ACU of 0.997
Martinez-Mas, 2019 [33]	187	CAD systems and ML techniques: KNN, LD, SVM, ELM	KNN classifier- ACC 60% LD, SVM and ELM classifier-ACC 85%

Sn - Sensitivity, Sp - specificity, AUC - area under the curve, ACC - Accuracy, SVM - Support vector machine, CAD - Computer-Aided Diagnostic, MLPs - multi-layer perceptrons, LS-SVMs - least squares support vector machines, RVMs - relevance vector machines, KNN - K-Nearest Neighbors, LD - Linear Discriminant, ELM - Extreme Learning Machine

malignancy (M-features) and five ultrasound features suggestive of a benign mass (B-features). A mass is classified as malignant if at least one M-feature and none of the B-features are present, and vice versa. If no B- or M-features are present, or if both B- and M-features are present, then the rules are considered inconclusive (unclassifiable mass) and a different diagnostic method should be used [37].

In the case of inconclusive results using the IOTA 'simple rules', two logistic models may present a viable alternative. Logistic Regression model 1 (LR1) uses 12 demographic and ultrasound variables, while Logistic Regression model 2 (LR2) uses six demographic and ultrasound variables. Both regression models showed excellent diagnostic performance. For LR 1 at cut-off level of 10%, the sensitivity and specificity of this model reached 92% and 75%, respectively. For LR2, at cut-off level of 10%, the sensitivity and specificity of this model reached 92% and 75%, respectively. The results of these models match those of experienced sonographers.

Another model with good reported performance is the Assessment of Different Neoplasias in the Adnexa (AD-NEX) [38]. This model is based on serum CA125 levels, two clinical parameters, and six ultrasound parameters (Table II). This method can predict the probability of malignancy in five main categories (benign, borderline,

stage I malignant disease, stage II–IV malignant disease and metastases), enabling clinicians to optimize the surgical treatment.

However, logistic models are not useful in all cases. About 7% of adnexal masses that are considered appropriate for surgical removal cannot be accurately classified even by the more experienced ultrasound examiners using subjective assessment. Valentin et al showed that logistic regression models to estimate the risk of malignancy, CA 125 measurements and the RMI are not helpful in these cases [39].

Nowadays, AI technology promised to provide a viable alternative to logistic regression. According to Tu et al, it has several advantages over logistic models. ANN require less formal statistical training, less ability to implicitly detect complex nonlinear relationships between dependent and independent variables, and the possibility to detect all interactions between variables [40]. In 1999, Timmerman et al introduced the first variant of ANN (ANN1) that used the following parameters: papillary projections, blood flow, CA125 level and the menopausal status. According to calculations using sophisticated mathematical models, the probability of malignancy >45% revealed a sensitivity and specificity of 87.5% and 92.7%, respectively. Thereafter, a second version was created (ANN2) based on papillary projections, smooth

surface, unilocular cyst, ascites, bilateral lesions, tumor marker CA125 and the menopausal status. The probability of malignancy >60% resulted in the sensitivity and specificity of 93.8% and 95.1%, respectively [41].

In 2012, Acharya et al developed an adjunct CAD technique that uses both images of the ovary acquired by 3D sonography and data mining algorithms to differentiate accurately benign from malignant tumors. They used 1,000 benign and 1,000 malignant images obtained from 10 patients with benign and 10 with malignant disease, respectively, and based on these images they developed a decision tree classifier. This yielded a sensitivity of 92.5% and specificity of 97.7%. However, the small number of patients whose imagistic findings were used represents a notable weakness of this study [26].

In the same year, Acharya et al reported using a support vector machine (SVM) classifier together with a radial basis function to automatically classify benign and malignant ovarian tumor images. They obtained high performance (accuracy of 99.9%) due to the combination of the 16 texture features that quantify the subtle changes in the images belonging to both classes. Moreover, in order to help physicians with their diagnoses, the team developed a novel integrated index called the Ovarian Cancer Index, essentially a combination of the texture features. However, this study was also restricted to 20 patients. Also, the system is not completely automatic and depends on the operator's experience, since a gynecologist and radiologist still need to delineate a region of interest to enclose the suspicious portion of the image [27].

Two years later, Acharya et al developed an automatic CAD system for ovarian tumor classification. In order to improve lower heterogeneity from the previous algorithms, they used 3-D color Doppler images. This probabilistic neural network classifier obtained an accuracy of 99.8% on a database of 2600 images on 20 patients [28].

Khazendar et al proposed a new method using a support vector machine (SVM) for automatic ovarian tumor classification, based on two different types of features extracted from ultrasound images of the ovary: the histogram and local binary pattern. The system was implemented on 187 ultrasound images from 177 patients. Based on classification decisions of high, medium and low confidence, respectively, the method provided accuracies of 90%, 81% and 69% [29,30]. Although this model was developed using a relatively large cohort of patients, numerous images were considered ineligible for inclusion in the high-confidence range [32].

Lu et al developed and evaluated several SVM on 425 patients with adnexal masses and they achieved an accuracy of 84.38% [31]. Their results showed that Bayesian models have the potential to provide a reliable preopera-

tive distinction between malignant and benign ovarian tumors, and to assist the clinician in making a correct diagnosis [31].

Aramendia-Vidaurreta et al described a new method for the automatic distinction of adnexal masses based on a neural networks approach. Their method combines the patient age with several features extracted from ultrasound images of the ovary (local binary pattern, fractal dimension, entropy, invariant moments, gray level co-occurrence matrix, law texture energy and Gabor wavelet). The performance of the method is very good, its accuracy being as high as 98.78%, with 98.50% sensitivity, 98.90% specificity, and an area under the curve of 0.997 [32].

Martinez-Mas et al used four machine-learning techniques (K-Nearest Neighbors (KNN), Linear Discriminant (LD), SVM and Extreme Learning Machine (ELM)) in order to provide automatic classification of the ovarian tumors with a high rate of accuracy. According to their results, the KNN classifier provides inaccurate predictions (less than 60% of accuracy) independently of the size of the local approximation, whereas the classifiers based on LD, SVM and ELM are robust in this biomedical classification (more than 85% of accuracy) [33].

One question that arises is "which is better: logistic models or artificial intelligence?" Several studies in the literature compared the performance of logistic models versus AI. Biagiotti et al compared the efficiency of ANN with that of multiple logistic regression (MLR) models on 226 patients with ovarian tumors (51 malignant and 175 benign cases). They developed a three-layer back-propagation network using the following variables: age, papillary projections, random echogenicity, peak systolic velocity, and resistance index. They showed that ANN had significantly higher sensitivity than MLR (96% vs 84%; McNemar test, $P = 0.04$) and could thus potentially help physicians differentiate between adnexal masses [25].

Holsbecke et al performed a comparison between logistic models and ANN models using data from 1,066 patients with ovarian tumors (800 patients with benign tumors and 266 patients with malignant tumors). Their results showed that the performance of the risk of malignancy index was similar to that of most logistic regression and artificial neural network models. The best result was obtained with a relevance vector machine with radial basis function kernel [42].

Obviously, there is a need for more prospective studies to compare and appraise the benefits of using logistic models and AI. Both methods show promising results in making the difference between benign and malignant ovarian masses. The integration of these techniques in

daily practice will allow timely and effective diagnosis, as well as proper management. An AI-assisted diagnosis could even allow non-specialists to confidently make decisions, which would normally require specialist input, such as, in emergency settings. Complete dependence on this technology is unlikely, but medical practitioners will eventually need to accept and to adapt to AI, changing the experience of clinical practice by contributing valuable opportunities for effective patient data analysis and informed decision making [43,44].

Conclusion

Both logistic models and AI can be efficiently used to distinguish between benign and malignant adnexal tumors. Both methods are suitable for analyzing massive amounts of data well in excess of what the human mind could. Both approaches have proved capable of providing automatic classification with a high rate of accuracy and, as such, they are expected to play an important role in future diagnostic procedures. These technologies, however, should not be viewed as a replacement, but rather as complementary tools for improved clinical practice.

Conflict of interest: none

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