


Prediction Model for Pre-eclampsia in a Low-Resource Setting: A Systematic Literature Review

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ABSTRACT

The mechanism of preeclampsia is still unknown, so early diagnosis and termination of pregnancy are definitive therapies. A prediction model to be implemented in a low-resource setting is needed to predict the risk of pre-eclampsia in pregnant women. Pre-eclampsia prediction models also play a role in clinical decision-making, assisting with information, education, and communication (IEC) and considering the administration of aspirin prophylaxis. This study aims to systematically review the development of pre-eclampsia prediction models in a low-resource setting. PubMed, ScienceDirect, and Wiley Online Library databases between January 2019 and June 2023 were systematically reviewed. Article identification, screening, and selection of relevant articles, as well as data extraction, were carried out independently by the authors following PRISMA guidelines. Of the six articles that met the requirements, models that used maternal characteristics, risk factors, and physical examination. Laboratory tests improved the accuracy of pre-eclampsia prediction models in a low-resource setting. Examination with Doppler ultrasound and biomarkers could significantly improve the sensitivity and specificity of prediction models but could not be universally applied in a low-resource setting.

Keywords: Low-resource setting, prediction model, pre-eclampsia.

ABSTRAK

Mekanisme preeklampsia masih belum diketahui pasti, sehingga saat ini tata laksana definitif adalah diagnosis dini dan terminasi kehamilan. Dibutuhkan model prediksi risiko preeklampsia pada ibu hamil yang dapat diimplementasikan di daerah dengan sumber daya rendah. Model prediksi preeklampsia juga berperan dalam pengambilan keputusan klinis, membantu komunikasi dan edukasi (KIE), serta pertimbangan pemberian profilaksis *aspirin*. Penelitian ini bertujuan meninjau secara sistematis pengembangan model prediksi preeklampsia di daerah dengan sumber daya rendah. Basis data PubMed, ScienceDirect, dan Wiley Online Library antara Januari 2019 sampai Juni 2023 ditinjau secara sistematis. Identifikasi artikel, penyaringan dan pemilihan artikel yang relevan, serta ekstraksi data artikel dilakukan secara independen oleh penulis dengan mengikuti pedoman PRISMA. Dari 6 artikel yang eligibel, diketahui karakteristik maternal, faktor risiko, dan pemeriksaan fisik. Pemeriksaan laboratorium akan memperbaiki akurasi model prediksi preeklampsia di daerah dengan sumber daya rendah. Pemeriksaan ultrasonografi Doppler dan *biomarker* secara signifikan dapat meningkatkan sensitivitas dan spesifisitas model prediksi, namun tidak dapat diterapkan secara umum di daerah dengan sumber daya rendah. **Lucky Pestauli Damanik. Model Prediksi Preeklampsia di Daerah dengan Sumber Daya Rendah: Tinjauan Sistematik.**

Kata Kunci: Sumber daya rendah, model prediksi, preeklampsia.

INTRODUCTION

The most common complication in pregnancy is the spectrum of hypertension in pregnancy; one of these complications is pre-eclampsia. Pre-eclampsia is the occurrence of hypertension over 20 weeks of pregnancy or immediately after giving birth up to 6 weeks postpartum. According to the International Society for the Study of Hypertension in Pregnancy (ISSHP), pre-eclampsia is defined as an increase in systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least two measurements with an interval of 4 hours in women who previously had normal blood pressure and accompanied by ≥1 conditions, including proteinuria (urine dipstick testing ≥2+), organ disorders, and uteroplacental dysfunction, either new onset or after 20 weeks of gestation.[1] The incidence of pre-eclampsia in developing countries is generally greater than in developed countries. The incidence of pre-eclampsia in developing countries, according to the World Health Organization (WHO), ranges between 2% and 10% globally.[2] The incidence of pre-eclampsia in developing countries is about 1.8%-16.7%, significantly higher than the rate in developed countries which is 0.4%.[2] The incidence of pre-eclampsia in Indonesia is very high, reaching 24%, and is the second highest cause of

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maternal death after severe bleeding.[3] Pre-eclampsia also contributes significantly to an increase in the incidence of premature birth, neonatal morbidity, and perinatal mortality.[2,3]

Risk factors of pre-eclampsia include low socioeconomic status, nulliparous, multiparous, obesity, history of chronic hypertension, age at pregnancy over 35 years, and hereditary history.[4,5] At least 90 percent of pre-eclampsia onset occurs at ≥ 34 weeks of gestation and has a good prognosis for mother and child. However, 10 percent of cases that occur at gestational age below 34 weeks are more severe, with a higher risk of premature birth. The risk of kidney and cardiovascular disease also increases in pregnant women with a history of pre-eclampsia. Early diagnosis and termination of pregnancy are definitive therapeutic options to avoid poor prognosis.[4,5]

The cause of pre-eclampsia is still unknown, so definite preventive measures are difficult. Pre-eclampsia biomarker examination has been proven to be able to predict high risk in early pregnancy (less than 16 weeks).[6] However, biomarker examination is expensive and quite difficult to be applied as a routine exam in all health care facilities, especially in a low-resource setting, while prediction of pre-eclampsia in early pregnancy has clinical utility for low-dose aspirin prophylaxis. An effective predictive model will help to assess early diagnosis, initial treatment, and management until delivery. A prediction model that can be implemented in a low-resource setting is needed to predict the incidence of pre-eclampsia in the early trimester.[4,6]

METHODS

1. Search Strategy

This research is a systematic literature review with a detailed workflow including data search strategies, study selection through quality assessment by eligibility criteria and quality assessment instruments, as well as data synthesis and extraction. The Boolean operator keywords used in the literature search are "prediction" AND "model" AND "pre-eclampsia" AND "low resource".

2. Information Sources

The database sources used in this research are PubMed, ScienceDirect, and Wiley Online Library.

3. Eligibility Criteria

Articles obtained through journal searches are then selected based on the exclusion and inclusion criteria. The inclusion criteria are articles that comply with the PICO framework, are original research, and are article sources from PubMed, ScienceDirect, and Wiley Online Library. The exclusion criteria are articles with no available full text, use of languages other than English, and publications over five years. The PICO format was as follows: P is the population or research participants representing pregnant women with hypertension, pre-eclampsia, or eclampsia; I (intervention) represents the pre-eclampsia prediction model currently used; C (comparison) there is no comparison/intervention; and O (outcomes) represents the expected results, in this case the pre-eclampsia prediction model, which can be applied in areas with low or limited resources.

4. Quality Assessment

The scientific journal selection process uses the PRISMA (preferred reporting items for systematic reviews and meta-analyses) method. The PRISMA flow diagram in this research is shown in **Figure**.

The initial search resulted in 156 data points based on the eligibility assessment using the standards for reporting qualitative research (SRQR) checklist to assess the quality of articles with 21 quality assessment components. Six articles meet the minimum achievement of 15 checklist components to be used as literature sources in this research.

5. Data Extraction

The data extraction process was performed independently to compare types of prediction models, research methods, level of accuracy, level of sensitivity, and specificity, as well as the potential for implementing pre-eclampsia prediction models in a low-resource setting.

RESULT

See in **Table.**

DISCUSSION

Assessment of the characteristics of pregnant women is a crucial aspect in developing prediction models that can be applied in a low-resource setting. Recognizing the characteristics of pregnant women who are susceptible to pre-eclampsia will make it easier to prepare anticipatory actions related to the outcome of pre-eclampsia experienced.[6,7]

Except for the research conducted by Sufriyana, *et al*, (2020), all studies contained information regarding the gestational age of pregnant women involved in developing the pre-eclampsia model. The characteristics

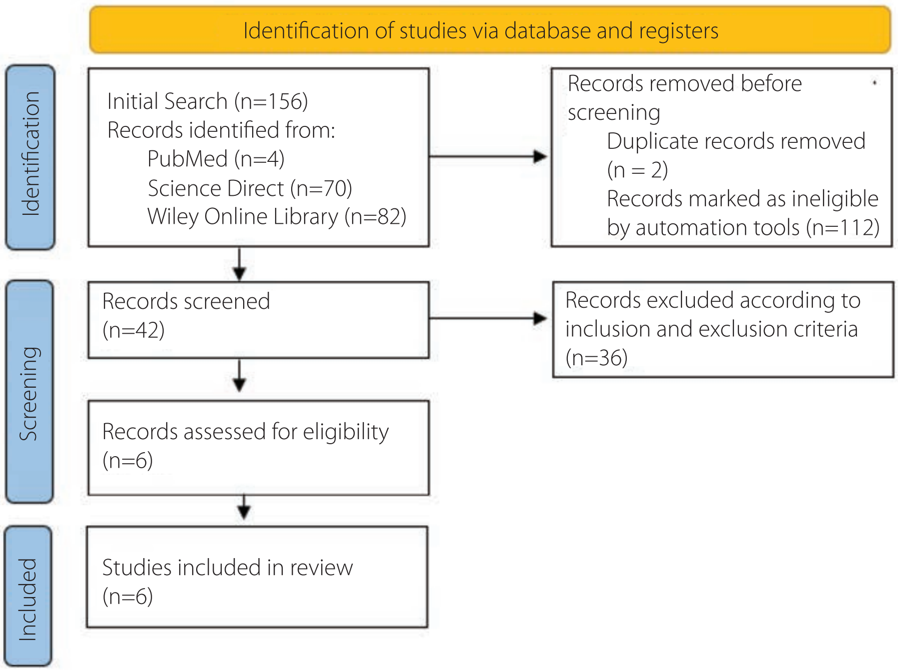

Figure. Workflow of identifying related studies


Table. Prediction model of preeclampsia in several studies.

Reference	Design	Objective	Outcome	Performance	Applicability
Awor, *et al*. 2023.[7]	Prospective cohort study	To develop and validate a prediction model for prenatal preeclampsia screening in a low resource setting	Six prediction models with maternal age ≥35 years, nulliparity, maternal history of preeclampsia, body mass index, diastolic pressure, white blood cell count, lymphocyte count, serum ALP, and end diastolic notch of the uterine arteries as the predictors.	Of the 6 models developed, prediction model 6 that contains history and physical exam, uterine artery Doppler indices, and maternal blood test as predictors of preeclampsia has the best performance with an accuracy level of 77.0%, sensitivity of 80.2%, specificity of 73.6%, AUC 84.9%, and McFaddens 0.30.	Even though model 6 has the best performance, model 5 is more likely to be applied in low-resource settings because it uses history, physical examination, and blood tests as predictors of preeclampsia.
Chen, *et al*. 2022.[9]	Retrospective case-control study	To examine predictors associated with the incidence of preeclampsia and develop a prediction model to estimate the risk of preeclampsia;	Three logistic regression (LR), CT (classification tree), and RF (random forest) models to develop a preeclampsia prediction model. After data analysis, the AUC for the LR, CT, and RF models was 0.778, 0.850, and 0.871, respectively (p value <0.05 for all pairwise comparisons).	The LR model sensitivity, specificity, PPV, and NPV values were 67.3%, 88.2%, 60.0%, and 91.2%, respectively, while the CT model's values were 79.6%, 90.4%, 68.4%, and 94.4%, respectively. The RF model has the best prediction efficiency with sensitivity, specificity, PPV, and NPV values of 79.6%, 94.7%, 79.6%, and 94.7%, respectively.	Further research is needed on a larger scale to validate the clinical application of the RF model.
Kadhim, *et al*. 2022.[10]	Case control	To develop a prognostic model to calculate the likelihood of severe preeclampsia in pregnant women in Iraq.	A prediction tool that was developed to determine the risks of pre-eclampsia.	The prediction model in this study has low positive predictive values 12.13%. This rate explained the low prevalence of pre-eclampsia in Iraqi women (3-5%). This finding also justifies the high rate of false positives in the available prediction tools.	This prediction model cannot be applied in a low-resource setting because it does not have a good level of accuracy.
Kusuma, *et al*. 2022.[12]	Prospective observational study	To develop the prediction models for the first-trimester prediction of pre-eclampsia (PE) using the established biomarkers, including maternal characteristics and history, mean arterial pressure (MAP), uterine artery Doppler pulsatility index (UtA-PI), and placental growth factor (PlGF), in combination with the ophthalmic-artery Doppler peak ratio (PR).	Three prediction models for preeclampsia. Model 1 consists of complete variables based on multivariate analysis, including age, body mass index, chronic hypertension, history of preeclampsia, diastolic blood pressure above 80 mmHg, history of type 2 DM, mean arterial pressure (MAP), uterine artery Doppler pulsatility index (UtA-PI), and placental growth factor (PlGF) combined with ophthalmic artery Doppler peak ratio (PR).	The sensitivity and specificity of model 2 are 71.8% and 71.2%, respectively, not much different from model 3, which is 70.4% and 74.9%, respectively. To predict preeclampsia, the area under the curve values of model 2 and model 3 were 0.7651 (95% CI: 0.7023-0.8279) and 0.7911 (95% CI: 0.7312-0.8511), respectively. Models 2 and 3 have the same negative predictive value, namely 96.9%, while the positive predictive values for models 2 and 3 are 16.8% and 96.9%, respectively.	The primary care model can be applied in a low-research setting even though it is not clinically superior to the complete model since the difference is not statistically significant.

Sufriyana, *et al*. 2020.[15]	Nested case-control	To develop and validate an artificial intelligence (AI)-based preeclampsia prediction model through machine learning applied to the BPJS Health national health insurance data set in Indonesia.	Six artificial intelligence-based algorithms were compared using SAS Enterprise Miner 14.3 (SAS Institute, Cary, NC, US) to develop a prognostic prediction model. These algorithms include logistic regression (RL) with an optimized learning machine, decision tree (DT), artificial neural network (ANN), random forest (RF), support vector machine (SVM), and ensemble (Ens.), which combines one algorithm with another.	The best model consisted of 17 predictors extracted by a random forest algorithm. 9 to 12 months to the event was the period that had the best AUROC in external validation by either geographical (0.88, 95% confidence interval (CI) 0.88-0.89) or temporal split (0.86, 95% CI 0.85-0.86).	Further research is needed to determine the effect of this prediction model to minimize the number of false positives.
Al-Rubaie, *et al*. 2020.[17]	Retrospective cohort study	To develop a model that can be effectively used to predict the incidence of preeclampsia	The outcome of this study is a risk prediction calculator for pre-eclampsia for Australian nulliparous women, which is the Western Sydney (WS) prediction model.	The final model of WS has similar accuracy to the National Institute of Health and Care Excellence (NICE) approach. This model has sensitivity of 18% (14–23) and specificity 97% (97–98). While using the NICE approach, the sensitivity rate is 37% (31–42) and the specificity 91% (91–92).	Despite having moderate performance, the WS model can be used as a prediction model in a low-resource setting.

of pregnant women considered in the research included the age of the pregnant woman, single or multiple pregnancies, socio-economic status, lifestyle such as smoking and drinking habits, body mass index (BMI), history of drug use, maternal history, and the presence or absence of comorbidities. These comorbidities included chronic hypertension, diabetes, autoimmune disorders, cardiovascular disorders, and kidney disorders. Other predictor variables used were supporting examinations such as mean arterial pressure (MAP), uterine artery Doppler pulsatility index (UtA-PI), and placental growth factor (PlGF) combined with ophthalmic artery Doppler peak ratio (PR).

Awor, *et al*, (2023) developed six preeclampsia prediction models with an initial sample of 1,004 participants; 281 participants were lost to follow-up. The 782 participants whose data were used received additional examinations, including complete blood tests, liver function tests, and kidney function tests. Of all these models, model 6 is the most ideal model for predicting the occurrence of preeclampsia in pregnant women based on the pregnant woman's medical history, physical examination, complete blood count, and uterine artery Doppler index value. But model 6 is still relatively difficult to implement with low-resources considering that the uterine artery Doppler index is not a routine examination. Uterine artery Doppler index examination is a good predictor with moderate sensitivity and specificity in predicting preeclampsia in the first trimester. However, this examination is not always available, especially in low- to middle-income countries. The same problem is encountered in the application of biomarkers as main predictors; the predictor variables have a high level of accuracy but low accessibility. Prediction model 5 can be further studied for implementation in a low-research setting because it does not require uterine artery Doppler index data, although the level of accuracy and specificity is lower than model 6.[7,8]

Chen, *et al*, (2022) research used a set of three logistic regression (LR), CT (classification tree), and RF (random forest) models to develop a preeclampsia prediction model. The study examined 916 pregnant women; 237 had preeclampsia. The preeclampsia predictors used in this study were family history of hypertension, body mass index before pregnancy, blood pressure ≥130/80 mmHg before pregnancy, chronic hypertension, and duration of hypertension. The RF model can be used as a practical screening approach to predict preeclampsia in the early second trimester. The predictors can be applied in a low-resource setting, but further, larger-scale research is needed to validate the clinical application of the RF model.[9]

Different results were found in research by Khadim, et al, (2022) on 200 pregnant women aged 28–32 weeks in Iraq. Using a self-developed questionnaire, data contained medical history, obstetrical and gynecological history, lifestyle, and medication history. Data containing age, family history, and body mass index in the first trimester of pregnancy were also collected to develop a preeclampsia prediction model. The MiniPIERS model was used in logistic regression analysis. The prediction model developed by Kadhim, et al, has a low positive predictive value. A model by only considering risk factors and/or routine laboratory examinations as the main predictors did not significantly predict preeclampsia. Clinical risk factors as a single predictor did not show good efficacy in predicting early-onset preeclampsia. Efficiency increased quite significantly when combined


with routine laboratory examination results as a predictor. Although these two variables as main predictors can facilitate a low-resource setting, the accuracy is poor.[10,11]

Kusuma, *et al,* (2022) stated that preeclampsia prediction models could vary depending on available resources. Prediction models with complete resources would be better than prediction models for basic health services. However, this difference was not statistically significant. Prediction models should be designed as efficiently as possible to be implemented in a low-resource setting. This study compares the models studied, both miniPIERS and fullPIERS (Preeclampsia Integrated Estimate of Risk) models. The fullPIERS prediction model can predict the risks and adverse effects on pregnant women with early-onset preeclampsia. The fullPIERS model has also gone through external and internal validation, which shows a level of accuracy with good sensitivity and specificity in predicting preeclampsia. The fullPIERS model is to predict adverse maternal outcomes with predictor variables including gestational age, chest pain and/or dyspnea, oxygen saturation, platelet count, and creatinine and aspartate transaminase concentrations. However, the fullPIERS model is difficult to implement because the resources needed to regularly perform the laboratory test are not widely available, especially in low- to middle-income countries. The same shortcomings were also found in the miniPIERS model even though fewer predictor variables were used in the miniPIERS model.[11-13]

Sufriyana, *et al*, (2020) conducted a nested case-control study on the BPJS Health national health insurance data set grouped into preeclampsia/eclampsia (n = 3,318) and normotensive pregnant women (n = 19,883) from all mothers with single pregnancies. This study analyzed data on the characteristics of the case group of single pregnant women with preeclampsia or eclampsia without any other diagnosis of PIH (pregnancy-induced hypertension) and the control group of single pregnant women without any diagnosis of PIH, including preeclampsia/eclampsia. A comparison of the prediction model was also carried out with 7 other studies obtained from 869 data in Pubmed, Embase, and Scopus. Based on systematic review, the model in this study had better performance in terms of accuracy, sensitivity, and specificity on all external and internal validation sets. The prediction model in this study had a good performance in predicting the risk of preeclampsia by analyzing 17 predictors extracted with the random forest algorithm. However, further research is needed to determine the effect of this prediction model to minimize the number of false positives.[15,16]

Al-Rubaie, *et al,* (2020) analyzed the sample of 12,395 births, divided into two groups for model development and temporal validation based on the year of birth (model development sample 2011–2012, validation sample 2013–2014). Of the entire study sample, 374 (3.0%) women assessed with the Western Sydney (WS) model had preeclampsia risk estimates of ≥8%, a predetermined risk threshold for considering aspirin prophylaxis. Of these, 54 (14.4%) had preeclampsia (sensitivity 18% (14-23), specificity 97% (97-98). Meanwhile, using the NICE approach, 1,173 (9.5%) women were classified as high-risk women, of which 107 (9.1%) had preeclampsia. (sensitivity 37% (31–42), specificity 91% (91–92). The final model in this study demonstrated similar accuracy to the NICE approach when a lower risk threshold of ≥4% was used to classify women as high-risk for pre-eclampsia. A WS risk model incorporating available maternal characteristics achieved moderate performance for the prediction of pre-eclampsia in nulliparous women. The WS risk model does not perform better than the NICE approach, but it has the advantage of providing individualized estimates of absolute risk, assisting communication and education (IEC) processes, informing decisions about further testing, and prophylaxis considerations for using aspirin.[17,18]

CONCLUSION

All studies evaluated used maternal characteristics and preeclampsia risk factors as predictors to develop prediction models. Almost all studies show positive results in the application of preeclampsia prediction models to determine the risk of preeclampsia. The use of biomarkers as predictors of preeclampsia has positive feedback on prediction models. However, biomarker examination will be very difficult to perform regularly in areas with limited resources, in terms of human resources, hospitals, and cost.

REFERENCES

1. Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2022;27(October 2021):148–69. DOI:10.1016/ j.preghy.2021.09.008.
2. Khan B, Yar RA, Khakwani A khan, Karim S, Ali HA. Preeclampsia incidence and its maternal and neonatal outcomes with associated risk factors. Cureus 2022 Nov 6;14(11) :e31143. DOI: doi: 10.7759/cureus.31143.
3. Wahyunindita RN, Sari RDP. Severe pre-eclampsia with partial hellp syndrome in Multigravida Preterm Pregnancy. Indones J Glob Heal Res. 2022;4(1):1–8. DOI: 10.37287/ijghr.v4i1.706.
4. Bisson C, Dautel S, Patel E, Suresh S, Dauer P, Rana S. Preeclampsia pathophysiology and adverse outcomes during pregnancy and postpartum. Front Med (Lausanne). 2023;10:1144170. DOI: 10.3389/fmed.2023.1144170.
5. Fox R, Kitt J, Leeson P, Aye CYL, Lewandowski AJ. Preeclampsia: Risk factors, diagnosis, management, and the cardiovascular impact on the offspring. J Clin Med. 2019 Oct;8(10):1625. DOI: 10.3390/jcm8101625.
6. MacDonald TM, Walker SP, Hannan NJ, Tong S, Kaitu'u-Lino TJ. Clinical tools and biomarkers to predict preeclampsia. EBioMedicine. 2022 Jan:75:103780. DOI: 10.1016/j.ebiom.2021.103780.
7. Awor S, Abola B, Byanyima R, Orach CG, Kiondo P, Kaye DK, et al. Prediction of pre-eclampsia at St. Mary's hospital lacor, a low-resource setting in northern Uganda, a prospective cohort study. BMC Pregnancy Childbirth 2023 Feb 8;23(1):101. DOI: 10.1186/s12884-023-05420-z.

8. Shayan A, Sourinejad H, Refaei M, Masoumi SZ, Tapak L, Soltani F. Predictors of preeclampsia based on a 10-year case-control study. J Fam Reprod Heal. 2019 Oct 22;13(1):14.
9. Chen X, Yuan L, Ji Z, Bian X, Hua S. Development and validation of the prediction models for preeclampsia: A retrospective, single-center, case-control study. Ann Transl Med. 2022 Nov;10(22):1221. DOI: 10.21037/atm-22-4192.
10. Kadhim AAM, Ali HM, Hameed RH. Analysis of a predictive model of preeclampsia risk in Iraqi women. Int J Health Sci (Qassim). 2022 Sep 13;6(S7):3878–91. DOI: 10.53730/ijhs.v6nS7.12675.
11. Xue Y, Yang N, Gu X, Wang Y, Zhang H, Jia K. Risk prediction model of early-onset preeclampsia based on risk factors and routine laboratory indicators. Life 2023 Aug 1;13(8):1648. DOI: 10.3390/life13081648.
12. Kusuma RA, Nurdiati DS, Wilopo SA. Alternatives of risk prediction models for preeclampsia in a low middle-income setting. Open Access Maced J Med Sci. 2022 May 16;10(B):1745–50. DOI:10.3889/oamjms.2022.9030.
13. Sufriyana H, Handayani L, Yuliana F, Syafi'i T. Potensi modifikasi model PIERS untuk prediksi luaran ibu dengan preeklamsia pada rumah sakit tipe B di Indonesia: Penelitian retrospektif di RSUD Ansari Saleh Banjarmasin, Kalimantan Selatan. Med Heal Sci J. 2018 Apr 28;1(1):32-44. DOI:10.33086/mhsj.v1i1.614.
14. Ukah UV, Payne B, Hutcheon JA, Ansermino JM, Ganzevoort W, Thangaratinam S, et al. Assessment of the fullPIERS risk prediction model in women with early-onset preeclampsia. Hypertension. 2018;71(4):659–65. DOI: 10.1161/HYPERTENSIONAHA.117.10318.
15. Sufriyana H, Wu YW, Su ECY. Artificial intelligence-assisted prediction of preeclampsia: Development and external validation of a nationwide health insurance dataset of the BPJS kesehatan in Indonesia. EBioMedicine. 2020;54:102710. DOI: 10.1016/j.ebiom.2020.102710.
16. Aljameel SS, Alzahrani M, Almusharraf R, Altukhais M, Alshaia S, Sahlouli H, et al. Prediction of preeclampsia using machine learning and deep learning models: A review. Big Data Cogn Comput. 2023;7(1):32. DOI: 10.3390/bdcc7010032.
17. Al-Rubaie ZTA, Hudson HM, Jenkins G, Mahmoud I, Ray JG, Askie LM, et al. Prediction of pre-eclampsia in nulliparous women using routinely collected maternal characteristics: A model development and validation study. BMC Pregnancy Childbirth 2020 Jan 6;20(1):1–14.
18. Al-Rubaie ZTA, Askie LM, Hudson HM, Ray JG, Jenkins G, Lord SJ. Assessment of NICE and USPSTF guidelines for identifying women at high risk of pre-eclampsia for tailoring aspirin prophylaxis in pregnancy: An individual participant data meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2018 Oct 1;229:159–66. DOI: 10.1016/j.ejogrb.2018.08.587.