Models, Applications, and Open Issues in the Intelligent Prediction of Preeclampsia: A Review

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Abstract

Preeclampsia (PE) is a placental dysfunction characterized by proteinuria and hypertension that affects approximately 10% of pregnancies worldwide. Because PE is multifactorial and pathogenic through multiple pathways and mechanisms, there is currently no effective treatment. Early detection and intensification remain the main clinical strategies. This review collects 99 related papers, discusses the challenges faced by the traditional methods of diagnosing and predicting PE, introduces the ML techniques related to predicting PE, and summarizes the standards, indices, and mechanisms that can address these challenges. This review aims to bridge the knowledge of Machine Learning (ML) and PE by discussing and evaluating the prediction of PE from the perspective of both medical practitioners and ML researchers. It also compares the traditional PE prediction approaches with the ML-based PE prediction approaches, highlights the state of the art in PE prediction, and suggests open issues for future research.

Keywords: Machine learning, Preeclampsia, Disease prediction

1 Introduction

Preeclampsia (PE) is a serious medical condition of placental dysfunction disorders that can cause over 500,000 newborn or fetal deaths and more than 70,000 maternal deaths worldwide each year [1]. However, its etiology and pathogenesis are still not fully understood and no effective treatments are available currently, because PE involves a series of dynamic changes that are extremely complex. Since dealing with this complexity requires the analysis and evaluation of heterogeneous clinical medical data, which are usually messy, random, and large in volume, traditional statistical methods face many difficulties in analyzing the occurrence and development of diseases results.

Machine Learning (ML) is the technique that can discover the complex patterns hidden in the large data, capture the multi-layered and interactive non-linear relationship between indicators, and build models based on correlation factors [2]. Therefore, ML can quickly analyze a large amount of clinical medical data, efficiently build and evaluate disease models, and apply these models to predict diseases over messy, random, and heterogeneous medical data, while meeting the requirements of evidence-based medicine and precision medicine. Accordingly, ML has been applied to medical diagnosis, medical image analysis, pattern recognition, computer vision, optical character recognition, biometric recognition, bioinformatics, and many other fields [3].

However, ML and disease diagnosis and prediction have very different knowledge bases. Most of the current efforts are often made from the perspective of either medical practitioners or ML researchers, which leads to great difficulties in exploring, implementing, and using such state-of-the-art techniques in practice. To fill this gap, this review provides a comprehensive overview of the most recent advances in applying ML techniques to build PE models and applying such models to predict PE based on medical clinical data. About 100 papers related to ML and PE are grouped and analyzed from the perspective of both medical practitioners and ML researchers, along with the background of ML and PE. Our goal is to build a bridge between the domains of PE diagnosis and prediction and ML research and to present the state-of-the-art of cross-disciplinary algorithms, mechanisms, and applications. This review also suggests the challenges and open issues in PE diagnosis and prediction. To the best of our knowledge, this review is the first to review the intelligent models and approaches for predicting PE and analyze their pros and cons from the perspective of both medical practitioners and ML researchers.

The rest of this paper is organized as follows: Section 2 summarizes the relevant surveys. Sections 3 and 4 present the background of ML and ML in disease prediction. While Section 5 introduces the pathophysiology of PE and its biomarkers, indexes and evaluation of PE, Section 6 summarizes the ML in predicting PE, and Section 7 provides the challenges and open issues, followed by the conclusions in Section 8.

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DOI: https://doi.org/10.70003/160792642026072704003

2 Related Surveys

Some researchers reviewed the applications and breakthroughs of ML in medicine [3-5], while others focused on the applications of ML in specific medical domains, including obesity [6], radiation oncology [2], ophthalmology [7], cardiology [8], brain diseases [9], neurodegenerative diseases [10], medical imaging [11], Psychology and Psychiatry [12], and complications of pregnancy [13].

Regarding PE, while Magee et al. presented this hypertensive disease in pregnancy and the best available evidence from an academic and practical perspective [14], Rana et al. discussed the factors, development, and risks related to PE [15], Phipps et al. focused on the pathogenic role of antiangiogenic proteins and reviewed the novel therapeutic strategies for PE [16], and Chaemsaithong et al. summarized the different methods, recommendations, risk assessment for PE [17].

Regarding predictive approaches in healthcare, while Alanazi et al. critically reviewed the existing predictive models using ML [18], Wright et al. reviewed the competing risks for predicting patient-specific risks of delivery with PE [19], and Poon et al. reviewed the approaches using screening to predict PE in the first trimester of pregnancy [20].

Similar to our proposed survey, Aljameel et al. discussed the related approaches that apply ML in predicting PE [21]. However, their review is based on the 25 papers that were published between 2018 and 2022, and our survey collected 99 related papers, aiming to provide a global view of the current progress in applying ML in PE prediction. All mentioned surveys are summarized and listed in Table 1.

Table 1. Related surveys

Domain	Study	Purposes and contents
ML in medicine	[3] [4] [5]	Breakthroughs, advanced approaches & examples in systems & scenarios
ML in medicine	[6]	in obesity
	[2]	in radiationoncology
	[7]	in Ophthalmology
	[8]	in cardiology
	[9]	in brain diseases
ML in medicine	[10]	in neurodegenerative diseases
	[11]	in medical images
	[12]	in psychology & psychiatry
	[13]	in complications in Pregnancy
PE	[14]	best evidence available
	[15]	factor & development & risk
	[16]	novel therapeutic strategy
	[17]	method & recom. & risk
PE predicion	[18]	prediction models
	[19]	risks of PE prediction
	[20]	predicting PE using screening
PE prediction using ML	[21]	based on 25 papers
	this paper	based on 100+ papers

3 ML

ML is a group of algorithms that focus on finding relationships and patterns in data, enabling computer systems to learn from data [4]. Deep Learning (DL) is a subset of ML that aims to solve complex problems by using neural networks to simulate the organization and function of the human brain. This review considers DL as part of ML and does not discuss DL separately.

ML methods can typically be divided into supervised learning, unsupervised learning, and reinforcement learning, as shown in Figure 1.

Supervised learning refers to the algorithms that predict the output of data based on labeled training data. Supervised learning algorithms can be used for both classification and regression tasks. While classification tasks identify the categories of data, such as normal or diseased, regression tasks predict the outcomes of data with continuous values, such as responses to treatment. Having sufficient labeled data is a must for supervised learning algorithms [22]. Typical supervised learning algorithms include K-Nearest Neighbors (KNN), Logistic Regression (LR), Naive Bayes (NB), Support Vector Machine (SVM), Decision Tree (DT), Random Forest (RF), and Artificial Neural Network (ANN).

Unsupervised learning refers to the method used to identify the structure of unlabeled data. Although unsupervised learning can discover new relationships and propose new hypotheses, it is more commonly used to group data or reduce feature dimensionality when dealing with large volumes of data with huge feature dimensions to improve the resource efficiency of the tasks. Commonly used unsupervised algorithms include K-means clustering, hierarchical clustering, and principal component analysis [23]. Supervised and unsupervised learning methods can be combined to form semi-supervised learning methods [11]. Semi-supervised learning works by combining labeled and unlabeled data during model training. It allows unsupervised methods to improve the performance of supervised methods by providing additional data to standardize prediction models.

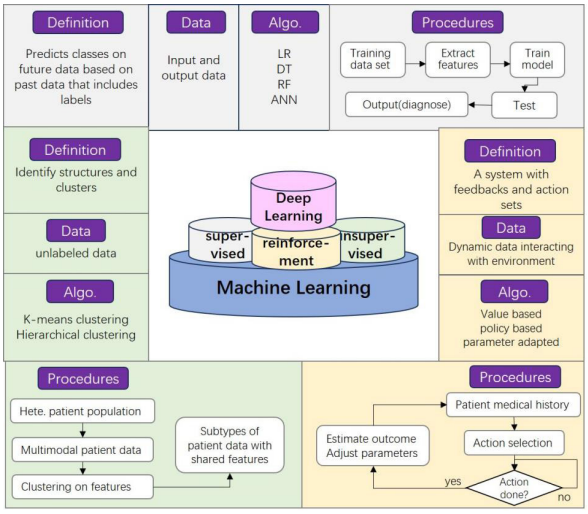

Figure 1. ML categories

Reinforcement learning involves an intelligent agent and a set of actions. The learning process interacts with the environment by performing actions that are estimated by reward functions. Such an estimation is considered the response of the environment, and the action with the best estimate is taken by the process to adjust the model for the next action. Reinforcement learning can be applied in situations where data are generated, treatment variables (such as the A/B test) are manipulated, and other features (such as the covariates) are controlled [24].

4 Prediction of Disease with ML

4.1 Predicting Disease Risks

A disease risk prediction model estimates the probability of future events related to the disease using a mathematical formula that is based on several risk factors for the disease. Disease occurrence risks are classified into levels. Disease risk prediction relies on ML-based pattern recognition approaches to deal with the huge biomedical data size and data complexity.

It is possible to predict the incidence of some diseases by combining ML and some other techniques. As listed in Table 2, reference [25] proposed a pathological slice image analysis system to identify and diagnose breast cancer using DL, reference [26] constructed a model using ML to predict the incidence of Acute Kidney Injury, and reference [27] proposed a prediction model using a variety of ML algorithms for urinary tract infection. Although reference [28] proposed an ANN-based image analysis system that could screen benign and malignant thyroid nodules, and reference [29] applied ML to analyze data and showed that the combination of low sensitivity and high specificity could be the criteria for early detection of severe sepsis and septic shock. Other models based on ML have been applied to predict the incidence of delirium [30], the risk of non-traumatic subarachnoid hemorrhage [31], the cervical intraepithelial neoplasia [32], and the diabetes and hypertension [33], with improved prediction accuracy.

Table 2. The comparison of disease occurrence predictions using ML

Study	Year	ML algorithm	Disease	Models for prediction
[25]	2017	SVM, RF, CNN	Breast cancer	DL-based scoing system, give scores concordant with pathologists, can identify the cases that may be misdiagnosed
[26]	2018	GBT	Acute kidney injury	Given the same sensitivity, ML algorithms outperform the SOFA score system in specificity, accuracy, and other metrics
[27]	2018	XGBoost, SVM, LR, Adaboost, DT, RF, NN	Urinary tract infections	XGBoost outperforms the other proposed models, approaches, and ML algorithms, it has the highest accuracy in diagnosing positive urine culture results
[28]	2018	ANN	Thyroid cancer	Computer-aided diagnosis of thyroid cancer is as good as radiologists
[29]	2019	RF	Sepsis & Septic shock	RF predicted the onset of severe sepsis and septic shock with low sensitivity but high specificity
[30]	2020	LR, DT Forest, GBM Gradient Boosting	Post-microvascular decompression delirium	ML algorithms predict the occurrence of delirium after microvascular decompression with 96.7% accuracy
[31]	2020	SVM	Nontraumatic subarachnoid hemorrhage	SVM combined with EHR data can accurately predict the risk of adverse outcomes for critically ill patients with nontraumatic subarachnoid hemorrhage
[32]	2020	CNN	Cervical neoplasms	For colposcopic image classification, CNN model has a performance comparable to that of experienced colposcopists
[33]	2021	RF	Diabetes hypertension	RF models presented the highest accuracy in predicting both diseases, outperforming the US and UK risk scores in terms of AUC by 35.5% for diabetes and 13.5% for hypertension

4.2 Predicting Treatment Outcomes and Decisions

In order to predict the risk of diseases and treatment outcome based on available data for early intervention, we summarize the currently proposed models as listed in Table 3. As reference [34] applied RF model to predict the progression of myopia in children. While the ANN-based model was applied to predict the Alzheimer disease progression of patients [35], the Gradient Boosting Decision Tree (GBDT) model was used to predict the symptom remission rate after transsphenoidal pituitary adenoma resection in patients with acromegaly [36]. Although reference [37] constructed blood pressure prediction models using SVM, DT, and RF based on the indexes of patients' physical examination and showed the models performing well in controlling hypertension and complications, reference [38] showed that the ANN model had the largest AUC followed by the LR model and the NB model, in predicting 30-day mortality after hip fracture, and reference [39] showed the gradient lifting tree model had the best performance in the prediction of the survival time and nervous system function of patients with cardiac arrest. For gynecological tumors, although multiple ML models had been developed to predict the survival rate of patients with ovarian cancer, RF and XGBoost models demonstrated the best performance [40].

Table 3. The comparison of predictions for patient outcomes and treatment decisions using ML

Study	Year	ML algorithm	Disease	Models for prediction
[34]	2018	RF	Myopia development prediction in Chinese school children	RF showed high accuracy in predicting dioptres at age of 18 (the AUC ranged from 0.903 to 0.986 for 3 years, 0.875 to 0.901 for 5 years, and 0.852 to 0.888 for 8 years)
[35]	2018	LSTM NN RNN	Predicting Alzheimer progression	Predicts AD progression at patient' next visit with over 99% accuracy, outperforming the baseline methods
[36]	2020	GBDT	Predicting remission after transsphenoidal surgery in patients with acromegaly	The GBDT model on 8 significant features has the best performance in both training (AUC = 0.8555) and test cohorts (AUC = 0.8178)
[37]	2019	SVM, C4.5DT, RF, XGBoost	Hypertension outcomes	XGBoost achieved AURs of 0.88, 0.84, and 0.83 for sepsis onset and 24&48 hours before onset, respectively, superior to SIRS, MEWS, SOFA, qSOFA for sepsis onset
[38]	2021	ANN NB, LR	Predicting 30-day mortality after hip fracture	ANN model has the highest AUC for 30-day mortality (0.92), followed by LR (0.87) and naive Bayes (0.83)
[39]	2021	LR, SVM XGB	Predicting out-of-hospital cardiac arrest patients	AUCs of LR, SVM, and XGB for predicting neurological, outcome were 0.819, 0.771, and 0.956, respectively
[40]	2022	KNN, DT, RF AdaBoost, XGBoost SVM	Ovarian cancer survival prediction	RF and XGBoost have the best performance in classification and regression approaches, respectively

5 PE's Pathophysiology, Biomarkers, Indexes, and Evaluations

PE is a type of Hypertensive Disorders in Pregnancy (HDP) characterized by abnormally elevated blood pressure during pregnancy. PE typically consists of 6 stages, as shown in Figure 2. The International Society for the Study of Hypertension in Pregnancy (ISSHP) has recommended classifications for hypertensive disorders [41]. The International Federation of Gynecology and Obstetrics (FIGO) HDP Screening and Prevention Guidelines (2019 edition) has further divided PE into 1) early-onset PE, 2) preterm PE, 3) late-onset PE, and 4) term PE, emphasizing that the incidence and risk of short- and long-term perinatal death are higher in early-onset PE than in late-onset PE [42].

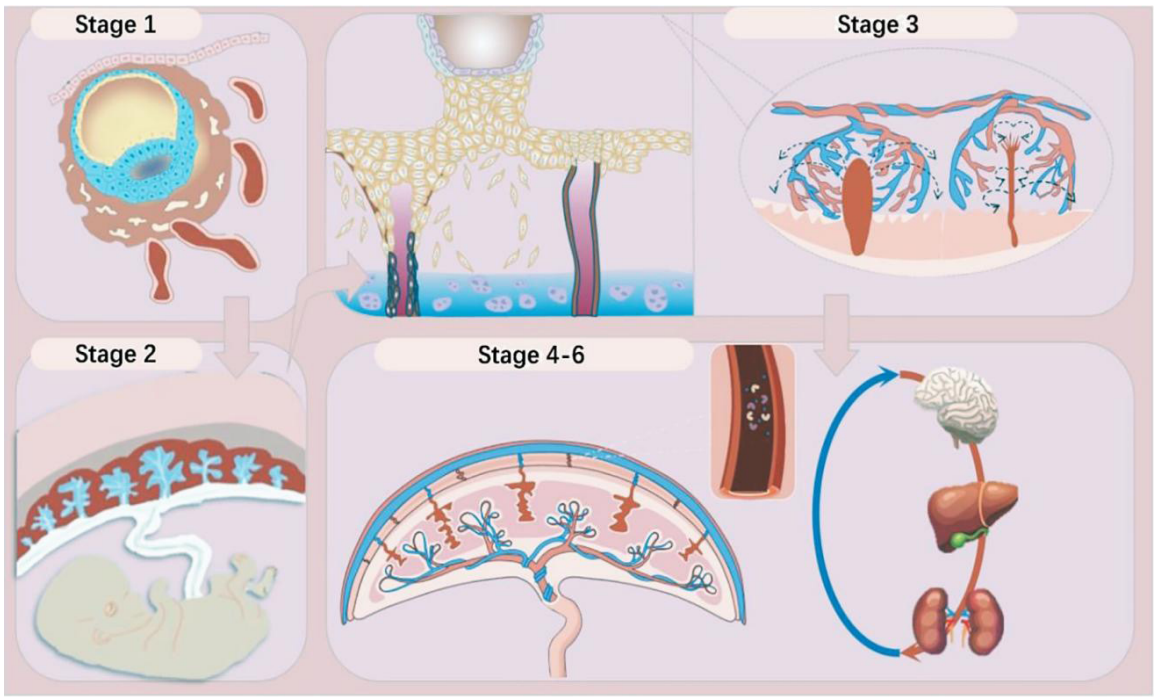

Figure 2. The six stages of PE

Early-onset PE is of fetal origin and is primarily caused by placental dysplasia and superficial trophoblast infiltration leading to disruption of uterine spiral artery remodeling and vasospasm, resulting in reduced uteroplacental blood supply and impaired placental function. Late-onset PE may be caused by the interaction between placental aging and maternal genetic susceptibility to cardiovascular and metabolic disease [43]. Early-onset PE often leads to serious adverse outcomes for both the pregnant woman and the newborn, although late-onset PE is more common.

5.1 Pathophysiology

In early pregnancy, placental abnormalities such as superficial implantation, abnormal remodeling of the spiral arteries, and disruption of trophoblast differentiation can lead to relative placental perfusion deficiency, ischemia, and hypoxia. Once in the maternal circulation, these factors promote the activation of an inflammatory response and alter maternal vascular endothelial function, leading to hypertension and other clinical manifestations. Environmental, immune, and genetic factors may also play an important role in the pathophysiology of PE cocurrently [15].

The pathogenesis of PE has been described by a two-step model: (1) The dysplasia and dysfunction of placental trophoblast cells lead to the failure of uterine spiral artery remodeling, resulting in insufficient placental perfusion. (2) The ischemia and hypoxia of the placental organs caused by insufficient placental perfusion produce a large number of toxic and inflammatory molecules, resulting in systemic hypertension and systemic vascular endothelial dysfunction, leading to PE [19]. This two-step model was refined to a six-step model in 2014 [44].

5.2 Biomarkers

Although the pathophysiology of PE remains unclear, the diagnosis and subclassification of PE based on biomarkers of specific causes may help to identify patients at risk, monitor disease progression, and provide effective interventions. Recent research has shown that screening and treatment in early pregnancy can reduce the time newborns spend in the intensive care unit by 70% and subsequently improve neonatal and pregnancy outcomes [45]. According to a separate guide for early screening and prevention of PE published by FIGO in 2019, maternal characteristics (MC) and many indices were used [46].

5.3 MC

Current research has shown that the most important risk factors for PE are a history of PE, followed by chronic hypertension, pre-pregnancy diabetes, a pre-pregnancy BMI > 30 kg/m, and the use of assisted reproductive technology. Clinical practice guidelines [47-51] recommend that the clinical risk factors for women at high risk of PE include a history of PE in pregnancy, multiple pregnancies, chronic hypertension, autoimmune diseases such as antiphospholipid syndrome or systemic lupus erythematosus (SLE), chronic kidney disease, and type 1 or type 2 diabetes, as listed in Table 4.

Traditional PE risk screening is an assessment of clinical risk factors in early pregnancy. Only using MCs to screen high-risk groups is limited, although the prediction is simple and easy to use. Some papers reported that the Detection rate (DR) of predicting PE based on medical history and MCs was only 34%, and could be improved to 40% using the high-risk clinical prediction indicators recommended by the NICE guidelines, or even higher using ACOG and USPSTF recommended screening approaches [52]. Other ultrasound indicators and biomarkers might be combined to further improve the predictive accuracy.

5.4 Indices

UtPI is a resistance index (RI) of uterine artery blood flow. Since placental insufficiency is caused by failure of uterine spiral artery remodeling, while a successfully remodeled uterine spiral artery lacks the surrounding smooth muscle and thus does not activate a pulsation. Because the resistance of the uterine spiral artery decreases significantly with increasing weeks of gestation, poorly formed placentas may be characterized by persistently high uterine artery blood flow resistance.

MAP is the average of the systolic (sBP) and diastolic (dBP) blood pressure readings and represents the total average arterial blood pressure in each cardiac cycle. It is an important parameter that reflects the adequacy of blood supply to tissues and organs. The increase in basal blood pressure will increase placental blood flow velocity, reduce maternal-fetal exchange efficiency, and lead to placental insufficiency [53].

PAPP-A is a glycoprotein synthesized by the placenta. Its concentration increases gradually during pregnancy and decreases rapidly after delivery. In the presence of low calcium, PAPP-A protein is activated, releasing neutralized IGF1 and IGF2 molecules that contribute to placental implantation and chorionic villus proliferation in normal pregnancies by activating the IGF1R pathway, which induces endometrial cell regression and supports trophoblast cell proliferation [54-55].

Placental protein 13 (PP13) is a glycoprotein encoded by the LGALS13 gene that is mainly secreted by syncytiotrophoblasts. Serum levels of PP13 increase slowly with gestational age. By binding to polysaccharide chains of cell surface proteins, PP13 prevents excessive adhesion of maternal erythrocytes to the inner wall of the spiral arteries, stabilizes the blood flow rate, and forms the placenta [55].

PlGF is a protein synthesized by trophoblast cells that acts as a ligand for VEGFR and promotes placental angiogenesis. The concentration of PlGF in early and mid-pregnancy increases with advancing gestational weeks, peaking at around 30 weeks and then gradually decreasing [56]. In patients with PE, the concentration of PlGF is significantly lower than that in women with normal pregnancies, suggesting that a decrease in maternal serum PlGF is associated with PE.

Endogelin (Eng) is mainly derived from vascular endothelial cells and placental syncytiotrophoblasts, and is a receptor for Transforming Growth Factor-β (TGF-β).

sEng is an extracellular segment protein produced by the cleavage of Eng proteins at the membrane, which can exist freely in maternal plasma. By binding to free TGF-β ligands, sEng acts as a neutralizing antagonist of TGF signaling, inhibiting TGF signaling-dependent vascular endothelial proliferation and vasodilation, and negatively affecting uterine spiral artery remodeling in normal pregnancy [57].

5.5 Evaluating the Prediction of PE

Current research has recognized that the best approach to screening for PE should fully consider the factors that influence the development of PE and discover the hidden patterns behind the data. Prediction of PE can be based on a model using a combination of MCs, ancillary laboratory tests and specific biomarkers.

Poon et al. [58] combined MC, UtPI, PAPP-A, and PLGF to develop a joint early prediction model for PE with predictive sensitivity for early-onset and late-onset PE, and Akolekar et al. [59] reviewed the maternal factors and medical history, specific biomarkers, and relevant ancillary laboratory tests of 33,602 pregnant women and developed a prediction model for PE. Reference [60] showed that using the same combination could achieve a good prediction for early-onset PE, preterm PE, and term PE. Odibo et al. [61] combined PP13, PAPP-A, and UtA-PI for PE prediction with no improvement in the prediction of second trimester PE. Abdelaziz et al. [62] found that the combination of early pregnancy MAP, UtA-PI, and sEng could improve the prediction of early-onset PE and late-onset PE. Scazzocchio et al. [63] combined MC, MAP, and UtA-PI to predict PE. Parro-Cordero et al. [66] constructed different combinations of models of PE using LR based on the clinical, biochemical, and ultrasound markers in the first trimester of pregnancy. Although Crovetto et al. [64] found that the model including MC, MAP, PI, and PlGF had a higher DR for Early-onset PE and Late-onset PE, while Zhang et al. [65] used BMI, race, fetal number, PE history, MAP, PlGF, and PAPP-A to achieve a higher DR for early-onset and late-onset PE.

All of the models described above are listed in Table 5. The prediction models based on LR or statistical methods are often straightforward and explainable, and the weights represent how the features affect the models. The algorithms are simple and easy to implement, but they cannot fully exploit the characteristics of the data, resulting in low performance. However, there are large differences in the performance of these models due to the different research methods, populations, predictors, and data processing methods used. Therefore, selecting the core indicators and building a simple but efficient prediction model are the main concerns.

Table 4. Risk factors of hypertensive disorders in pregnancy PE

Guidline	Year	High risks	Medium risks	Recommendations
ACOG [48]	2019	•History of PE •Multifetal gestation •Chronic hypertension •Diabety&renal disease •Autoimmune disease	• Multifetal gestation • Chronic hypertension • Obesity (body mass index > 30), • Family history of PE (mother or sister) •Sociodemographics (Afro-American race, low socioeconomic status) • Personal history: 35+ years old, low birth weight or small for gestational age, previous adverse pregnancy outcome, parity >10 years	•Recommend low-dose aspirin if patient has 1+ high risks •Consider low-dose aspirin if patient has 1+ Medium - risks
NICE [49]	2019	• pregnancy with hypertensive disease or chronic kidney disease • autoimmune disorders (systemic lupus erythematosus antiphospholipid syndrome) • diabetes •chronic hypertension	• Nulliparity • 40+ years old • parity >10 years • BMI >35 kg/m2 initial visit • Family history of PE • Multi-fetal pregnancy	• Advise pregnant women at medium/high risks for PE to take 75-150 mg of aspirin daily from 12 weeks until delivery
USPSTF [51]	2021	•History of PE, especially with adverse outcome • Multifetal gestation • Chronic hypertension • Pregestational diabetes • Kidney disease • Recommend low-does aspirin. • Autoimmune disease • multiple medium risks	• Nulliparity or Obesity (BMI>30) • Family history of PE (mother or sister) • Black (social, not biological) • Low income, 35+ years old • Personal history (low birthweight or small for gestational age pervious adverse pregnancy outcome parity >10 years) •In vitro conception	•Recommend low-does aspirin.

COGA [50]	2020	• History of PE • Family history of PE • Obsity • Autoimmune disease • diabetes • Chronic hypertension	• Nulliparity or parity >10 years • Systolic pressure ≥130mmHg or diastolic pressure ≥80mmHg, quantify proteinuria in early pregnancy ≥0.3g/24h or Persistent random proteinuria ≥(+) •Multiple gestation	•Use low-dose aspirin (preferably 50–150 mg/day), starting before 16 weeks of pregnancy, in women at increased risk of PE
ISSHP [41]	2021	• Prior PE, • Chronic hypertension, • Pre-gestational diabetes, • Maternal BMI > 30 • Chronic kidney disease • Anti-phospholipid syndrome/ SLE • Assisted reproduction therapies	• High maternal age • Placental Abruption History • History of FGR or dead-birth • Short sexual relationship (< 6 months) before pregnancy • Multiple gestation or Primiparity • Primipaternity - both altered paternity and parity > 5 years, • Connective tissue diseases	• Use low-dose aspirin (preferably 150 mg daily) started before 16 weeks of pregnancy in women in increased risk for PE
ESC [47]	2018	• History of PE • Chronic kidney disease • Autoimmune disease • diabetes • Chronic hypertension	•Nulliparity or 40+ years old, • parity >10 years • BMI > 35 at first visit, • Family history of PE • Multi-fetal pregnancy	•Pregnant women at medium or high risks for PE should begin taking 100–150 mg of aspirin daily at the beginning of week 12 and continue until week 36–37

Table 5. First-trimester prediction of PE, AUC=AUC (95% CI), FPR=fixed false-positive

Study	Year	Screening	Datasets	Detection rate (% (95% CI)) for FPR					
				Early-onset PE			Late-onset PE		
				AUC	FPR (5%)	FPR (10%)	AUC	FPR (5%)	FPR (10%)
[58]	2009	MC, UtPI, PLGF, PAPP-A	7,797 singleton pregnancies at 11 &13 weeks'gestation		93.1%			35.7%	
[59]	2011	MAP, UtPI, PTX3, MC, PAPP-A, PLGF, PP13, inhibin-A, β-hCG, activin-A, sEng, p-selectin	Combined first-trimester screening for aneuploidies was performed in 36,743 singleton pregnancies		91.0%	95.2%		60.9%	71.1%
[61]	2011	PP13, PAPP-A, UtA-PI	477 women with singleton pregnancies 11-14 weeks gestation	0.85	68%	68%			
[62]	2012	MAP, UtA-PI, sEng	1,898 women with singleton pregnancies (11-14 weeks)	0.86		83.8%	0.83		80.3%
[60]	2013	MC, UtPI, PAPP-A, PLGF	Combined first-trimester screening for aneuploidies was performed in 65,960 singleton pregnancies		93.4%	96.7%			
[63]	2013	MC, MAP, UtA-PI	At first trimester Ultrasound (11-14 weeks) in 5,170 women	0.96	69.2%	80.8%	0.71	29.4%	39.6%
[66]	2013	MC, UtA-PI, PlGF	5,367 asymptomatic pregnant Women (11-14 weeks)		33.3%	46.7%			
[64]	2015	MC, MAP, UtA-PI, PlGF, SFLT-1	9,462 pregnancies screened in the first trimester	0.871	87.7%	91.2%	0.871	68.3%	76.4%
[65]	2019	MC, MAP, PlGF PAPP-A	3,270 pregnant women undergoing first trimester trisomy screening (11-14 weeks)		87.5%	87.5%		40%	48.5%

Table 6. Indexes, applications, and performance of PE predictions (F1=F1-score)

Study	Samples	Indexes	Outcome	ML Alg.	Detection rate (% (95% CI)) for FPR						
					AUC	Prec	Acc	Reca.	F1	Sen.	Spec.
[67]	11,006	Systolic blood pressure routine lab. indicator	Late onset PE	LR			0.962			0.703	0.870
				DT			0.874			0.648	0.885
				NBC			0.899			0.500	0.915
				SVM			0.892			0.137	0.923
				RF			0.923			0.679	0.935
				SGB			0.973			0.603	0.991
[77]	113	Circulating RNA	Severe PE	Ada -Boost	0.964		0.89			0.88	0.92
[68]	3,759	Demographics pregnancy history laboratory data	PE	LR	0.853	0.184	0.769	0.710	0.293		
				RF	0.914	0.422	0.914	0.789	0.550		
				SVM	0.915	0.362	0.899	0.667	0.467		
				XGBoost	0.955	0.447	0.920	0.789	0.571		
[69]	1,452	Clinical characteristic season of pregnancy risk factors final PE status	PE	LR	0.713					0.649	0.797
				KNN	0.742					0.729	0.754
				C5.0DT	0.788					0.736	0.846
				DA	0.687					0.477	0.891
				RF	0.758					0.737	0.776
				SVM	0.791					0.800	0.780
[70]	11,152	Clinical variables MAP, β-HCG PAPP-A UtAPI	PE	DNN	0.57	0.43	0.60	0.58	0.49		
				LR	0.69	0.52	0.54	0.60	0.56		
				SVM	0.79	0.56	0.68	0.77	0.65		
				DT	0.71	0.61	0.70	0.62	0.60.		
				RF	0.86	0.82	0.74	0.42	0.56		
[71]	233	Clinical characteristics measured in the first trimester of pregnancy, risk factors, the MAP, UtA-PI, and PLGF, PP-13 and PAPP-A.	All PE	DT	0.93	0.91	0.928	0.94	0.93		
				NB	0.98	0.96	0.986	0.96	0.98		
				SVM	0.98	0.71	0.855	0.78	0.88		
				RF	0.94	0.91	0.928	0.94	0.93		
			Early-onset PE	DT	0.95	0.93	0.941	0.75	0.86		
				NB	0.88	0.67	0.912	0.80	0.92		
				SVM	0.91	0.67	0.912	0.80	0.73		
				RF	0.94	0.83	0.912	0.71	0.77		
			Late-onset PE	DT	0.80	0.93	0.882	0.93	0.93		
				NB	0.72	0.96	0.853	0.87	0.92		
				SVM	0.76	0.93	0.824	0.87	0.90		
				RF	0.84	0.93	0.882	0.93	0.93		
			Monder-ate PE	DT	0.80	0.85	0.824	0.92	0.88		
				NB	0.68	0.88	0.735	0.79	0.84		
				SVM	0.49	0.81	0.706	0.81	0.81		
				RF	0.79	0.65	0.706	0.94	0.77		
			Severe PE	DT	0.70	0.67	0.794	0.44	0.53		
				NB	0.67	0.50	0.824	0.50	0.50		
				SVM	0.64	0.17	0.735	0.20	0.18		
				RF	0.76	0.33	0.765	0.33	0.33		
[72]	800	Clinical risk factors, routine lab indicators	Early-onset PE	LR	0.86					0.736	0.965
				DT	0.77					0.648	0.968
				SVM	0.93					0.670	0.999
[73]	328	57 Features (UtA-PI placental analytes MAP)	Severe PE Eclamp-sia	LR	0.56					0.53	0.58
				SVM	0.59					0.44	0.70
				RF	0.64					0.61	0.61
				XGBoost	0.62					0.60	0.57

6 ML in Predicting PE

Most studies on PE prediction have used LR or traditional statistical methods, which do not fully and effectively utilize the features of the data. Since ML algorithms can build prediction models with high accuracy, they can build PE prediction models to achieve better performance [13].

As shown in Table 6, Jhee et al. [67] applied several algorithms to construct predictive models for late-onset PE based on the electronic medical records of 11,006 pregnant women. It has shown that such models can effectively predict late-onset PE, and the stochastic gradient-enhanced model has the best predictive performance. The study [68] showed that the risk of developing PE can be predicted with good discriminative ability based on clinical parameters collected in early mid-pregnancy, and the best prediction result was obtained with the XGboost model [68]. The research conducted by Manoochehri et al. [69] showed that the accuracy of the models in predicting PE was 0.713, 0.742, 0.788, 0.687, 0.758, and 0.791 respectively, and the SVM-based model achieved the highest accuracy. Liu et al. [70] applied 5 ML algorithms, including RF, DNN, LR, SVM, and DT, to build PE prediction models based on the clinical and laboratory data obtained from prenatal screening in early pregnancy, and the RF model achieved the best results. Reference [71] evaluated the performance of prediction models for PE based on DT, NB, SVM, and RF. It showed that DT and SVM models had the best prediction of early-onset PE, and NB and RF models had the best performance in predicting all types of PE. Xue et al. [72] investigated the risk factors, clinical characteristics, and routine laboratory indices of pregnant women in early pregnancy and built predictive models of early-onset PE using LR, DT, and SVM. The results showed that the clinical risk factors alone are not significant in predicting early-onset PE, while the risk factors combined with routine laboratory indexes were significant. Lin et al. [73] developed an ML model to classify discrete gestation points with an unbiased classifier for a population of undelivered pregnancies. By incorporating known risk factors and indicators of pulmonary embolism and eclampsia, they showed that the model was useful in screening for early pregnancy cases in the pregnancy cohort.

While references [74] and [75] applied ANNs to effectively determine the risk of preterm PE occurrence from demographic characteristics and past medical history, combined with biomarker values, reference [76] also applied Eelastic Net Algorithm and Gradient Enhancement Algorithm to develop predictive models for PE and compared them with LR-based prediction methods. In addition, ML models based on genes have been used to predict PE [77] and the outcomes of PE [78], models based on radient boosted trees have been used to predict the risk of postpartum complications [79], CNN-based models have been used to classify the ultrasound images of the two groups of pregnant women [80], models based on KNN and SVM [81] have been used to predict premature PE, models based on RF and gradient-enhanced trees [82] have been applied to predict the adverse outcomes of 1647 women at high risk of PE. Wang et al. [83] developed ML-based models to predict postpartum cardiovascular risk in women with PE. Huang et al. [84] used ANN to investigate how changes in maternal peripheral blood parameters and clinical indicators affect the perinatal outcome of patients with PE combined with FGR and its prediction. Li et al. [85] studied 1,000 patients with PE who were full-term at 3 months postpartum and had decreased postpartum blood pressure by using latent class cluster analysis (LCCA) to screen for and identify a number of associated risk factors. Melinte-Popescu et al. [86] evaluated the models based on DT, NB, KNN, and RF in predicting HELLP syndrome and its subtypes. However, there are arguments that prediction using ML methods performs less well than traditional methods [87].

7 Challenges and Open Issues

7.1 Dealing with Big Data and Data Bias

Most of the achievements in the field of ML have been achieved through experimentation and experience, lacking complete theoretical foundations and inference mechanisms. Since a large amount of data is required for the accuracy of ML models, most hospitals do not have the equipment and resources capable of handling ML models. Although hospitals have the huge amount of medical data available, not all of them can be used for ML [9] because the data type, data annotation, and image standard are inconsistent among hospitals, which leads to poor data mining as well as model overfitting. Most ML-based prediction models have a high risk of bias due to the exclusion of participants, small sample size, mishandling of missing data, and failure to address overfitting. Some researchers have argued that ML models should be validated in independent cohorts rather than developing new methods that are only effective in a specific research scenario [88]. Clinical researchers need to acquire and use large, unified, high-resolution, multicenter validated or international datasets.

7.2 Data Security and Privacy

Data security and privacy are major concerns for ML-based approaches. Disclosure of patient data will not only lead to a breach of patient privacy but will also be used by lawbreakers in illegal ways, posing great security risks to the society. To address these concerns, data anonymity and security should be strengthened. Administrative policies should be established to improve the legal awareness of medical staff, and to strictly control and monitor each visitor's right to view electronic medical records. Systems and mechanisms should be developed to protect the data privacy and security.

7.3 ML-based Prediction Improvement in Disease Diagnosis

There is a discrepancy between the answers provided by ML algorithms and the answers required by clinicians.

Clinicians need to make a yes or no decision, whereas ML algorithms only provide probabilities [14]. Many clinical studies use AUC to represent predictive accuracy. When ML algorithms are applied and compared to traditional statistical approaches, ML models typically provide only marginal accuracy gains, representing a questionable trade-off between model complexity and accuracy. Even a very high AUC does not guarantee robustness, as an AUC of 0.99 and an overall event rate of 1% is possible and may result in all negative cases being correctly predicted while a few positive events are not. A high AUC may also be due to overfitting of the ML model.

ML techniques provide powerful ways to deal with the nonlinearity, high dimensionality, and complexity in the data being predicted. However, many simple medical prediction problems are inherently linear. For these problems, feature selection, often based on known strong predictors, plays the most important role, and ML methods are unlikely to provide substantial improvements.

When faced with new tests or diagnostic tools, physicians should remain the mainstay of clinical disease diagnosis, with ML providing the necessary support as an adjunct technology, because predictive analytics models can be misused before physicians determine whether the models are applicable to their current setting and patients.

Therefore, the quality of medical data should be improved through input management, and medical professionals should be trained in the relevant theories and skills of computer information technology. Interdisciplinary collaboration should be encouraged to improve the knowledge base of clinical staff and their ability to use computer technology.

8 Conclusion

This paper reviews the ML techniques for predicting PE from the perspective of both medical and computer professionals. We introduce the main concepts, algorithms, and approaches of ML in medicine to help medical professionals understand the necessary background of ML. We briefly review the pathophysiology of PE and the significant MCs, indices, and biomarkers for PE to help computational researchers gain domain knowledge related to PE. We also systematically review the state of the art of ML in predicting PE in current research and suggest challenges and open issues for future research. We believe that ML can help biomedical scientists and medical professionals improve the efficiency of predicting outcomes by identifying and summarizing meaningful patterns from large data sets. In addition, some comparative studies have found that ML-based analysis can identify new risk predictors that are more accurate than the traditional models.

Acknowledgements

This work was supported by Guangxi Education Department's Project on Improving the Basic Research Ability of Young and Middle-aged Teachers in Universities (grant titile: Research on Statistical Network Delay Predictions in Large-scale SDNs, grant no: 2023ky0812).

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