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Original Article

Prevalence of Thalassemia in the Vietnamese Population and Building a Clinical Decision Support System for Prenatal Screening for Thalassemia

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Abstract. ***Introduction*: The prevalence of thalassemia among the Vietnamese population was studied, and clinical decision support systems for prenatal screening of thalassemia were created. The aim of this report was to investigate the prevalence of thalassemia in the Vietnamese population, building a clinical decision support system for prenatal screening for thalassemia.**
***Methods*: A cross-sectional study was conducted on pregnant women and their husbands visiting the Vietnam National Hospital of Obstetrics and Gynecology from October 2020 to December 2021. A total of 10112 medical records of first-time pregnant women and their husbands were collected.**
***Results*: A clinical decision support system was built, including 2 different types of systems for prenatal screening for thalassemia (an expert system and 4 AI-based CDSS). One thousand nine hundred ninety-two cases were used to train and test machine learning models, while 1555 cases were used for specialized expert system evaluation. There were ten key variables for AI-based CDSS for machine learning. The four most important features in thalassemia screening were identified. The accuracy of the expert system and AI-based CDSS was compared. The rate of patients with Alpha thalassemia is 10.73% (1085 patients), the rate of patients with beta-thalassemia is 2.24% (227 patients), and 0.29% (29 patients) of patients carry both alpha-thalassemia and beta-thalassemia gene mutations. The expert system showed an accuracy of 98.45%. Among the AI-based CDSS developed, the multilayer perceptron (MLP) model was the most stable regardless of the training database (accuracy of 98,5% using all features and 97% using only the four most important features).**
***Conclusions*: When comparing the expert system with the AI-based CDSS, the accuracy of the expert system and AI-based models was comparable. The developed expert system for prenatal thalassemia screening showed high accuracy. AI-based CDSS showed satisfactory results. Further development of such systems is promising with a view to their introduction into clinical practice.**

Keywords: Thalassemia, Vietnamese population, Clinical decision support system, Expert system, AI-based system.

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Introduction. Thalassemia is an inherited autosomal recessive disease characterized by impaired synthesis of hemoglobin protein chains.[1] A normal mature hemoglobin molecule (HbA) consists of two pairs of alpha and beta chains. Normal adult blood also contains ≤ 2.5% hemoglobin A2 (HbA2) (consisting of alpha and delta chains) and <2% hemoglobin F (HbF, fetal hemoglobin), which has gamma chains instead of beta chains.[2] Thalassemia is caused by a gene mutation of the gene responsible for globin chain synthesis, based on which alpha-thalassemia and, beta-thalassemia, delta-beta-thalassemia are distinguished.[3] Such a gene can be inherited from one parent or two. The child's body produces fewer or no hemoglobin chains. The production of the other chains that make up globin does not end. As a result, unstable protein components are produced that destroy the blood cells.[4] Thalassemia is thus the result of reduced synthesis of at least one globin polypeptide chain (beta, alpha, gamma, delta), resulting in abnormal erythrocytes that are microcytic, often irregularly shaped, and prone to hemolysis. This results in anemia and often in iron overload.[5]

The severity of the disease depends on the number of mutated alleles. In humans, the alpha chain of hemoglobin is encoded by two pairs of genes, while the beta chain has only one pair. Patients with one alpha + allele are clinically normal and are called asymptomatic carriers. Heterozygotes with defects in 2 of the 4 genes (small alpha thalassemia) tend to develop microcytic anemia of mild to moderate severity but with a subclinical course. Defects in 3 of the four genes significantly impair alpha-chain synthesis, in which hemolytic anemia and splenomegaly are common. A defect in all 4 is a fatal condition that causes intrauterine fetal death.[6] Minor beta-thalassemia occurs in asymptomatic heterozygotes with a mild to moderate clinical picture of microcytic anemia. Intermediate beta-thalassemia presents a variable clinical picture due to the inheritance of 2 beta-thalassemia alleles. Large beta-thalassemia (Cooley's anemia) occurs in homozygous patients or complex heterozygotes due to a severe beta-globin defect. These patients develop severe anemia and bone marrow hyperactivity.[7,8] In addition, it is rare to find simultaneous disorders in both alpha- and beta-chain at once, but in this case, the disease may be milder because there is little imbalance between the two types of chains.[3] Thus, severe forms of the disease seriously affect physical development, causing patients to need continuous blood transfusions for life with many complications in the liver, heart, endocrine glands, and bones. The disease is life-threatening, worsening the patient's quality of life, and involves expensive treatments that burden the family and society.[9]

Worldwide, an estimated 7% of the population carries the thalassemia gene, and each year between 300,000 and 500,000 babies are born with severe homozygosity for the disease.[10,11] In Vietnam, more than 5 million people carry the gene; every year, more than 100,000 children carry the gene, and 1,700 children have the severe disease due to mutations in both genes.[12] Thalassemia is distributed in all provinces and ethnic groups throughout the country, especially ethnic minorities in mountainous provinces.[12]

Thalassemia is a preventable disease screening pregnant women and their husbands at risk of carrying the disease gene to prevent having children with the disease.[13,14]

Nowadays, modern technology has been researched and applied in medicine to support doctors in patient care and practice specialization.[15] A Clinical Decision Support System (CDSS) is "any electronic or non-electronic system designed to aid directly in clinical decision making, in which characteristics of individual patients are used to generate patient-specific assessments or recommendations that are then presented to clinicians for consideration".[16] CDSSs are classified as expert knowledge-based systems and artificial intelligence (AI).[17] CDSSs have many advantages, such as reducing the rate of misdiagnosis, improving efficiency and patient care, and reducing the risk of medication errors.[18] For thalassemia, there have been studies around the world applying AI in screening carriers with high efficiency. In 2002, Amendolia and colleagues[19] studied and built a real-time classification system based on Artificial Neural Networks (ANNs) to distinguish thalassemia gene carriers and normal people with an accuracy of 94%, a sensitivity of 92% and a specificity of 95%. In 2013, Masala et al.[20] compared the performance of The Radial Basis Function (RBF) network, The Probabilistic Neural Network (PNN), and The K-Nearest Neural Network (KNN) algorithms in thalassemia screening with 304 data samples. The results show that the RBF algorithm had a sensitivity of 93% and a specificity of 91%, similar to the results of KNN of 80% and 91% and PNN of 89% and 73%.[20]

The screening for thalassemia in Vietnam is still mainly based on the two indexes (mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH)) and performed manually, and no CDSS has been built yet. This causes many difficulties in disease prevention at primary health care facilities and in ethnic minority areas because of the limited understanding of thalassemia not only by the people but also by the grassroots medical staff. The requirement is to build AI software and an expert knowledge-based system for thalassemia screening that can be applied to even primary healthcare facilities.

Thus, developing and introducing into clinical

practice modern CDSSs for screening thalassemia in Vietnam is an urgent task. These systems can significantly assist doctors in making optimal decisions, even in primary healthcare institutions. Special attention should be paid to CDSSs based on machine learning algorithms, which remain poorly studied.

Therefore, our research was carried out with the following objectives:

1. Investigating the prevalence of thalassemia in the Vietnamese population
2. Building a clinical decision support system for prenatal screening for thalassemia.

Material and Methods

Study design. This cross-sectional study was conducted from October 2020 to December 2021. Data were collected using a convenient sampling method. We collected data on pregnant women and their husbands when they came to the Vietnam National Hospital of Obstetrics and Gynecology for annual screening of congenital disabilities through medical records. Data were collected from the medical records of patients who came to the hospital before the study.

Ethical approval of the study. The research was approved by the Vietnam National Hospital of Obstetrics and Gynecology Ethics committee, Minutes 54/5 of 2020-09-12. The research has been performed in accordance with the Declaration of Helsinki.

Study subjects. A total of 10112 medical records of first-time pregnant women and their husbands were collected, of which 1992 cases were used to train and test machine learning models while 1555 cases were used for specialized knowledge system evaluation. All patients underwent routine screening of thalassemia: peripheral blood smear, complete blood count (CBC), hemoglobin quantification by high-performance liquid chromatography (HPLC) and capillary electrophoresis (CE), and iron status tests. Detection of hemoglobin gene mutations by polymerase chain reaction (PCR) was performed for 1,364 patients and 658 newborns to assess the prevalence of different forms of thalassemia in the Vietnamese population. The multiplex ligation-dependent probe amplification (MLPA) technique has been used for the molecular detection of alpha-thalassemia. The Reverse Dot-Blot PCR technique has been used for the molecular detection of beta-thalassemia.

Data analysis. Two CDSS models for thalassemia pre-screening have been created: 4 AI-based CDSS for machine learning and an expert system. The basic difference between these two types of systems is that one is based on the knowledge base gathered from the knowledge of experts, and the other is based on computer mining knowledge from medical data. The specialized expert system was built based on the guideline for prenatal screening for thalassemia of the Vietnamese Ministry of Health.

The following independent variables were used in expert system CDSS: 4 most important indicators from CBC result (according to MID and MDA algorithms), including hemoglobin (HGB), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), red blood cell distribution width (RDW), serum ferritin concentration from iron status tests result, HbA2 and HbF levels from HPLC result. In addition, one should take into account the history of hydrops fetalis and having children or family members diagnosed with thalassemia.

There were 10 key variables for AI-based CDSSs for machine learning: the dependent variable was whether a patient had a thalassemia gene; 9 independent variables, including 7 from the CBC result were hematocrit (HCT), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), hemoglobin (HGB), red blood cell distribution width (RDW), red blood cell (RBC) and the other 2 are iron status: serum iron and serum ferritin. In addition, AI-based CDSSs for machine learning were evaluated using the four most important indicators above-mentioned (according to MID and MDA algorithms).

Data from 1992 pregnant women and their husbands were used to train and test 4 machine learning models, which were K-nearest neighbors (KNN), Support vector machine (SVM), Random Forest (RF), and Multilayer perceptron (MLP). The purpose of these models is the screening for thalassemia gene in pregnant women, husbands, and both pregnant women and husbands. Thus, we used data from all participants and divided them into 2 subsets, 1 with data from pregnant women only and the other from the husbands. After analyzing the dependent variable, whether the participant had a thalassemia gene or not, we realized that there were more participants without a thalassemia gene than those who did, which caused an unbalance in the dataset and resulted in the inaccuracy of all models. To solve this problem, we performed Synthetic Minority Over-sampling Technique (SMOTE). This method was introduced in 2002 by Nitesh Chawla et al.;[21] the idea is based on the K-Nearest Neighbors algorithm. We get one sample randomly from the minority layer a and one of its k nearest neighbors in the feature space, then we randomly choose a k nearest neighbors b and draw a line between these samples in the feature space. New samples are created on this line as the combination of a and b. These new samples helped balance the datasets, meaning the number of participants with the thalassemia gene is now equal to those without this gene. Datasets were then standardized using the z-score method; in particular, we used a StandardScaler

command from the sci-kit-learn library. Hyperparameters were found using grid search. All 4 models were tested using 10-fold cross-validation using these datasets and evaluated by 4 indices: accuracy, precision, recall, and F1-score to find the best one.

Results

Prevalence of types of thalassemia. Ten thousand one hundred twelve pregnant women and their husbands performed the CBC, HPLC, and iron status during the study period. Based on the CBC, HPLC, and iron status results, 1,364 pregnant women and their husbands were prescribed a genetic test due to the suspected presence of thalassemia genes. The genetic test resulted in 1,085 (10.73% of the total number of pregnant women and their husbands) alpha-thalassemia cases and 227 (2.24%) beta-thalassemia cases. A small ratio of 0.29% inherited both α– and β–thalassemia genes, and 0.23% were others, including HbE disease, alpha thalassemia/HbE, beta-thalassemia/HbE and hemoglobin Constant Spring disease (**Table 1**). Among 658 fetuses of parents with identified thalassemia genes who performed the genetic testing, the frequency of α-thalassemia (61.85%) was also higher than β-thalassemia (13.07%) and others (including HbE disease, α-thalassemia/HbE, and β-thalassemia/HbE) (0.61%) (**Table 2**).

Determining the features of the CBC, HPLC, and iron status test needed to screen for thalassemia. After using MID and MDA algorithms, we found that 4 indices included, HGB, MCV, MCH, and RDW were the most important ones in the screening of thalassemia from the database containing 10112 cases having CBC, HPLC, and iron status results (**Figures 1, 2**).

Selection and evaluation of the effectiveness of AI models in screening for thalassemia.

The experimental result with general CBC and iron status database. According to **Table 3**, when using the 4 most important indicators in thalassemia screening instead of using them all in CBC and iron status database, the Accuracy and Precision indices decreased but not much. With several models, the result was even more improved. For example, with the SVM model, Accuracy and Precision indices were increased (95% and 91.25% versus 94.5% and 90.12%).

KNN model using only 4 important features and training with the general CBC and iron status database (pregnant women and their husbands) had an accuracy of 97%, a precision of 93.75%, a recall of 98.68%, and an F1-score of 98.15% for original data and an accuracy of 92.5%, a precision of 85.9%, a recall of 98.68%, and an F1-score of 90.91% for SMOTE; MLP model had an accuracy of 97%, a precision of 92.68%, a recall of 99.23%, and an F1-score of 96.20% for original data and an accuracy of 94.5%, a precision of 88.24%, a recall of 98.68%, and an F1-score of 93.17% for SMOTE. SVM and RF models showed similar but slightly lower results for some indices (**Table 3**).

The experimental result with CBC and iron status database of pregnant women. With the data filtered for pregnant women, the training and testing are similar to the full one, including pregnant women and their husbands. The results are shown in **Table 4**.

The results showed that among the 4 training models, the KNN and MLP models were the best with 96.93%

Table 1. The frequency of different types of thalassemia in patients.

Types of thalassemia		Pregnant women		Husband		Total	%
		N	%	N	%		
Patients who performed genetic testing	Alpha thalassemia	566	6.40	519	40.83	1085	10.73
	Beta thalassemia	117	1.32	110	8.65	227	2.24
	Co-inheritance of alpha and beta-thalassemia	7	0.08	22	1.73	29	0.29
	Others	14	0.16	9	0.71	23	0.23
Patients who did not perform genetic testing		8137	92.04	611	48.07	8748	86.51
The total number of cases that performed the CBC and iron status test		8841	100	1271	100	10112	100

Table 2. Prevalence of thalassemia types in fetuses who underwent genetic testing.

Types of thalassemia	N	%
Alpha thalassemia	407	61.85
Beta thalassemia	86	13.07
Co-inheritance of alpha and beta-thalassemia	19	2.89
Others	4	0.61
Normal	142	21.58
Total	658	100

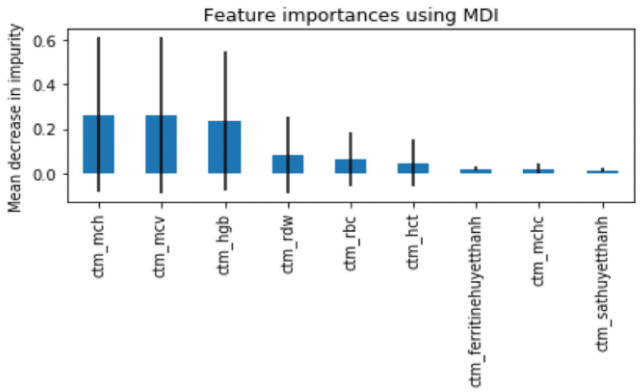

Figure 1. From left to right, feature importance using the MDI algorithm.

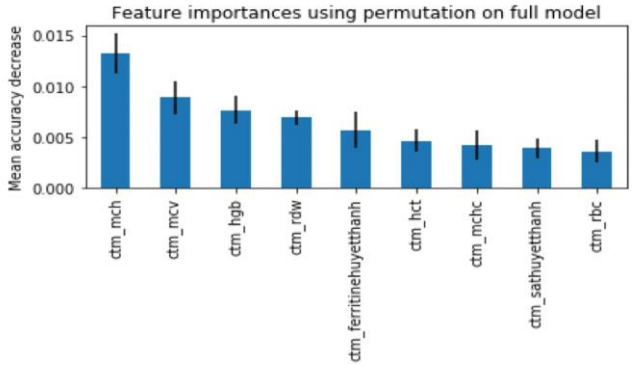

Figure 2. From left to right, feature importance using the MDA algorithm.

and 96.91% accuracy, 93.22% and 93.25% precision, 98.21% and 100% recall when using all CBC and iron status features. Wherein, with only the 4 most important features, the accuracy of the KNN and MLP models impressively increased from 96.93% to 97.53% and 96.91% to 97.81%. The accuracy of the SVM model also increased from 95.68% to 96.91% (**Table 4**). One special issue with this database was that after balancing the dataset with SMOTE technique, the result was improved for some indexes.

Experimental result with CBC and iron status database of husband. Similar to data on complete blood counts and iron status from pregnant women, the packaged models were not influenced by gender. With full CBC and iron status, the RF model showed the highest accuracy at 97.55%, precision index at 95.46%, and recall index at 100% (**Table 5**). Using only 4 important features did not change the results, except for the multilayer perceptron (MLP) model, whose accuracy was increased significantly to 97.44%. One remarkable issue with this database was that after balancing the dataset with SMOTE technique, the result of the models was decreased for some indexes (**Table 5**).

Evaluation of the effectiveness of the expert system (ES) in screening for thalassemia and comparison with AI models. To build an expert system (ES) in screening for thalassemia, we applied the rules in **Table 6**.

The effectiveness of the expert system was evaluated in the same CBC, HPLC, and iron status database used to test the AI models, including 396 pregnant women and husbands who met the inclusion criteria (presence of thalassemia gene by PCR). However, the result showed that 323 cases were determined the risk of having thalassemia by the software, and 73 cases that were not. The reason for 73 cases was that patients had performed

Table 3. Comparing the results of models using the 4 most important features with models using all features in general CBC and iron status database (pregnant women and their husbands). Precision and Recall indices were calculated for thalassemia carrier.

Model	Accuracy (%)		Precision (%)		Recall (%)		F1-Score	
	Original data	SMOTE	Original data	SMOTE	Original data	SMOTE	Original data	SMOTE
All CBC and iron status indices								
KNN	98	95.5	93.87	90.12	100	99.12	98.66	95.67
SVM	95	94.5	94.5	90.17	97.15	97.15	95.34	94.04
RF	97	95.5	93.24	85.24	98.86	96.45	96.08	92.45
MLP	98,5	95.5	94.67	89.8	100	99.23	97.65	94.73
Only 4 most important indices (HGB, MCV, MCH, RDW)								
KNN	97	92.5	93.75	85.9	98.68	98.68	98.15	90.91
SVM	94.5	93.5	90.12	87.18	96.05	96.05	93.59	93
RF	96	92.5	91.46	84.27	98.68	96.15	94.94	90.68
MLP	97	94.5	92.68	88.24	99.23	98.68	96.20	93.17

Table 4. Comparing the results of models using the 4 most important features with models using all features in CBC, and iron status database of pregnant women. Precision and Recall indices were calculated for the thalassemia carrier.

Model	Accuracy (%)		Precision (%)		Recall (%)		F1-Score	
	Original data	SMOTE	Original data	SMOTE	Original data	SMOTE	Original data	SMOTE
All CBC and iron status indices								
KNN	**96.93**	**97.53**	**93.22**	**93.33**	**98.21**	**100**	95.65	**96.55**
SVM	95.68	92.6	91.52	83.33	100	98.21	93.91	90.16
RF	**96.91**	91.36	91.8	80	98.21	**100**	**95.72**	88.9
MLP	**96.91**	**97.53**	**93.25**	**93.33**	**100**	**100**	95.65	**96.55**
Only 4 most important indices (HGB, MCV, MCH, RDW)								
KNN	**97.53**	**97.87**	**93.38**	**93.41**	98.45	**100**	**96.75**	**96.74**
SVM	96.91	90.74	91.8	79.71	96.43	97.83	95.73	88
RF	96.22	91.12	90.74	79.45	97.56	99.54	95.65	87.6
MLP	**97.81**	**97.65**	93.21	**93.28**	**99.84**	**99.73**	**95.72**	96.43

Table 5. Comparing the results of models using the 4 most important features with models using all features in CBC and iron status database of husbands. Precision and Recall indices were calculated for thalassemia carrier. Precision and Recall indices were calculated for the thalassemia carrier.

Model	Accuracy (%)		Precision (%)		Recall (%)		F1-Score	
	Original data	SMOTE	Original data	SMOTE	Original data	SMOTE	Original data	SMOTE
All CBC and iron status indices								
KNN	92.31	92.31	95	94.72	90.48	90.23	92.68	92.23
SVM	94.87	94.62	95.24	94.94	94.52	94.31	95.36	95.18
RF	**97.55**	92.31	**95.46**	95.46	**100**	90.48	92.67	92.76
MLP	97.91	97.44	94.46	95.46	96.55	91.92	97.68	97.68
Only 4 most important indices (HGB, MCV, MCH, RDW)								
KNN	91.44	90.84	94.86	94.54	90.12	89.87	91.64	91.52
SVM	94.45	94.16	94.83	94.52	93.96	93.72	95.04	94.98
RF	96.44	84.87	95.32	94.22	99.87	91.24	97.67	87.24
MLP	97.44	94.18	96.42	95.44	100	95.95	97.62	95.18

only CBC tests, neither serum ferritin nor hemoglobin variant analysis, and no related history, which caused a lack of indicators to predict. 323 cases left were evaluated and calculated, shown in **Tables 7** and **8**. There were 5 incorrect cases in risk assessment (false positive) and no false negative cases, which meant no thalassemia patients were left out. Comparing the expert system with the AI model, the accuracy of the expert system was 98.45%, while that of the KNN and MLP models was 97%, the RF model – 96%, and the SVM model – 94,5% when using only the 4 most important features (**Table 8**).

Discussion. The present study analyzed the prevalence of different thalassemia types among pregnant women and their husbands who came to the Vietnam National Hospital of Obstetrics and Gynecology. The prevalence of different thalassemia types in fetuses of parents with established, according to PCR tests, thalassemia genes was also evaluated. The prevalence of alpha-thalassemia in pregnant women, husbands, and fetuses was higher

Table 6. Summary of rules in ES.

Evaluation	Indices	Values	Conclusion	Prediction results
Anemia	HGB	Pregnant women: >= 110 Husband: >=130	Non-anemia	Insufficiency of data
		Pregnant women: <110 Husband: <130	Anemia	
The size of red blood cell	MCV	< 85	Microcytic erythrocyte	
		85-100	Normal-size RBC	
		>100	Macrocytic erythrocyte	
The amount of hemoglobin	MCH	< 28	Hypochromic erythrocytes	
		28-32	Normochromic erythrocytes	
		> 32	Hyperchromic erythrocytes	
Iron deficiency	Ferritin	< 13	Iron deficiency	
		>= 13	Non- Iron deficiency	
The risk of thalassemia carrier if the patient performed the CBC test and ferritin blood test	HGB, MCV, MCH, RDW, Ferritin		-Possible types of thalassemia -Recommendation for performing genetic testing searching for thalassemia mutations	High risk of thalassemia
The risk of thalassemia carrier if the patient performed the CBC test, ferritin blood test and hemoglobin variant analysis test	HGB, MCV, MCH, RDW, Ferritin, HbA2, HbF			
History of hydrops fetalis or having children or family members diagnosed with thalassemia			Yes or no	Low risk or high risk of thalassemia

Table 7. Evaluation of the effectiveness of the expert system (ES).

	High risk	Low risk	Unknown (n=73)	Indicators	
Patients with thalassemia	113	0	36	True positive	113
				True negative	205
Patients without thalassemia	5	205	37	False positive	5
				False negative	0

Table 8. Comparison between the expert system and AI model when using only the 4 most important features in general CBC, HPLC and iron status database (pregnant women and their husbands).

	Expert system	AI model			
		KNN	SVM	RF	MLP
Accuracy (%)	98.45	97	94.5	96	97
Sensitivity (%)	100	-	-	-	-
Specificity (%)	97.62	-	-	-	-

than in beta-thalassemia carriers. (**Tables 1, 2**).

The prevalence may have been because women whose babies had hydrop details in the previous pregnancy or the fetuses with alpha thalassemia would show clinical manifestations, so they would go for a check-up and perform prenatal screening tests to do the treatment or prevent thalassemia for the next pregnancy. The same reason could explain why the prevalence of alpha-thalassemia carriers of pregnant women who were screened for thalassemia was also higher than beta-thalassemia at the prenatal diagnostic center in Central Obstetrics Hospital in the study conducted by Dang.[22]

In our study, 8841 pregnant women were screened by CBC, HPLC, and iron status test; the prevalence of alpha-thalassemia carriers was 6.4%, the prevalence of beta-thalassemia carriers was 1.32%, the prevalence of co-inheritance of alpha and beta-thalassemia was 0.08% (**Table 1**), which were higher than those studied by Nguyen Khac Han Hoan. In this study, the percentages of pregnant women carrying the alpha-thalassemia carriers, beta-thalassemia carriers, and co-inheritance of alpha and beta-thalassemia were 1.11%, 0.52%, and

0.07%, respectively. However, in both studies, the percentage of pregnant women and pregnant women with alpha-thalassemia carriers was the highest (6.4%, 61.85%, and 1.11%, 71.3%).[23] However, our results were lower compared to the research of Sheng He et al. (8.1% and 3.4%)[24] and Naili Husna's study (alpha gene carrier thalassemia is 9.8%).[25] The difference in size, region, and country can explain the reason for these differences.

Nowadays, one of the most important components in family planning and pregnancy is detecting and preventing hereditary pathologies in future offspring. In this regard, genetic tests and consultations are conducted for future parents, based on which final decisions are made. The clinical decision support system (CDSS), which is currently being widely implemented in various fields of medicine, can undoubtedly provide significant assistance to physicians in the diagnosis and prognosis of hereditary pathologies.[26]

Thalassemia is a complicated disease without a cure, excluding allogeneic hematopoietic stem cell transplantation. Currently, the best strategies for thalassemia management are screening for thalassemia based on family history, cell blood count, serum iron, and ferritin. However, this is a challenge for primary health care facilities and ethnic minority areas due to the limited understanding of thalassemia not only by the population but also by the grassroots medical staff. To solve this problem, the authors conducted a clinical decision support system to support physicians in screening and diagnosing thalassemia. The clinical decision support system (CDSS) is a system comprising 2 different systems: The expert system (ES) and the AI-based clinical decision support system (AI-based CDSS).

The Expert system is a knowledge-based clinical decision support system encoding the experts' knowledge into an automated system.[27] The operating principle of the ES is the simulation of the procedure of diagnosis and screening for thalassemia done by medical physicians. It aims to support doctors dealing with complicated cases, especially at the commune health centers facing a shortage of qualified health workers. Like other expert systems, it comprises three main parts: The knowledge base, the inference engine, and the EHR front-end interface. The knowledge base includes a set of if-then rules built based on red blood cell indices, ferritin, and hemoglobin electrophoresis results using the guideline for prenatal screening for thalassemia of WHO and the Vietnam Ministry of Health (**Table 8**).

The guideline comprises recommendations proposed by experts and used by medical physicians to screen and diagnose thalassemia in clinical practice; thus, it is reliable and suitable for the racial characteristics of Vietnamese people. The system also includes a knowledge update interface, with which the experts can enrich the knowledge base by directly updating their clinical experience and new medical knowledge. This part is important to ensure the accuracy and the update of the expert system because the knowledge of thalassemia can be updated and changed over time. The inference engine is an essential part of the expert system, which applies the if-then rules of the knowledge base to the patient's clinical data to create an inference. Development of the inference engine is an important step when building an expert system to increase the system's accuracy in the research; the three-layer model was applied.

The EHR front-end interface of the model has 2 sections: the input section and the output section (**Figure 3**). The input section includes 9 boxes to enter patients' clinical information, including cell blood count, plasma iron, and ferritin. The output section, which includes 3 boxes, shows the conclusion drawn by the inference engine. The conclusions drawn by the expert system predict the risk of thalassemia, whether it is high risk or low risk, and the physicians can identify if this case requires diagnostic genetic testing.

The advantage of the expert system is that it is possible to explain how the system makes the recommendation, and due to this, it has high reliability and accuracy. Another advantage of our ES is that it is deployed on the Internet; thus, users can access the ES on any computer and at any time with an internet connection. The evaluation of the effectiveness of the developed expert system (ES) in thalassemia screening in the present study showed a high accuracy of 98.45%.

Unlike the ES, The AI-based clinical decision support system does not use the knowledge base. Instead, it uses a form of AI called machine learning (ML), which allows computers to learn from past experiences and/or find patterns in clinical data to make decisions; thus, it does not require writing rules. Machine learning describes the computer algorithms to determine patterns in very large datasets. Over the past years, ML has been applied in a wide range of medical fields and demonstrated impressive results, especially in clinical decision support, patient monitoring, and management.[28] Many ML techniques have been applied in building CDSS, in which K-nearest neighbors, Support vector machine, Random Forest, and Multilayer perceptron (MLP) are the most common techniques.[29]

To optimize the clinical decision support system (CDSS), before constructing the CDSS, the authors conducted to determine the features of the CBC, HPLC, and iron status needed to screen for thalassemia. After using MID and MDA algorithms found that 4 parameters, including HGB, MCV, MCH, and RDW, were the most important ones in screening for thalassemia from the database containing over 10000 cases having CBC, HPLC, and iron status results. This report is consistent with the recommendation of WHO in screening for thalassemia; HGB, MCV, and MCH are the parameters currently used in screening for thalassemia in clinical

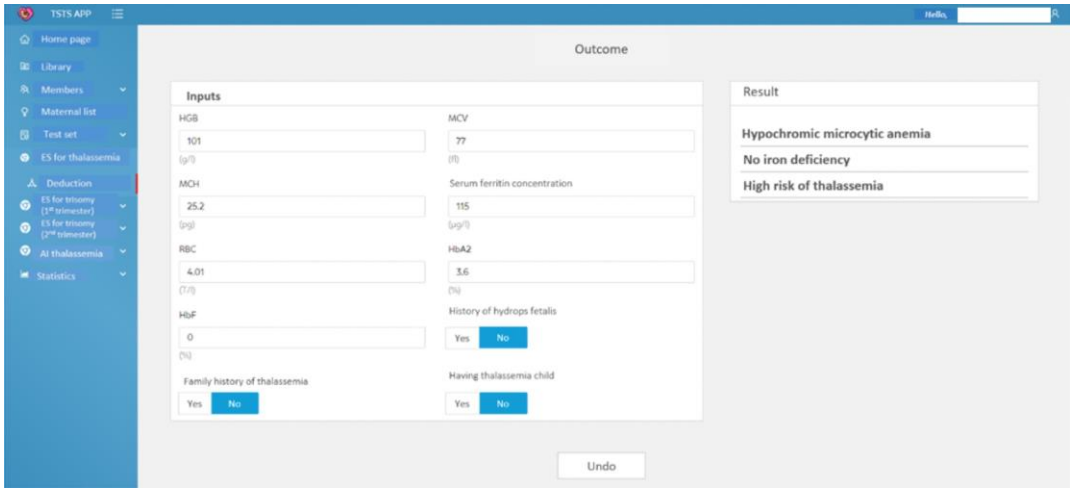

Figure 3. Screenshots of the web-based ES after submission of laboratory data.

practice.

In the research, the authors built an AI-based CDSS, including the AI algorithm and the EHR front-end interface.

To determine the most appropriate AI algorithm for constructing AI-based CDSS, the authors conducted to train the dataset on 4 models, SVM, KNN, MLP, and RF, then evaluated them on 4 indices: accuracy, precision, recall, and F1-score to choose the most appropriate one.

The obtained result showed that the MLP model was the most stable regardless of the training database. Particularly, when training with the general CBC and iron status database for 4 most important features, it had an accuracy of 97%, a precision of 92.68%, a recall of 99.23%, an F1 score of 96.20% for original data, and an accuracy of 94.5%, a precision of 88.24%, a recall of 98.68% and an F1-score of 93.17% for SMOTE. When training with the database of pregnant women, it had an accuracy of 97.81%, a precision of 93.21%, a recall of 99.84%, an F1-score of 95.72% for original data, and an accuracy of 97.65%, a precision of 93.28%, recall of 99.73%, F1-score of 96.43% for SMOTE. Especially with only 4 important features selected above, the model's results were extremely impressive since the accuracy of MLP increased from 96.91% to 97.81%. Another remarkable thing about this database is that after balancing data with SMOTE, the results had a significant difference between the models. Thus, it is possible to temporarily conclude that with only the data of the pregnant woman, the model is no longer confounded by the cell blood count data of the husband. When training with the database of husbands, it had an accuracy of 97.44%, a precision of 96.42%, a recall of 100%, and an F1 score of 97.62% for original data and an accuracy of 94.18%, a precision of 95.44%, a recall of 95.95% and an F1-score of 95.18% for SMOTE.

With such high accuracy, it is possible to apply MLP to construct an AI-based CDSS to predict the risk of thalassemia. In fact, this has been proven by previous research. Al Agha et al.[30] proposed an AI model for thalassemia prenatal screening built by training and evaluating 3 models, including KNN, NB (Navies Bayes), and MLP, among which the MLP model got the highest accuracy with 99.73%. Egejuru et al.[31] proposed to apply MLP to build an AI model for thalassemia classification. In the research, the accuracy of the MLP was 98.11%. Like the ES, The EHR fronted interference of the AI-based CDSS has two sections: An input section and an output section (**Figure 4**). The difference between the two systems is that the ES concludes the type of anemia and whether patients are at high risk or low risk, while the AI-based predicts the risk of thalassemia in the percentage form.

Despite its advantage, the adoption of AI in medicine is rife with challenges, including the impossibility of explaining the logic that ML uses to make an inference (black box). In AI-based CDSS, the users and researchers can only know the inputs and outputs, but it is challenging to understand how it works inside. Therefore, the accuracy of the AI-based CDSS is questionable.[17] To deal with this problem, the authors compared it to the ES by testing both ES and AI-based CDSS with 396 cases of thalassemia. The result showed that when testing on the same dataset, the AI-based CDSS got an accuracy of 94.5%, 96%, and 97% (depending on the algorithm used) when using four important features slightly lower than ES with 98.45%. Thus, it is possible to apply the AI-based CDSS in screening for thalassemia. However, it should be noted that the proposed AI-based CDSS for thalassemia screening is experimental. The advantage of algorithms built on deep machine learning over physician-based assessments requires more in-depth and comprehensive research. According to a meta-analysis of publications on the use of AI in CDSS models for various diseases, no advantage of algorithms built on deep machine learning over physician estimates was noted.[32] It is noteworthy that the effectiveness and safety of AI-based CDSS vary and are ambiguous: there are both successes and failures.[33] Regarding the proposed AI-based CDSSs, it is important to note that future advances

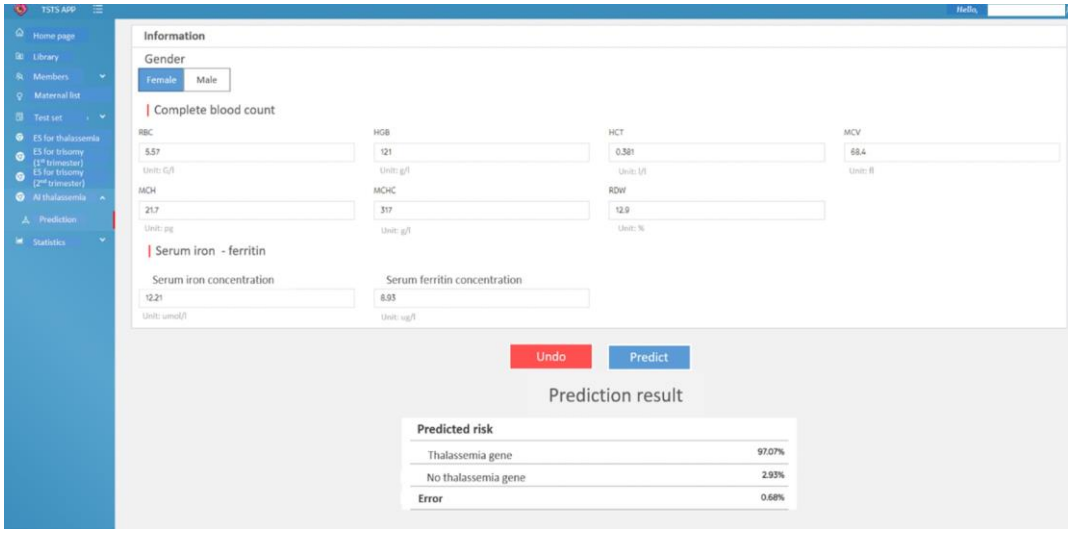

Figure 4. Screenshots of the web-based AI model after submission of laboratory data.

in genetic diagnosis of thalassemia may require a significant revision of these CDSS and new studies to confirm the effectiveness and safety of such systems. AI-based CDSSs are an emerging but understudied field, requiring much effort before showing real progress.

Conclusions. Based on PCR tests, it was found that among pregnant women and their husbands who came to Vietnam National Hospital of Obstetrics and Gynecology, the rate of patients with Alpha thalassemia was 10.73% (1085 patients), the rate of patients with beta-thalassemia is 2.24% (227 patients), and 0.29% (29 patients) of patients carry both alpha-thalassemia and beta-thalassemia gene mutations. The authors successfully built expert and 4 AI-based CDSS for prenatal screening for thalassemia. The expert system developed based on WHO, and Vietnamese Ministry of Health rules and guidelines for prenatal thalassemia screening showed an accuracy of 98.45%. Among the AI-based CDSS developed, the MLP model was the most stable regardless of the training database (accuracy of 98,5% using all features and 97% using only the 4 most important features). When comparing the expert system with the AI-based CDSS, comparable accuracy of the expert system and AI-based models was established. Thus, AI-based CDSS showed satisfactory results. Further development of such systems is promising with a view to their introduction into clinical practice.

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