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Research Article

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Prediction of Treatment Option by Human Chorionic Gonadotropin (hCG) Levels in Ectopic Pregnancy using Machine Learning

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Abstract

Aim: *The objective of this study is to construct a model using a random forest to predict the treatment option of ectopic pregnancy based on hCG levels, as well as to confirm the model's accuracy.*

Methods: *We selected 17 variables related to ectopic pregnancy and extracted data from our records for cases of possible ectopic pregnancy. We then divided the cases into two groups: 1) laparoscopic surgery and 2) MTX or conservative treatment. We created a model for predicting the prognosis of ectopic pregnancy. Afterward, we confirmed the model's accuracy using the test data. Additionally, we compared the model's accuracy with that of two specialized obstetrician-gynecologists (OB/GYNs) specialists who judged the same data. This study was approved by our ethics committee.*

Results: *One hundred and twenty-eight patients were eligible for this research, of whom 52.3% (67) underwent laparoscopic surgery and 7.0% (9) had emergent laparoscopic surgery. MTX and conservative treatment, including normal pregnancies or miscarriages, were 25.0% (32) and 25.0% (32), respectively. The model's accuracy using a random forest was 87.3%, and the area under curve (AUC) was 0.784. The two OB/GYNs judged the same data with respective accuracies of 77.3% and 79.7%.*

Conclusion: *In conclusion, this model using a random forest was superior to the judgment of specialists. Moreover, this research is new in the fact that it has presented a numerical model involving multiple risks that, until now, have been judged empirically by humans. In the future, it may help develop and elucidate a more extensive prediction system for ectopic pregnancy.*

Keywords: Ectopic Pregnancy, Human Chorionic Gonadotropin, Machine Learning, Random Forest

1. Introduction

Ectopic pregnancy is an important cause of maternal morbidity and mortality; 1.3–2% of all pregnancies are diagnosed as ectopic pregnancies [1]. Ectopic pregnancy is diagnosed by serum human chorionic gonadotropin (hCG), urinary hCG, transvaginal ultrasonography, computed tomography, vascular endothelial growth factor, disintegrin and metalloprotease-12 and hysterosalpingography [2]. In particular, the sensitivity and specificity of transvaginal ultrasonography in diagnosis are currently 84.4% and 98.9%, respectively [3,4]. Changes in hCG levels, as well, are important indicators of ectopic pregnancy. Barash et al. reported that β-hCG values in approximately 99% of viable intrauterine pregnancies increase by about 50% in 48 hours [5]. The remaining 1% have a slower rate of increase or decrease, and these include miscarriages and nonviable intrauterine or ectopic pregnancies [5]. Moreover, several papers have suggested that ectopic pregnancy should be suspected when a patient in their first trimester has abdominal pain or bleeding [2,5].

Ectopic pregnancy treatments involve surgical intervention, medical treatment using methotrexate (MTX), and expectant treatment [2]. There have been numerous studies on which of these is the best treatment. Recently, there have been reports of systems that use artificial intelligence to support diagnosis and treatment decisions, and one particular paper on ectopic pregnancy used machine learning. Alberto et al. developed a three-stage classifier to predict the treatment for ectopic pregnancy and tested this with four different algorithms. The best of the four was the support vector machine, with accuracy, sensitivity, and specificity of 96.1%, 96.0%, and 98.0%, respectively [6].

There are numerous machine learning methods, and the Support Vector Machine is one method for constructing a pattern discriminator for classifications [7]. Therefore, this machine is highly accurate at classifying the given information. However, one weakness of artificial intelligence is that it is a so-called "black box" regarding why the classifications were made [8].

On the other hand, random forests enable classification using a decision tree and allow us to know which input variables were involved in the classification. A random forest is a machine learning algorithm proposed by Leo Breiman in 2019 [9]. While decision trees may lead to overlearning, a random forest generates multiple, relatively simple decision trees by randomly selecting explanatory variables and then averaging the output of each to reduce variance and achieve predictions with a lower rate of error.

Until now, there has been no report of a support system for the selection of treatment for ectopic pregnancy using a random forest. The purpose of this study was to construct such a support system for the diagnosis and treatment selection of ectopic pregnancy using a random forest and to confirm its accuracy. In addition, we investigated what explanatory variables were important in these decisions [10].

2. Methods

2.1. Study Design and Participants

Data were collected from all records of all cases managed for suspected ectopic pregnancy at Osaka Medical and Pharmaceutical University for December 2014-March 2021. This study was approved by our institutional review board (No. 2830), and consent was not required due to its retrospective design. We identified the final treatment for all suspected ectopic pregnancies as either 1) laparoscopic surgery or 2) MTX or expectant treatment. Those who underwent laparoscopic surgery after MTX or observation were added to the group 1.

2.2. Variable Selection

Several indicators for the diagnosis and treatment decision for ectopic pregnancy have been reported [1,11-13]. In this study, we considered all possible indicators and selected 17 variables associated with the prediction of treatment option in cases of ectopic pregnancy (Table 1). We assumed that abdominal pain and vaginal bleeding were the presenting symptoms on the first suspected day. We then determined the estimated pregnancy weeks from the last menstrual period or date of implantation. In addition, we named the HCG level on which we based our diagnosis as "Diagnosed HCG" and the days on which we measured it as "Diagnosed pregnant days". The HCG level on the day of the blood test one or two days prior to the diagnosis was designated as "-1 Diagnosed HCG" or "-2 Diagnosed HCG", respectively, and the day of the blood test itself was designated as "-1 Diagnosed pregnant days" or "-2 Diagnosed pregnant days". If there was no blood test one or two days before the diagnosis, "0 as a meaningless value" was substituted. Substituting a meaningless value does not mean that the value 0 is a missing value, but rather that the variable is skipped and analyzed by other variables.

Attribute	Description
Age	-
G	Gravida
AIH	Artificial insemination with husband's semen
IVF	In vitro fertilization
Vaginal bleeding	Patient's symptoms at the first visit
Abdominal pain	Patient's complaint at the first visit
GS	Gestational sac outside the uterus by ultrasonography at the first visit
Mass	Intra-abdominal mass by ultrasonography at the first visit
Fetal heart beat	Fetal heart beat outside uterus by ultrasonography at the first visit
Abdominal bleeding	Intra-abdominal bleeding by ultrasonography at the first visit
First visit day	
Diagnosed pregnant days	Number of days of pregnancy at the first visit
Number of days pregnancy diagnosed from last menstrual period or embryo transfer	
Diagnosed HCG	HCG value used for diagnosis
-1 Diagnosed pregnant days	Number of days of pregnancy with HCG measured before one of the diagnoses

-1 Diagnosed HCG	HCG value prior to one of the diagnoses
-2 Diagnosed pregnant days	Number of days of pregnancy with HCG measured before two of the diagnoses
-2 Diagnosed HCG	HCG value prior to two of the diagnoses

Table 1: Database Variables

2.3. Random Forests

Random forest is a type of machine learning developed by Leo Breiman in 2019 [9]. Random forests are a combination of tree predictors in which each tree depends on the values of a random vector sampled independently and with the same distribution for all trees in the forest [14]. The candidates for the explanatory variables in the database are X1, X2...X N, and the input values are entered as Input. The number of explanatory variables is then selected in random combinations and a decision tree such as Tree 1 is constructed. The same process is repeated to construct N decision trees (including Tree 2, Tree 3…, and Tree N). In each decision tree, the target objective variable is searched for and obtained as the result. The output values are then summed and averaged to obtain the final output value.

2.4. Model Verification

We created datasets from past records, and entered 17 explanatory variables and two objective variables "required laparoscopic surgery ultimately or not" into a random forest, created a trained model with 80% of the data, and then checked our model's accuracy with 20% of the data. In addition, we compared the accuracy of these models with the prediction accuracy of two experienced obstetrician-gynecologists (OB/GYNs).

Individual names and IDs in this dataset were anonymized. They were not known to the AI model nor to the two OB/GYN physicians.Therefore, both the AI model and the OB/GYN physicians studied under equal and unbiased conditions.

2.5. Explanatory Variable Importance

In a random forest, the importance of the explanatory variables can be expressed quantitatively using the remaining data that were not used for training [15]. The equation to derive the importance of the explanatory variables is shown below:

$$MSE = \frac{1}{N}\sum_{k=1}^{N}(f_k - y_k)^2$$

$$Imp' = \frac{1}{N_t}\sum_{i=1}^{N_t}(MSE_i - MSE_i')$$

fk: The k th learning data
yk: The k th predicted data
N: Number of data
$MSE\ i$: Mean Squared Error (MSE) when Out-of-Bag (OOB) data is used for the decision tree and a correct prediction is performed.
$MSE\ i$': Description of OOB data; we randomly sorted data of a variable m and used it for decision tree i and MSE when we predicted that it would not be correct.
Nt: Number of trees

We have shown the explanatory variable importance to learn which variables were important for the decision in the model used in this study.

2.6. Performance Measures

To guarantee the validity of the results and to evaluate the classification rule accuracy of the test datasets, we performed a fivefold cross-validation (CV), which is a technique used to assess how a classifier performs when classifying new instances of a task. Using a conventional personal computer (Intel Core i9; 2.4 GHz; 32 GB RAM), we trained the dataset using random forests and an obtained fivefold CV for the training accuracy (TR ACC), test accuracy (TS ACC), and area under the receiving operating characteristic curve (AUC-ROC).

2.7. Statistical Analyses

To compare clinical parameters between those patients who underwent an operation, we used a t-test ($P < 0.05$ was considered significant) for comparisons. Data were analyzed using SPSS software (Mac version 20.0 J; IBM, Chicago, IL, USA).

3. Results

In total, we identified 128 cases of suspected ectopic pregnancy at Osaka Medical and Pharmaceutical University in December 2014–March 2021. Among these, 52.3% (67) underwent laparoscopic surgery and 7.0% (9) had emergent laparoscopic surgery. MTX treatment and conservative treatment, including normal pregnancies or miscarriages, were 25.0% (32) and 25.0% (32), respectively. Three cases required MTX or conservative treatment followed by emergency laparoscopic surgery, and the machine learning system remembers the two processes.

Table 1 shows the explanatory variables. We extracted a total of 17 variables by referring to previous reports. For HCG levels, the third and second before diagnosis, the HCG level used for diagnosis, and the estimated number of days of pregnancy were then extracted.

The mean age of all patients was 31.2 years, 11.7% (15) were undergoing fertility treatment, and 5.5% (7) were undergoing IVF. Among all patients, 55.4% (71) had vaginal bleeding and 54.6% (70) had abdominal pain. Regarding the ultrasound findings, 23.4% (30) had a fetal sac outside the uterus, 5.4% (7) had a fetal heartbeat, 53.1% (68) had an intra-abdominal mass, and 55.4% (71) had intra-abdominal bleeding.

The mean (range) estimated gestational age at the day of visit to the hospital was 48.3 (33–89) days. The mean (range) of HCG levels used for diagnosis was 5,424 (1.9-93,388) mIU/mL, the mean (range) of HCG measured one day before was 2,050 (0-18,301) mIU/mL, and the mean (range) of HCG measured two days before was 1,608 (0-17,436) mIU/mL.

Table 2 shows the median and range of each variable for (1) laparoscopic surgery and (2) MTX or Expectant.

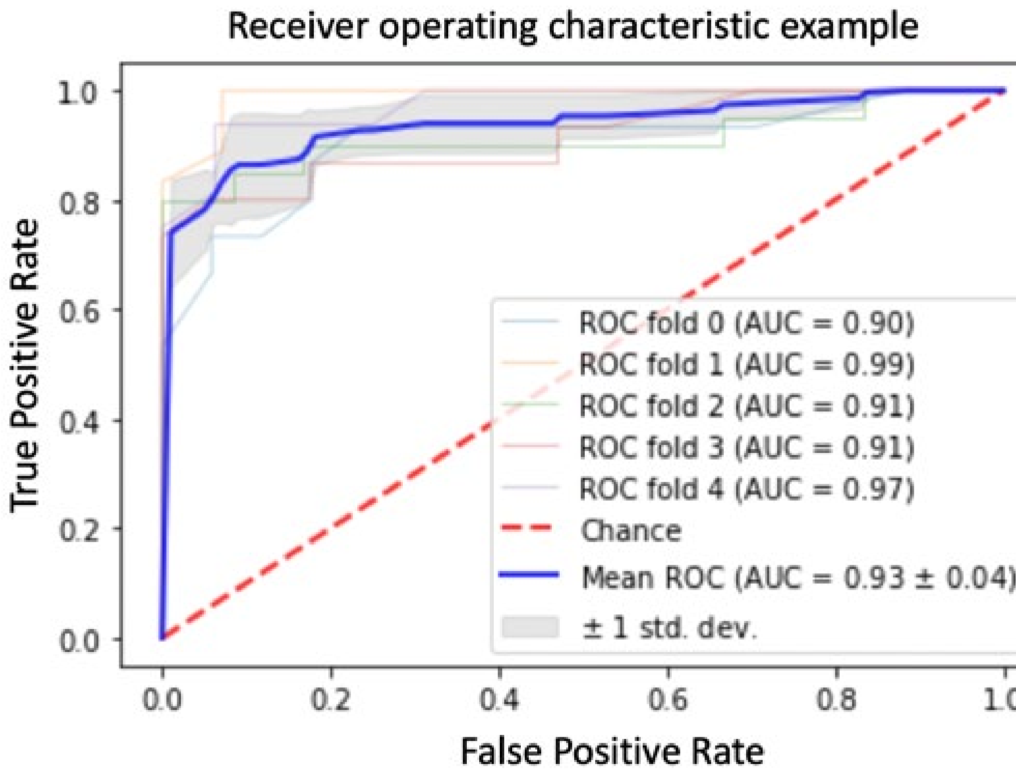
	(1) Laparoscopic surgery N = 67	**(1)MTX or Expectant N = 64**	**P value**
Age (years, median, range)	30.0 (18–44)	32.0 (22–44)	0.318
G (median, range)	2 (0–2)	1 (0–2)	0.893
AIH (n, %)	3.0% (2)	3.1% (2)	0.937
IVF (n, %)	3.0% (2)	7.8% (5)	0.205
Vaginal bleeding (n, %)	52.2% (35)	56.2% (36)	0.501
Abdominal pain (n, %)	56.7% (38)	48.4% (31)	0.449
GS (n, %)	41.7% (28)	1.5% (1)	<0.0001
Mass (n, %)	62.6% (42)	40.6% (26)	<0.018
Fetal heartbeat (n, %)	10.4% (7)	0.0% (0)	< 0.009
Abdominal bleeding (n, %)	61.1% (41)	45.3% (29)	<0.100
First visit days (median, range)	46.5 (35–75)	45.0 (33–77)	0.091
Diagnosed pregnant days (median, range)	16.0 (2–48)	18.0 (0–52)	0.695
Diagnosed HCG (mIU/L, median, range)	5,565.0 (404 – 93,388)	772.0 (0 - 26,308)	<0.0001
-1 Diagnosed pregnant days (days,median, range)	6.5 (0–41)	15.0 (0–50)	<0.0001
-1 Diagnosed HCG (mIU/L,median, range)	2,978(0-18,301)	1,179 (0-17,553)	0.022
-2 Diagnosed pregnant days (days,median, range)	4.5 (0-35)	12.0(0-48)	<0.0001
-2 Diagnosed HCG (mIU/L,median, range)	526.5 (0-6,153)	1,088 (0-17,436)	<0.0001

Abbreviations: G, Gravida; AIH, Artificial insemination with husband's semen; IVF, in vitro fertilization

Table 2: Patient Variables in Every Treatment Group

3.1. Performance of the Random Forest

We achieved a TS ACC of 87.1% and an AUC-ROC of 0.93 for the dataset (Figure 1). The sensitivity and specificity were 90.4% and 83.3%, respectively (Table 3).



ROC: Receiver operating characteristic example
AUC: Area under the curve

Figure 1: ROC and AUC for Treatment Decision-Making

	Random forest	**OB/GY1**	**OB/GY2**
Accuracy	87.1 (± 1.1)	76.4	79.7
Sensitivity	90.4 (± 0.8)	82.1	82.1
Specificity	83.3 (± 0.9)	72.1	77.0
AUC	0.93 (± 0.04)	0.77	0.79

Table 3: Comparison of Random Forest Model and Obstetrician-Gynecologists

The same findings were judged by two qualified OB/GYNs and cross-checked with the actual results; their accuracies were 77.3% and 79.7%, their sensitivities were 82.1% and 82.1%, their specificities were 72.1% and 77.0%, and their AUCs were 0.77 and 0.79, all respectively (Table 3). Therefore, this random forest model may be able to make better decisions than experienced OB/GYNs.

3.2. Explanatory Variable Importance

Table 4 shows the explanatory variable importance as determined by the random forest model [16]. The most important explanatory variable was the HCG value prior to two of the diagnoses (-2 Diagnosed HCG at 27.6%). The second most important factor was the number of days of pregnancy with HCG measured before two of the diagnoses (-2 Diagnosed pregnant days at 22.8%). The third most important factor was the HCG value used for the diagnosis (Diagnosed HCG).

	Explanatory variable importance
-2 Diagnosed HCG	27.6%
-2 Diagnosed pregnant days	22.8%
Diagnosed HCG	10.8%
-1 Diagnosed HCG	10.3%
-1 Diagnosed pregnant days	6.1%

Diagnosed pregnant days	5.6%
First visit day	4.8%
Maternal age	3.9%
Gestational sac outside the uterus	2.8%
Abdominal pain	1.2%
Gravida	1.0%
Abdominal bleeding	0.9%
Vaginal bleeding	0.8%
Abdominal mass	0.5%
Fetal heart beat	0.3%
IVF	0.2%
AIH	<0.1%
IVF: In vitro fertilization	
AIH: Artificial insemination with husband's semen HCG: Human chorionic gonadotropin	

Table 4: Explanatory Variable Importance

3.3. Decision Tree

Figure 2 shows a decision tree. Class 1 is the surgical group; Class 2 is the MTX or expectant group. This decision tree tells us the numerical value the model bases its diagnosis on when making a decision. For example, if the -2 Diagnosed HCG is below 38.75 mg/dl and the Diagnosed HCG is above 1854.5 mg/dl, the model will decide to need an operation. However, if the -2 Diagnosed HCG is less than 38.75 mg/dl and the Diagnosed HCG is less than 1,854.5 mg/dl and less than 500.0 mg/dl, an operation is not required. Moreover, if the date of presentation and the two previous diagnosed visits are the same and the diagnosed HCG is less than 3,396 mg/dl, it predicts that surgery is not needed if the presentation date is 5.7-7.5 weeks of gestation.

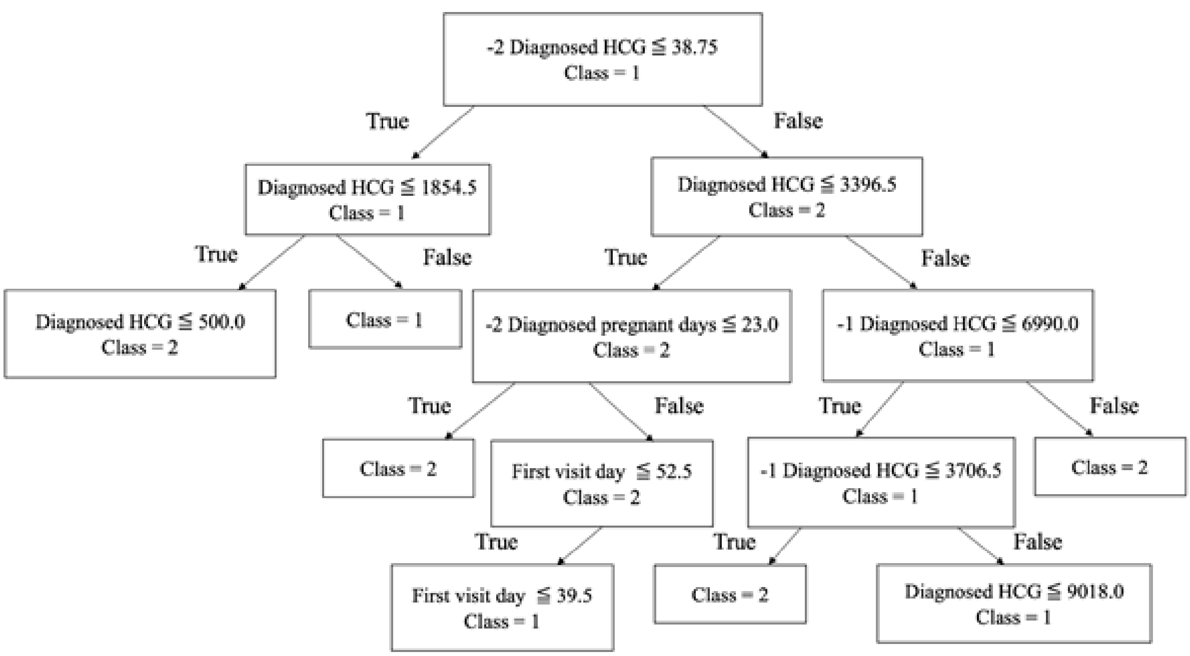


Figure 2: Decision Tree

Class 1 is the surgical group; Class 2 is the MTX or expectant group.
Unit: -2 Diagnosed HCG; mIU/L , -1 Diagnosed HCG ; mIU/L , Diagnosed HCG ; mIU/L, -2 Diagnosed pregnant days ; days, First visit day ; days

This decision tree shows the basis on which the model made its decision by proceeding to the decision tree from the top.

4. Discussion

In this study, the appropriate treatment for a suspected ectopic pregnancy could be selected with a high accuracy of 87.1% (AUC 0.93) by inputting the 17 variables used in the usual diagnosis, including HCG levels. In the field of obstetrics and gynecology, early diagnosis is difficult due to the number of complex mechanisms, especially in cases of ectopic pregnancy [2,17]. This is because the initial symptoms of an ectopic pregnancy are similar to other complications, such as miscarriage and ovarian cyst torsion [18]. Currently, there are various technologies that can help detect ectopic pregnancies [19]. For example, there is ultrasonography and a number of blood tests that can measure multiple markers (e.g., beta-HCG and progesterone) [1,20,21]. Treatment needs to be started as soon as the diagnosis is confirmed in order to reduce the risk of rupture of the fallopian tubes or other organs. The three approaches to the management of ectopic pregnancy are surgery (salpingostomy or salpingectomy), methotrexate treatment (MTX), or expectant management. Surgical treatment is the gold standard for patients with high HCG levels and intense symptoms of suspected ectopic pregnancy. There have been various reports on whether patients should undergo expectant treatment or not. Rodrigues SP et al. showed that asymptomatic patients with β-HCG levels < 2000 IU/l could be treated with expectant management [9,22]. Joshua H et al. (2014) reviewed the management of ectopic pregnancy, and they indicated that β-hCG values in approximately 99% of viable intrauterine pregnancies increase by about 50% within 48 hours. The remaining 1% of patients have a slower rate of increase, and these patients may have pregnancies that are misdiagnosed as either nonviable or necessitating expectant management [5].

In addition, in recent years, information and communication technologies (ICT) have been added to traditional diagnostic technologies. Artificial intelligence (AI) is being applied in the clinical field and has been implemented in various other fields [23]. AI algorithms are computational models that attempt to solve problems that cannot be solved using statistical methods [24]. Therefore, the development of AI algorithms that can help predict or classify diseases from a knowledge base can be applied in various ways as clinical decision support systems (CDSS).

CDSSs based on computational techniques have been developed in the obstetrical field to predict pregnancy outcomes [25]. There have been various reports on the prediction of emergency cesarean section, some using random forests and some using CNNs. One problem with AI technologies is that they have been referred to as "black boxes," or systems whose inputs are not visible to the user. However, in recent years, explainable AI (XAI) has been developed [26]. De Ramon Fernandez et al. constructed a decision support system for ectopic pregnancy using three algorithms, including a support vector machine (SVM)6. They reported that the accuracy, sensitivity, and specificity in SVM were 96.1%, 96%, and 98%, respectively [6].

Although these algorithms are highly accurate, the problem is that they are black boxes that do not know what risk factors are involved in the final decision. To overcome these problems, we constructed a model to support diagnosis and treatment decisions for ectopic pregnancy using a random forest, which is an algorithm based on visible decision trees.

A random forest model is a type of machine learning that only analyzes input variables and then outputs appropriate decisions. The reason for the decision is a black box, but the basis for the decision is simply expressed as a decision tree in order to provide as much explanation as possible. In the random forest model, input values for the candidate explanatory variables in the database are X1, X2,…,Xn. The number of explanatory variables is chosen in random combinations, and a decision tree, such as Tree1, is constructed. The same process is repeated to build N decision trees. In each decision tree, target variables are searched and obtained as results. Each decision tree is then constructed by the Classification and Regression Trees (CART) algorithm; however, the decision tree method has one drawback in that it can be prone to overlearning [14]. Random forests have the advantage of being less prone to overtraining because the model is built by ensemble learning [27]. Moreover, in a random forest, explanatory variables are randomly selected to generate multiple relatively simple decision trees, and the output of each decision tree is eventually averaged in order to reduce variance and to make predictions with a lower error [28]. In addition, we used explanatory variable importance to determine which risk factors contribute to the decision support model we developed. This method is not a decision tree analysis that elucidates the decision process, which has been used in the past, but an analysis using machine learning. As well, it was written only to clarify the basis for the decision itself. The explanatory variable importance is a quantitative expression of the importance of explanatory variables using the remaining data that were not used for training in the random forest [15]. The explanatory variable importance has been described in various scientific papers as an analysis of factors in diagnosis [29]. Furthermore, as a discussion of the weeks of gestation and the results of this study, Daniela Carusi et al. report that an ectopic pregnancy is possible if no fetal sac is seen in the uterus at 6 weeks of gestation, counting from the date of ovulation or implantation [30]. In this study, the -2 Diagnosed pregnant day attribute accounted for 22.8% of the explanatory variable importance (total of 100%). The -1 Diagnosed pregnant days and Diagnosed pregnant days attributes were the top explanatory variables at 6.1% and 5.6%, respectively.

On the other hand, abdominal bleeding, vaginal bleeding, and abdominal mass were the explanatory variables of the importance of less than 1%. These were variables that previous findings could have provided a basis for judgment, however, the results of this study indicated that they were less critical variables [31,32].

As a result of examining the explanatory variables in this model, the most important one was found to be -2 Diagnosed HCG, followed by the -2 Diagnosed pregnant days, and then Diagnosed HCG. This indicates that not only are HCG level, symptoms, and ultrasound findings at the time of diagnosis important, but so is the

HCG level and its trend before diagnosis.

There are limitations to this study, and generalizability is the main one. In order to maintain generalizability, this data was subjected to a fivefold cross-validation. As well, since the model was constructed using data from a single facility and tested at that facility, further model construction needs to be considered in the future.

5. Conclusion

This model using a random forest was superior to the judgment of specialists in the field. Moreover, Moreover, this research is new not only in its use of artificial intelligence to predict treatment methods for ectopic pregnancies but also in the fact that it has presented a numerical model involving multiple risks that, until now, have been judged empirically by humans. It is the first report of its kind to build a model that predicts the treatment of ectopic pregnancy using a random forest. In the future, this study may help in building and elucidating a larger, more comprehensive prediction system for ectopic pregnancy.

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