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Research Progress on Recurrence Indicators of Endometriosis

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Abstract: ***Endometriosis (EMS) is a refractory gynecological disease with a high recurrence rate. Its clinical symptoms are mainly dysmenorrhea and infertility, showing diverse manifestations. Due to the atypical clinical symptoms and low specificity of diagnostic markers, the recurrence of EMS cannot be detected in time, which puts great pressure on patients both physically and mentally. Moreover, neither single clinical symptoms nor serological examinations can accurately diagnose the recurrence of EMS, and laparoscopic examination, as the gold standard for diagnosis, is an invasive examination. Therefore, it is urgent to find a prediction scheme with high sensitivity and specificity. Although some studies have shown that certain progress has been made in the diagnostic models of EMS, there is still a lack of systematic review of high - precision prediction models for the recurrence of EMS in the postoperative population. This review systematically summarizes the advantages and disadvantages of various single detection indicators, and at the same time sorts out and summarizes the combined detection models of serological markers and digital prediction models, providing reference for predicting risk factors in the research of the EMS recurrence system.***

Keywords: Endometriosis, Prediction, Recurrence.

1. Introduction

Endometriosis (EMS) is a refractory gynecological disease that seriously affects the physical and mental health of patients. It is characterized by typical clinical symptoms such as dysmenorrhea, abnormal menstruation, and infertility [1]. It refers to the presence of endometrial tissue outside the uterine body, affecting about 10% of women of childbearing age [2], and has a very high recurrence rate. Its recurrence usually means that after all visible lesions are removed by the initial surgery, after a period of asymptomatic time, the clinical symptoms and/or imaging evidence related to endometriosis appear again. Although a variety of drugs and surgeries have been found for the treatment of EMS, since the etiology of EMS is not fully understood, especially the mainstream theory of "retrograde menstruation" [3], and it is also an estrogen - dependent disease, as long as the ovarian function is normal and menstruation resumes, it will lead to the recurrence of EMS. For patients, EMS not only means physical pain but also bears a huge economic burden.

The huge challenges faced in clinical practice are precisely because the clinical symptoms of endometriosis (EMS) are similar to those of various gynecological diseases such as dysmenorrhea and pelvic inflammatory disease. Imaging examinations often yield a variety of results. Commonly used serological markers, such as carbohydrate antigen 125 (CA - 125), which is a commonly used tumor marker, are often used in the diagnosis and monitoring of EMS in gynecological diseases. However, its sensitivity and specificity for the single - diagnosis of EMS are both low, and there is no clear threshold for diagnosing EMS, which often leads to doctors delaying the diagnosis of EMS. Only laparoscopic surgery is the “gold standard” for diagnosing EMS, which can accurately diagnose EMS. It is an invasive examination and relatively expensive. At present, the predictive value of a single indicator is limited, while the combined detection of multiple indicators can achieve a more accurate judgment of the recurrence risk. If the recurrence of EMS can be effectively predicted at an early stage, it will be of great significance for formulating individualized treatment plans, optimizing long - term management, and improving the prognosis. Currently, most studies focus on the diagnostic models of EMS, and there is no clear summary of the recurrence prediction for patients after EMS surgery. In particular, there is a lack of reviews that systematically sort out and critically compare emerging artificial intelligence models. This paper hopes to fill this gap and provide a clear direction for future research on the recurrence prediction of EMS.

2. Limitations of a Single Recurrence Prediction Indicator

2.1 Clinical and Surgical-related Predictive Indicators

Is the relationship between the patient's age and the recurrence risk of endometriosis (EMS) a simple non-linear relationship? Theoretically, EMS is an estrogen-dependent disease. After a woman is over 35 years old, her ovarian function gradually declines with age. After age 40, there is an obvious downward trend in ovarian function, and the corresponding estrogen level also decreases. The recurrence risk of EMS should be reduced. Many studies, such as the report by Selcuk S et al. [4], also point out that female patients aged ≤35 years at the time of surgery have a high risk of postoperative recurrence. This may be related to the fact that younger patients have a strong estrogen secretion and more conservative surgeries due to the need to preserve fertility. However, this statement may not apply to all patients. Advanced age does not completely lead to a reduction in the recurrence risk of EMS [5]. Multiple previous surgeries and pelvic adhesions may provide a favorable environment for the recurrence of EMS, resulting in a relatively high recurrence risk. Therefore, as a predictive factor, the predictive efficacy of age should be comprehensively evaluated in combination with the patient's specific fertility status and estrogen level.

The staging of endometriosis (EMS) has always been an independent risk factor for recurrence and is the most definite predictive indicator [6]. Staging of EMS is carried out according to the staging criteria of the American Fertility Society (AFS). Stages III - IV are independent risk factors for recurrence. The theoretical basis lies in the fact that the higher the stage, the higher the degree of EMS lesions, the wider the scope of infiltration, and the higher the degree of pelvic adhesions. This increases the technical difficulty for surgeons to completely remove the lesions, and any residual microscopic lesions can lead to the recurrence of EMS in the future.

At the same time, the specific location and type of endometriosis (EMS) lesions also affect the increase in its recurrence risk. Deeply infiltrating EMS and bilateral ovarian endometriomas are recognized as high - risk recurrence predictors because of their more complex lesion locations and more invasive lesions. For ovarian endometriosis, the thickness of the cyst wall and the location of the cyst are both crucial risk factors for postoperative recurrence. A thicker cyst wall indicates a higher degree of fibrosis of the lesion, stronger lesion activity, and it is easier to leave residual lesions during the operation. In addition, bilateral cysts are prone to be complicated with adhesions in the rectouterine pouch. This situation not only increases the difficulty of the operation but also creates an environment more conducive to the recurrence of EMS and the formation of adhesions, greatly increasing the risk of postoperative recurrence.

For patients in the childbearing period with fertility requirements, the core lies in controlling the progression of the disease, relieving clinical symptoms, promoting the patients' fertility, and preventing disease recurrence. Drug therapy is the first - choice treatment, but the efficacy and side effects of various drugs need to be weighed. Gonadotropin - releasing hormone agonist (GnRH - a) is a routine drug for short - term postoperative treatment, usually used for no more than 6 months. However, long - term use of GnRH – a [7] can lead to a decrease in the level of estradiol in the body, inhibit ovarian function, and cause menopausal - like symptoms, so it can only be used for a short time, which leaves hidden dangers for the recurrence of endometriosis (EMS). Therefore, there is an urgent clinical need for drugs more suitable for long - term use. Progestin drugs are the first - line drugs for the long - term management of EMS patients. Among them, dienogest is more beneficial than GnRH - a in relieving patients' pain, reducing the volume of masses, and has fewer side effects. It has a significant effect on improving the patients' quality of life and the state of sex hormone disorder. Its more excellent safety profile ensures that it can be used for a long time, significantly prolonging the recurrence - free survival period of patients. In addition, some other progestin drugs such as dydrogesterone and gestrinone are also used clinically. It is worth noting that the limitations of single - drug therapy have shifted the focus of clinical treatment of EMS to combination therapy strategies, which have gradually become the standard treatment for EMS. That is, after the course of GnRH - a treatment, sequential use of progestin drugs such as dydrogesterone can improve hormone levels and effectively extend the recurrence interval.

2.2 Imaging Predictive Indicators

Postoperative imaging follow-up is a necessary means to detect the recurrence of endometriosis (EMS), but it is limited by the clinical experience of ultrasound physicians and the choice of imaging techniques. Transvaginal ultrasound is the preferred examination method 3 - 6 months after surgery due to its advantages such as no need to hold urine and high resolution. It has high specificity in diagnosing ovarian endometriosis and can intuitively observe the size, location, scope and blood flow of cysts [8][9]. However, it has obvious limitations in diagnosing some deeply infiltrating EMS [10]. It is restricted by the clinical experience and operation techniques of ultrasound doctors, and its sensitivity is poor for deep pelvic areas such as the uterosacral ligaments and rectovaginal septum [11]. Although the combined application of transabdominal ultrasound and transvaginal ultrasound can significantly improve the detection rate [12], it still has high requirements for the operating physicians. In recent years, magnetic resonance imaging (MRI) has become increasingly prominent in diagnosing deeply infiltrating EMS [13]. The high soft - tissue resolution of this method can better indicate the degree of invasion of the lesions to the surrounding tissues. At the same time, since the lesion effusion of endometriosis contains a large amount of deoxyhemoglobin and hemosiderin, these substances will cause varying degrees of interference to the magnetic field. The multi - modal MRI technology can image different features in the patient's body through the susceptibility sequence, and can more intuitively evaluate the size and scope of EMS lesions, especially the degree of adhesion with structures such as the ureter and intestine [14][15][16][17], It has greatly improved the specificity of diagnosis. However, the cost of MRI is too high, and it requires a high professional level of the operating physicians, which limits its use as a first-line method. All of the above imaging methods are used for the lagged diagnosis of endometriosis (EMS) recurrence. They can only detect the recurrence when the lesion is large enough. Therefore, future research should focus on developing new technologies for "detecting molecular recurrence" or "functional recurrence" to diagnose EMS recurrence earlier before the morphological changes occur, so as to achieve early intervention and prevent recurrence.

2.3 Serum Biomarkers

2.3.1 Carbohydrate Antigen 125

As the most commonly used and classic tumor marker, carbohydrate antigen 125 (CA-125) is often used in the diagnosis and monitoring of endometriosis (EMS) in gynecological diseases. However, its sensitivity and specificity for the single diagnosis of EMS are both low, and there is no clear threshold for the diagnosis of EMS. But a research survey [18] found that when the preoperative CA125 > 92.1 U/ml, the risk of recurrence increases, which requires clinicians' attention and prevention. However, new research has found that the elevated levels of preoperative CA-125, insulin-like growth factor-1 (IGF-1), and carbohydrate antigen 199 (CA-199) in patients have certain value in diagnosing the recurrence of EMS, and the combined

detection of the three has a higher predictive efficacy [19].

2.3.2 Other emerging serum markers

The causes and pathways of endometriosis (EMS) are still unclear. The widely accepted theory in research is the retrograde menstruation theory, but a single theory cannot explain the entire mechanism of EMS. Current research [20] suggests that the mechanism of EMS occurrence is related to multiple theories such as immune - inflammatory response, endocrine mechanism, and epigenetics, but the specific process remains unclear. People generally explore other serum markers, such as inflammatory immune factors (IL - 6, IL - 8, TNF - α), angiogenesis factors, and auto - antibodies. Among them, microRNA (miRNA) is considered to have high specificity and sensitivity in diagnosing EMS and is easy to detect. miRNA is an endogenous non - coding RNA molecule that can regulate gene expression and is widely present in animals, plants, and viruses [21]. Some studies [22][23] have found that the level of miRNA is significantly elevated in EMS patients and can be used as a serum marker for diagnosing the recurrence of EMS. With the progress of related technologies such as gene sequencing, more and more specifically expressed miRNAs in EMS have been identified. A study by Wang et al. [24] analyzed and found that there were significant differences in 6 miRNAs (miR - 199a, miR - 122, miR - 145, miR141, miR - 542 - 3p, and miR - 9) between the normal control group and EMS patients, which can be used to identify EMS. At the same time, another study [25] found that the expression levels of miR - 135a and miR - 1271 were related to the r - AFS staging, further confirming the prominent performance of miRNA in predicting the recurrence of EMS. A single recurrence prediction index often cannot accurately predict the recurrence of EMS. Under the general trend, research focuses on multi - factor integrated models to evaluate the recurrence risk of EMS.

3. Evolution of the Multi-index Joint Strategy

3.1 Combined Detection of Serological Markers

Single serological indicators are often easily confused with other gynecological diseases and cannot detect the recurrence of endometriosis (EMS) in a timely manner. Clinically, the combined detection of multiple indicators is usually used to diagnose the recurrence of EMS. Many studies have also shown that the combined detection of multiple indicators is often more specific and sensitive than single - indicator detection. Common combined detections of serological marker indicators include tumor markers + inflammatory factors, miRNA series, and proteomic/metabolomic profiles. The most common and frequently used tumor marker is CA - 125. Its single - indicator detection has poor diagnostic efficacy, specificity, and sensitivity for the recurrence of EMS. However, studies have found that the combined detection of CA - 125 with other serological indicators greatly improves the specificity and sensitivity of the diagnosis of EMS recurrence. For example, CA - 125 combined with insulin - like growth factor - 1 (IGF - 1) [26]. Insulin - like growth factor - 1 (IGF - 1) can promote cell proliferation and inhibit apoptosis. A high level of IGF - 1 indicates a very high risk of EMS recurrence. The combined detection of CA - 125 and insulin - like growth factor - 1 (IGF - 1) has better diagnostic efficacy and stronger specificity than the single detection of either indicator. The miRNA series is currently a hot topic in the field of EMS diagnosis and is considered to play a role in a variety of gynecological diseases [27]. Studies have found that the level of a single miRNA changes significantly in patients with EMS recurrence. The diagnostic efficacy of the combined detection of a single miRNA with other indicators such as paired box gene (PAX) [28] or multiple miRNA series is better than single detection. However, due to the limited number of current studies on the diagnosis of EMS recurrence based on miRNA levels and the small sample size of existing studies, the definite association between miRNA levels and EMS recurrence cannot be determined.

3.2 Advantages and Disadvantages of Machine Learning Prediction Models

Clinical physicians often diagnose the recurrence of endometriosis (EMS) through clinical symptoms, gynecological examinations, imaging examinations, and serological examinations, and make comprehensive judgments based on their own clinical experience. This is also a simple multi - index combined detection. Some studies have shown that the combined use of ultrasound and serum markers such as tumor markers and miRNA series, or the comprehensive evaluation of the patient's personal situation, the type and duration of medication is significantly better than single - index detection [29]. Based on this, some studies have proposed the establishment of an EMS recurrence prediction model, incorporating risk factors related to EMS recurrence, in order to diagnose EMS recurrence early and intervene and treat it in a timely manner. Currently, the common one is the traditional logistic regression prediction model [30]. The data of the factors screened in clinical practice are easy to obtain, showing a certain degree of practicality. However, when dealing with some complex multi - dimensional data, the applicability of this prediction model is often limited. It is necessary to find a more stable and powerful prediction model. The machine - learning prediction model emerged as the times require due to its simplicity of use and strong operability. Among them, the decision tree model [31] can comprehensively detect pain - related parameters, with simple and clear classification and low professional requirements, which is convenient for clinical application and popularization. However, it can only target patients with pain symptoms and cannot identify early EMS recurrence or patients without pain symptoms. At the same time, some parameters are too subjective, which will affect the accuracy of the model.

As a single model, the prediction accuracy of the decision tree model is often inferior to that of ensemble models or other more complex models. The random forest model is an ensemble learning method that can build a large number of decision tree models and make predictions based on comprehensive information. Compared with a single decision tree model, it has higher universality, can effectively handle datasets with a large number of features, and can also rank the contributions of each feature to the prediction results, helping doctors identify the most risky factors for EMS recurrence. However, this model involves building a large number of decision tree models, resulting in slow prediction speed and high memory usage. The biggest drawback is that it cannot

provide a clear decision - making path. Using a high - performance gradient boosting model can better address this drawback. This model generates charts to display and classify different types of samples as clearly as possible, facilitating doctors to make more evidence - based diagnoses. However, it should be noted that the model's interpretation of feature data is overly complex, and if the input in the model does not represent real medical laws, it may induce doctors to make incorrect clinical decisions. Nevertheless, the gradient boosting model is currently the most powerful and flexible solution. For EMS recurrence prediction, this model can achieve extremely high prediction accuracy and provide individualized explanations that convince clinical doctors. To address its shortcomings, using a medical imaging AI framework and incorporating a large amount of medical imaging data can accurately identify the regions most relevant to recurrence. The interpretation is very intuitive and more in line with the habits of clinical doctors.

4. Conclusions

EMS is a common gynecological disease, which is the result of the combined action of multiple factors and has an extremely high recurrence rate. At present, a unified standard for EMS recurrence has not been established. Clinically, some rely on serological tests, while others rely on imaging evidence. Different diagnostic criteria make it difficult to integrate and compare most medical research results. Meanwhile, the lack of specificity in patients' clinical symptoms, the uncertainty of imaging examinations, and the absence of clear diagnostic markers also lead to the fact that EMS recurrence is often not detected in a timely manner in clinical practice, which is also the current difficulty in diagnosing EMS recurrence.

Single clinical prediction indicators often cannot accurately and timely diagnose the recurrence of endometriosis (EMS). The clinical symptoms of EMS recurrence are often similar to those of gynecological diseases such as dysmenorrhea, infertility, and pelvic inflammatory disease. Imaging examinations often yield a variety of results, and the commonly used serum markers have low specificity for diagnosing EMS recurrence. The uncertainty of these examinations leads to delayed diagnosis of EMS recurrence in clinical practice. For patients, this not only means a huge economic burden but also causes great mental pain. Based on this, most studies generally attempt multi - factor combined diagnosis in order to improve the accuracy of diagnosis. However, most of these studies are retrospective, and there is no very effective way to predict EMS recurrence.

In recent years, with the rise of the artificial intelligence field, people's attention has turned to machine - learning prediction models. Compared with the previous single traditional logistic regression prediction model, this kind of model can comprehensively consider various factors and rank their risks in terms of importance. It has a certain predictive efficacy for the risk prediction of EMS recurrence. In particular, the gradient boosting model is extremely accurate in predicting EMS recurrence in patients, which is currently the most powerful solution. However, it also has certain drawbacks. The model data is often too complex for clinicians to fully understand. Some existing studies suggest that if a large amount of medical imaging data, along with multiple recurrence risk factors such as clinical symptoms, serological examinations, gynecological examinations, and imaging examinations, are incorporated into the model, it can not only improve the accuracy of recurrence prediction but also be more convenient for clinicians to understand and treat. At present, the model combined with medical imaging data will be a more reliable solution for EMS recurrence prediction.

The research should further combine medical imaging data, utilize more powerful artificial intelligence, and improve the model to enhance the accuracy of predicting endometriosis (EMS) recurrence. This review aims to summarize and generalize the current risk factors for diagnosing EMS recurrence, and proposes that the focus of the research lies in the combined detection of multiple factors. Moreover, the gradient boosting model should be further improved to ultimately achieve precise treatment and individualized long - term management of EMS.

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