The Value of White Blood Cells and Platelets Indices in Prediction of Tubal Ectopic Pregnancy Rupture

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Abstract

Background: Ectopic tubal pregnancy (ETP) and its potential rupture present significant threats to maternal health, necessitating immediate identification. Blood count indices have been extensively researched, yielding conflicting results. The objective of the study is to assess the potential relevance of white blood cell (WBC) and platelet indices, specifically the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), and platelet distribution width (PDW), in predicting the rupture of ectopic pregnancy (EP). **Methods:** The prospective cohort study was undertaken at Al-Elwiya Maternity Teaching Hospital in Baghdad from July 2022 to July 2023. The study involved 100 pregnant women in their first trimester, comprising 50 with ectopic tubal pregnancies and 50 with intrauterine pregnancies (control group). The ETP group was categorised as ruptured and unruptured patients. Upon diagnosis, the white blood cell (WBC) counts, neutrophil levels, lymphocyte counts, neutrophil/lymphocyte ratio (NLR), platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), and platelet-to-lymphocyte ratio (PLR) of all patients were assessed. The average age of all participants was 31.32 ± 4.03 years. Out of the 50 ETP cases, 20 (40%) underwent rupture. The blood indicators of patients with ETP were markedly distinct from those of healthy controls. **Results:** In the ETP group, patients with ruptured tubes demonstrated markedly elevated lymphocyte counts and reduced NLR in comparison to those with unruptured tubes, with p-values of 0.015 and less than 0.001, respectively. They had a significantly increased MPV value relative to other ETP (P=0.002), however their PLR was markedly reduced (<0.0001). The PLR exhibited notable discriminating power, attaining an Area Under the Curve (AUC) of 0.815. At a threshold of 88.646, the sensitivity was measured at 90%, while the specificity was observed at 85%. Moreover, the NLR demonstrated moderate discriminatory ability with an AUS of 0.750. **Conclusion:** PLR and NLR demonstrated robust to adequate discriminative capability for forecasting tubal rupture, exhibiting high sensitivity and specificity.

Keyword: Ectopic Tubal Pregnancy, Ruptured Tubal Pregnancy, NLR, PLR, Platelet Indices, WBC Indices.

Introduction

Ectopic pregnancy, usually occurring in the first trimester, is a critical medical emergency with potentially fatal outcomes. It presents a significant risk to women of childbearing age, with roughly 10% of all pregnancy-related fatalities resulting from ectopic pregnancy. Prompt diagnosis and intervention are essential to prevent problems, safeguard mother health, and preserve future fertility.[1] A significant issue with ectopic pregnancy is that one-third of patients are asymptomatic, complicating early diagnosis. Approximately 9% of asymptomatic cases ultimately advance to rupture, potentially resulting in significant internal haemorrhage and fatality.[2] Fertilisation and embryo implantation entail intricate interactions among chemical, hormonal, and anatomical elements. Essential anatomical elements in this process comprise ovaries, fallopian tubes, uterus, ovum, and sperm. Ideally, the embryo implants within the endometrial lining of the uterus to establish a viable intrauterine pregnancy. In ectopic pregnancies, foetal tissues implant outside the uterine cavity, predominantly in the fallopian tubes or, less typically, on abnormal or scarred regions of the uterus.[3] The prevalence of ectopic pregnancy has significantly increased during the past thirty years worldwide,

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particularly in underdeveloped nations, where early diagnostic capabilities remain inadequate.[4] This underscores the necessity for additional study into improved methods of detection and management. Timely diagnosis and care are essential to avert rupture and its severe sequelae. While human chorionic gonadotropin levels and transvaginal ultrasound serve as the principal diagnostic tools for ectopic pregnancy, extensive research has been undertaken to discover biomarkers that can facilitate the early detection of tubal pregnancy.[5,6] The examination of inflammatory indicators linked to ectopic pregnancy and its consequences has been a focus of research. A prior study indicated an elevation in mean platelet volume (MPV) during ectopic pregnancy, possibly linked to platelet activation in the pathophysiological mechanisms of ectopic pregnancy.[7] Moreover, Platelet Distribution Width (PDW), an indicator of platelet activity, diminished in tubal ectopic pregnancies (ETP) relative to intrauterine pregnancies.[8] White blood cells (WBCs) significantly indicate the body's reaction to ectopic pregnancy and its repercussions, particularly in cases of ruptured ectopic pregnancy.[9] During the initial phases of ectopic pregnancy, the growing embryo elicits an inflammatory response in the tissues of the fallopian tube. This localised inflammation draws immune cells, particularly white blood cells, to the implantation site. As a result, WBC counts may exhibit a slight increase, indicating the body's effort to control and address the aberrant pregnancy.[10] In tubal ectopic pregnancies, the predominant leukocyte populations in the fallopian tube tissue are macrophages and T-cells. The conclusive histological diagnosis is established through the biopsy of ectopic tissue.[10] As ectopic pregnancy advances and the fallopian tube becomes distended and impaired, the quantity of intraepithelial lymphocytes increases, indicating that these cells may be involved in modulating the inflammatory response associated with tubal ectopic pregnancy.[11] The macrophage population was seen to be twice in women with tubal ectopic pregnancy at the implantation site in the fallopian tube compared to a location distant from the implant site inside the same tube. Macrophages provide immune-regulatory functions in the reproductive system and secrete growth factors and cytokines that support tissue systems. They are also recognised for synthesising prostaglandins that can either enhance or diminish tubal smooth muscle contractility. An elevated quantity of macrophages may correspond with heightened levels of growth factors in the Fallopian tube, facilitating the tissue remodelling essential for blastocyst implantation. The upregulation of CXCL2 mRNA in locally cultured ovarian cells from a patient with an ovarian granulosa cell tumour indicates that CXCR2 ligands directly activate survival genes, thereby safeguarding the granulosa cell tumour from its detrimental effects.[11,12] The unconventional method of ectopic pregnancy may ultimately lead to the rupture of the fallopian tube, resulting in significant internal haemorrhage and provoking a robust systemic inflammatory response. Consequently, an increased number of white blood cells are discharged into the circulatory system. In situations of rupture, WBC counts exhibit a significant and abrupt increase, signifying a medical emergency that necessitates prompt intervention.[13] The Neutrophil/Lymphocyte Ratio (NLR) is a straightforward and readily computable metric obtained from the complete blood count (CBC), calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.[14] NLR has garnered significant attention as a prospective systemic inflammatory marker, as fluctuations in its value may indicate abnormalities in the immunological response of the body. It has been examined in numerous medical problems, including infectious diseases, autoimmune disorders, cardiovascular diseases, cancer, and their involvement in systemic inflammatory processes.[15] Additional investigations revealed reduced MPV values in patients with ectopic pregnancies, especially in instances of rupture.[16] Likewise, platelet distribution width (PDW), which indicates the variability in platelet size, was elevated in ruptured ectopic pregnancies, suggesting a possible severe inflammatory condition.[16] These findings underscore the complex interaction among platelet indices, inflammatory processes, and pregnancy-related variables in the context of ectopic pregnancy and rupture. The exact prognostic value of platelet indices in this context necessitates additional research; nonetheless, their ability to illuminate high-grade inflammatory conditions offers potential for enhancing diagnostic and prognostic understanding. Factors Influencing Haematological Indices In healthy women, various factors can affect haematological markers. The WBC count may be influenced by variables like infections, inflammation, stress, autoimmune disorders, haematological conditions such as leukaemia, and specific drugs (corticosteroids, aspirin, epinephrine, etc.). Platelet counts may fluctuate due to illnesses including idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), drug-induced thrombocytopenia, and bone marrow abnormalities. The ratios of NLR and PLR may indicate systemic inflammation, infections, certain malignancies, and cardiovascular disorders. Mean platelet volume (MPV) can be modified in disorders such as immune thrombocytopenic purpura (ITP), Bernard-Soulier syndrome, and certain anaemias, but a diminished MPV may indicate conditions like aplastic anaemia and lupus. PDW may be affected by factors that influence platelet production or those that result in heightened platelet breakdown.[17,18] Throughout a typical pregnancy, the body experiences numerous physiological alterations that may influence haematological markers. The white blood cell count increases during pregnancy, with leukocytosis manifesting as a physiological response to the stress of pregnancy, approaching the lower limit of the reference range. During pregnancy, platelets may experience increased destruction as the spleen grows due to heightened blood volume, resulting in a greater filtration and destruction of

platelets.[19] Subsequent research has shown that patients with ruptured ectopic pregnancies exhibit significantly elevated neutrophil-lymphocyte ratios (NLR) and platelet-lymphocyte ratios (PLR) compared to those with unruptured ectopic pregnancies.[20,21] Recent studies have validated the potential utility of the Neutrophil-to-Lymphocyte Ratio (NLR) and the Systemic Immunity-Inflammation Index (SII) in detecting tubal rupture in women with ectopic tubal pregnancy (ETP), which may assist in surgical decision-making; however, evidence concerning the advantages of Mean Platelet Volume (MPV) remain inconclusive.[22] The aim of this study was to investigate the changes in white blood cell (WBC) and platelet indices among patients with tubal ectopic pregnancy and to evaluate their effectiveness in predicting potential tubal rupture. Subjects and methodologies This prospective cohort study was undertaken in the Department of Obstetrics and Gynaecology at AL-Elwiya Maternity Teaching Hospital in Baghdad from July 31, 2022, to July 31, 2023. The Scientific and Research Ethics Committee of the Arabic Board of Obstetrics and Gynaecology granted approval for the study (Ethical Approval ID: 5), in conjunction with the scientific committee of AL-Elwiya Maternity Teaching Hospital. Subjects and cohorts: The study comprised 100 pregnant women with gestational ages of fewer than 13 weeks. Fifty individuals were identified with tubal ectopic pregnancy (ETP), while another fifty had viable intrauterine pregnancies (control group). All participants provided informed written consent. The exclusion criteria encompassed second trimester pregnancy, acquired or congenital haematologic disorders, pre-existing medical conditions influencing blood indices, medications affecting blood indices or platelet function and count, known chronic inflammatory diseases or connective tissue disorders, smoking, febrile conditions, and instances of heterotopic pregnancies. The diagnosis of ectopic trophoblastic pregnancy (ETP) was established based on serum β-hCG levels ranging from 1,500 to 3,500 mIU/mL, accompanied with the absence of intrauterine pregnancy on transvaginal ultrasonography (TVUS). In instances where the β-hCG levels fell below this range, the diagnosis depended mostly on an aberrant increase in β-hCG (35-55% over 48 hours) alongside sonographic identification of a tubal ectopic focus.[23] Group 1 comprised women with confirmed ETP who were hospitalised and placed under surveillance. Two subgroups were then established based on the progression of ectopic pregnancy: subgroup (A) comprised patients with a ruptured ectopic pregnancy, whereas subgroup (B) encompassed individuals with an unruptured ectopic pregnancy. The control group (Group 2) comprised pregnant women with a viable intrauterine pregnancy and a gestational age of under 13 weeks, who did not encounter loss, threatening, septic, or molar pregnancies throughout the trial. Patient assessment and data acquisition: Demographic and clinical information, including age, parity, gestational age, obstetrical history, prior medical history, surgical history, medication history, and social history, were gathered using a specialised questionnaire following the acquisition of patient permission. An assessment of the patient's vital signs, general condition, and abdominal and pelvic examinations was completed, followed by a transvaginal ultrasound examination with a 3.5 MHz transducer, performed by an experienced radiologist with the GE Voluson E6 U.S.A ultrasound system. Blood samples were obtained to assess β-hCG for pregnancy confirmation, and ethylenediaminetetraacetic acid (EDTA) anticoagulated blood was collected for a complete blood count (CBC). The 23 parameters of the complete blood count (CBC) were analysed using a Mindray haematology analyser (or a comparable method with Diacon) and are incorporated in this study as haematological indices, including white blood cell (WBC) count, neutrophil count, lymphocyte count, neutrophil to lymphocyte ratio (NLR), platelet (PLT) count, mean platelet volume (MPV), platelet distribution width (PDW), and platelet to lymphocyte ratio (PLR). Patients diagnosed with ETP were referred to the intensive care unit for meticulous monitoring. Ruptured ETPs were promptly escalated for surgical intervention, whilst unruptured cases were meticulously examined by regular follow-up. Statistical examination: Data were analysed using IBM SPSS Version 26. Descriptive statistics were reported as frequencies, means, and standard deviations; Chi-square tests were employed for categorical variables, whereas independent-samples t-tests were utilised to compare continuous variables across groups. Receiver operating characteristic (ROC) curve analysis was utilised to evaluate the efficacy of diagnostics. Statistical significance was established as a p-value of less than 0.Five Outcomes Characteristics of study groups Fifty percent of the 100 patients were diagnosed with an ectopic tubal pregnancy, with twenty (40%) undergoing rupture and thirty (60%) remaining intact. The mean age of the study population was 31.32 ± 4.03 years. The study groups exhibited no significant differences in terms of age, educational attainment, or residency; nevertheless, parity among females was noted. The control was much lower than the subjects (P<0.001). It is significant that none of the patients with ruptured ETP originated from the rural area, as indicated in Table 1.

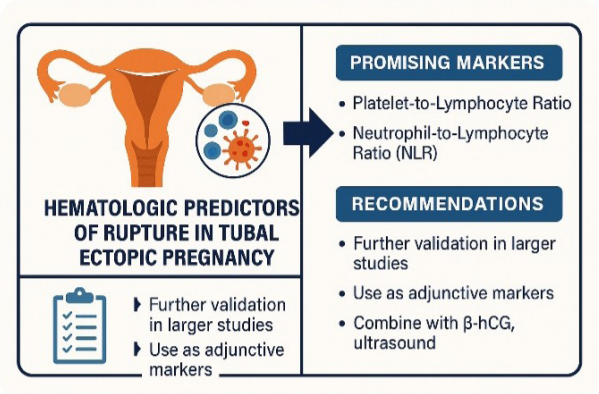

Figure 1: Graphical Abstract.

Table 1: Demographic Features of the Participants.

Variable		Ectopic Pregnancy		Control	P value
		Unruptured	Rupture		
Age (years) (mean ± SD		31.5±1.92	31.6±1.87	31.1±2.23	0.056
Parity (mean ± SD)		1.90±0.960	0.80±0.69	1.96±0.76	**<0.001**
Residency No. (%)	Rural	2 (66.7%)	0 (0.0%)	1 (33.3%)	0.337
	Urban	28 (28.9%)	20 (20.6%)	49 (50.5%)	
Education Level No. (%)	Illiterate	1 (25.0%)	0 (0.0%)	3 (75.0%)	0.266
	Primary	5 (62.5%)	1 (12.5%)	2 (25.0%)	
	Secondary	11 (35.5%)	7 (22.6%)	13 (41.9%)	
	University	13 (22.8%)	12 (21.1%)	32 (56.1%)	

Blood Indices in Study Groups

Table 2 shows blood indices of the participants.

The WBC indices exhibited significant variations, with mean levels of 10.53 for unruptured ectopic pregnancies, 10.99 for ruptured ectopic pregnancies, and 8.48 for intrauterine pregnancies. The p-value of 0.0001 indicates a statistically significant disparity in WBC indices across the groups. Upon further analysis of the WBC levels, several white blood cell subgroups exhibited significant variations. Substantial disparities existed between neutrophil and lymphocyte numbers. The mean neutrophil counts were 7.49 (unruptured), 7.88 (ruptured), and 3.42 (control), while the mean lymphocyte counts were 2.70 (unruptured), 3.10 (ruptured), and 1.84 (control), with all p-values being less than 0.001. The neutrophil-to-lymphocyte ratio (NLR) was considerably reduced in the control group and displayed variability among ETP subgroups ($p < 0.001$). Despite the moderate diagnostic potential of NLR, test interpretation should be approached with caution due to variability. The platelet count (PLT) exhibited no statistical difference between the experimental and control groups, with a p-value of 0.681. Conversely, mean platelet volume (MPV) demonstrated significant variations. The mean values for unruptured and ruptured ectopic pregnancies were 8.427 and 9.20, respectively, while the control value was 8.5. Despite a statistically significant p-value (0.003), the clinical relevance of MPV may be negligible, as it demonstrated limited efficacy in discrimination (AUC = 0.456). Platelet distribution width (PDW) exhibited considerable diversity as well. The average values for unruptured and ruptured ectopic pregnancies were 11.24 and 11.85, respectively, while the control value was 15.75. The p-value is 0.0001. Nevertheless, it proved inadequate in distinguishing between ruptured and unruptured instances of ETP. The Platelet/Lymphocytes Ratio (PLR) shown a significant correlation with decreasing ratios in cases of ectopic pregnancy, whether unruptured or ruptured, with a p-value of 0.0001. PLR exhibited the highest discriminative capability among all indices, indicating its potential utility in predicting ectopic rupture.

Table 2: The White Blood Cells and Platelet Indices of the Participant Groups.

Variables Mean ± SD	Ectopic Pregnancy (G1)		P value	Intrauterine Pregnancy (G2)	P Value (G1Avs G2)	P Value (G1Bvs G2)
	Un Ruptured (A)	Ruptured (B)				
WBC $x10^9$ /L	10.53±2.60	10.99±2.75	0.554	8.48±1.192	<0.001	<0.001
Neutrophil $x10^9$ /L	7.49±2.37	7.88±2.53	0.583	3.42±1.11	<0.001	<0.001
Lymphocyte $x10^9$ /L	2.70±0.50	3.10±0.6	0.015	1.84±0.57	<0.001	<0.001
NLR	2.98±1.46	2.71±1.22	<0.001	1.84±0.13	<0.001	0.002
PLT $x10^9$ /L	259.7±55.6	262.99±50.5	0.833	267.96±24.2	0.615	0.872
MPV (fL)	8.43±0.55	9.20±1.153	0.002	8.51±0.80	0.888	0.004
PDW (fL)	11.24±1.08	11.85±1.261	0.077	15.75±2.18	<0.001	<0.001
PLR	99.4±28.71	87.80±22.83	0.0001	157.59±43.9	<0.001	<0.001

The Receiver Operating Characteristic (ROC) curve of the participants. An analysis of the Receiver Operating Characteristic (ROC) curve was conducted on the variable parameters to ascertain the optimal cutoff point that distinguishes between ectopic pregnancies (both unruptured and ruptured) and the control group (intrauterine pregnancy). Receiver Operating Characteristic for White Blood Cell indices The ROC of WBC indicators is presented in Table 3 and Figure 2. The white blood cell count (WBC) measure produced an area under the curve (AUC) of 0.757, signifying moderate discriminative capability. The selected threshold for classification was 7.56. The study exhibited a sensitivity of 88.0% and a specificity of 72.0%, yielding a positive predictive value (PPV) of 75.8% and a negative predictive value (NPV) of 85.7%. The overall accuracy of this parameter was 80.0 percent. Neutrophils exhibited a robust discriminative capacity with an AUC of 0.928. The categorisation threshold was set at 4.320. The sensitivity and specificity were 86.0% and 80.0%, respectively. This resulted in a positive predictive value (PPV) of 81.13% and a negative predictive value (NPV) of 85.11%. The parameter achieved an accuracy of 83.0%. The AUC for lymphocytes was 0.888, indicating strong discriminating capability. The cutoff point was 2.340. Sensitivity and specificity were equilibrated at 82.0% and 84.0%, respectively. The positive predictive value (PPV) and negative predictive value (NPV) were 83.6% and

82.3%, respectively. The attained accuracy was 83.0%. The neutrophil-to-lymphocyte ratio (NLR) parameters produced an AUC of 0.779. The threshold established was 1.88. The sensitivity and specificity were 78.0% and 70.0%, respectively. The positive predictive value (PPV) was shown to be 72.2%, whilst the negative predictive value (NPV) was 76.0%. The total accuracy was 74.0%. Receiver Operating Characteristic of platelet indices Table 3 and Figure 2 present the receiver operating characteristic (ROC) curve analysis for the platelet indices as follows: The AUC for platelet count was 0.551, signifying comparatively diminished discriminating capability. The threshold was 269.740. Sensitivity and specificity were equilibrated at 50.0% and 56.0%, respectively. The positive predictive value (PPV) and negative predictive value (NPV) were 53.19% and 52.8%, respectively. The attained accuracy was 53.0%. The MPV measure had restricted discriminating capacity, yielding an AUC of 0.456. The threshold employed was 8585. The sensitivity was 52.0%, and the specificity was 50.0%. The positive predictive value (PPV) and negative predictive value (NPV) were 50.9% and 51.0%, respectively. The precision was 50.5%. PDW demonstrated significant discriminatory capability with an AUC of 0.965. The threshold was 12650. The sensitivity and specificity were significantly elevated at 92.0% and 88.0%, respectively. The positive predictive value (PPV) was 88.4%, and the negative predictive value (NPV) was 91.6%. The accuracy attained was an astounding 90.0%. The platelet-to-lymphocyte ratio (PLR) exhibited significant discriminative capacity, with an AUC of 0.921. The threshold utilised was 112.536. Sensitivity and specificity were effectively balanced at 92.0% and 82.0%, respectively. The positive predictive value (PPV) and negative predictive value (NPV) were 83.6% and 91.1%, respectively. The precision was 87.0%. The information is presented in Tables 3 and 5 and depicted in Figures 1 and 2.

Table 3 shows the evaluation of receiver operator characteristics to predict tubal pregnancy through various laboratory parameters.

Table 3: Shows the Evaluation of Receiver Operator Characteristics to Predict Tubal Pregnancy Through Various Laboratory Parameters.

Parameter	AUC	Cut-off	SN	SP	PPV	NPV	ACC
WBC x10^9/L	0.757	7.56	88.0	72.0	75.8	85.7	80.0
Neutrophils x10^9/L	0.928	4.320	86.0	80.0	81.13	85.11	83.0
Lymphocytes x10^9/L	0.888	2.340	82.0	84.0	83.6	82.3	83.0
N/L ratio	0.779	1.88	78.0	70.0	72.2	76.0	74.0
PLT x10^9/L	0.551	269.740	50.0	56.0	53.19	52.8	53.0
MPV (fL)	0.456	8585	52.0	50.0	50.9	51.0	50.5
PDW (fL)	0.965	12650	92.0	88.0	88.4	91.6	90.0
PLR	0.921	112.536	92.0	82.0	83.6	91.1	87.0

AUC: area under curve; SN: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value; ACC: accuracy.

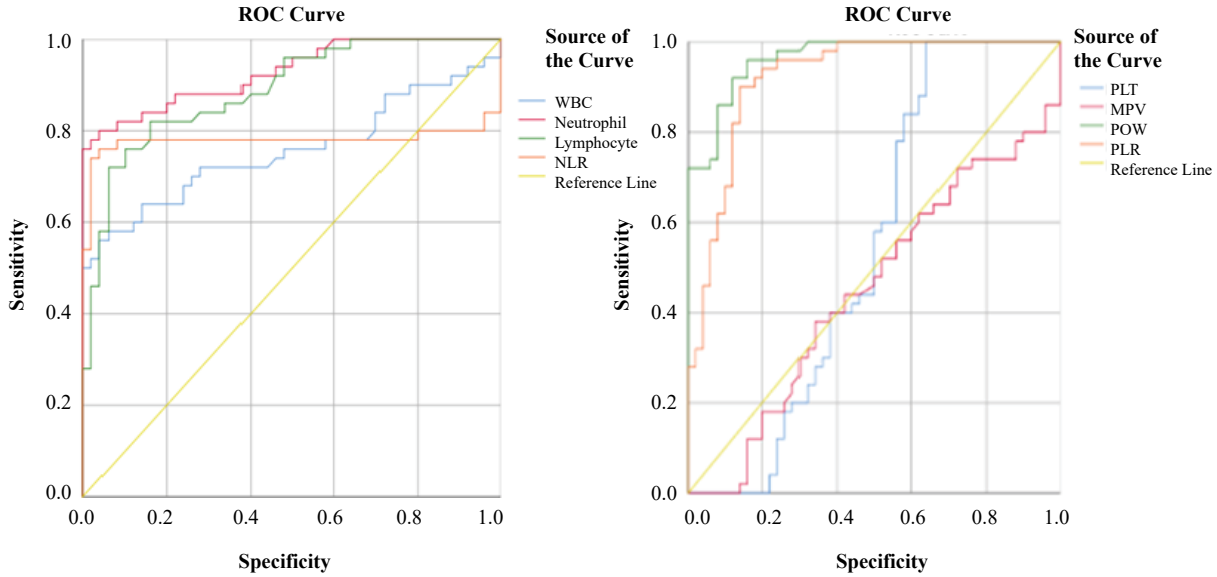

Figure 2: The ROC Curve Analysis of WBC and Platelet Indices in Prediction of Tubal Pregnancies.

Hematological Variables Variation between Unruptured and Ruptured Ectopic Pregnancies of the Participants

Table 4 illustrates the variance in haematological characteristics among the study groups. The white blood cell count (WBC) for unruptured ectopic pregnancies was 10.53 (±2.60), whereas ruptured cases demonstrated a somewhat elevated average of 10.99 (±2.75). A p-value of 0.554 signifies

the absence of a statistically significant difference in white blood cell counts between the two groups.

In the analysis of particular white blood cell subtypes, the average neutrophil count for unruptured ectopic pregnancies was 7.49 (±2.37), while for ruptured cases, it was 7.88 (±2.53). The difference is not statistically significant (p = 0.583).

Unruptured ectopic pregnancies exhibited an average lymphocyte count of 2.702 (±0.508), whereas ruptured cases showed a higher average of 3.102 (±0.605). The p-value of 0.015 highlights the statistical significance of the observed disparity in lymphocyte numbers.

A substantial difference in the neutrophil-to-lymphocyte ratio (NLR) was observed between unruptured and ruptured ectopic pregnancies. The mean NLR values are 2.98± 1.46 for unruptured instances and 4.71± 2.22 for ruptured cases, with a p-value of 0.0001.

In terms of platelet count (PLT), unruptured ectopic pregnancies demonstrated a mean of 259.72 (±55.62), while ruptured cases presented a marginally elevated mean of 262.99 (±50.52). The p-value of 0.833 indicates no statistically significant difference in platelet counts between the two groups.

Regarding mean platelet volume (MPV), unruptured ectopic pregnancies exhibited an average of 8.42 (±0.549), but ruptured cases demonstrated a higher average of 9.20 (±1.153). The p-value of 0.002 highlights the statistical significance of the disparity in MPV between the groups.

Platelet distribution width (PDW) exhibited a comparable tendency to mean platelet volume (MPV). Unruptured ectopic pregnancies exhibited a mean PDW of 11.24 (±1.082), while ruptured cases demonstrated a marginally elevated mean PDW of 11.85 (±1.261); however, this difference was not statistically significant.

The platelet-to-lymphocyte ratio (PLR) exhibited a substantial difference between unruptured and ruptured ectopic pregnancies. The mean PLR values are 87.805 ± 22.83 for unruptured patients and 129.40 ± 38.71 for ruptured cases, with a p-value of 0.0001.

Table 4: The Association of Various Hematological Indices among Ruptured and Unruptured Ectopic Pregnancy Groups.

Variables	Ectopic Pregnancy		P Value
	Unruptured	Ruptured	
WBC (cells/µL)	10.53±2.60	10.99±2.75	0.554
Neutrophil (µL)	7.49±2.37	7.88±2.53	0.583
Lymphocyte (µL)	2.702±0.508	3.102±0.605	**0.015**
NLR	2.98± 1.46	4.71± 2.22	**0.0001**
PLT (cells/µL)	259.72±55.62	262.99±50.52	0.833
MPV (fL)	8.42±0.549	9.20±1.153	**0.002**
PDW (fL)	11.24±1.082	11.85±1.261	0.077
PLR	87.805± 22.83	129.40± 38.71	**0.0001**

Blood Indices as a Predictor for Tubal Rupture

Among all indices, NLR and PLR exhibited medium to good discriminatory power of 0.750 and 0.815, respectively, as illustrated in Table 5 and Figure 3. At a cutoff of 2.50, the NLR predicted tubal rupture with 83.3% sensitivity and 80% specificity. A sensitivity of 90% was linked to a PLR cutoff of 88.646, accompanied by a specificity of 85%.

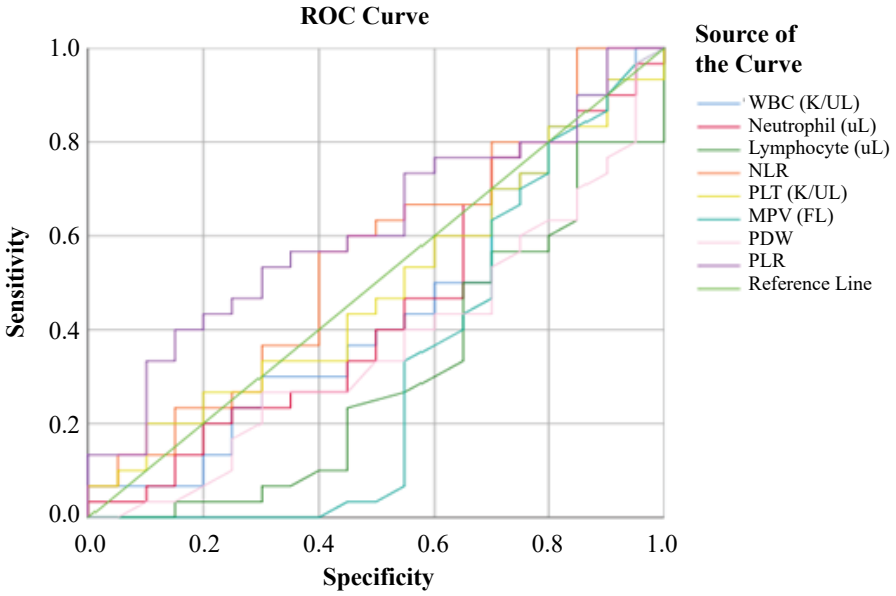

Figure 3: ROC Curve Analysis for Blood Indices in Predicting Ruptured Tubal Pregnancies.

Table 5: ROC Curve Analysis was Carried Out to In Determining the Value of Various Parameters in the ICU in Predicting the Tubal Rupture in Ectopic Gestation.

Parameter	AUC	Cut- off	SN	SP	PPV	NPV	ACC
WBC x10^9/L	0.442	10.7	50.0	40.0	42.8	76.9	21.6
Neutrophils x10^9/L	0.445	7.610	53.3	35.0	46.4	76.7	20.5
Lymphocytes x10^9 /L	0.305	2.85	50.0	35.0	44.8	75.5	20.3
NLR	0.750	2.50	83.3	80.0	88.7	83.1	86.3
PLT x10^9 /L	0.485	258.320	53.2	45.0	36.9	79.5	23.5
MPV (fL)	0.312	8.53	46.7	30.0	24.6	72.8	18.9
PDW (fL)	0.367	10.915	56.7	25.0	29.8	75.5	19.1
PLR	0.815	88.646	90.0	85.0	83.0	94.7	71.2

AUC: area under curve; SN: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value; ACC: accuracy.

Discussion

Identifying individuals at elevated risk for ruptured tubal ectopic pregnancies (ETP) is essential for reducing related morbidity and death, as well as for facilitating prompt clinical intervention. In our investigation, the rupture rate in cases with ETP was 40%, markedly lower than the 70% documented in a recent study from Karbala province.[24] Nonetheless, while both NLR and PLR exhibited more divergence between ruptured and unruptured ETP groups, PLR emerged as the superior predictor, evident from its elevated sensitivity and specificity. Consequently, the results indicate that PLR may serve as a valuable practical supplementary marker in assessing the risk of a rupture event. This study concurs with previous studies suggesting that there is no significant link between age and ETP or their consequent effects.[25] However, a significant difference in parity across the groups was noted, suggesting that parity may be a crucial factor in the incidence and outcomes of ectopic pregnancy, since lower parity could be associated with an increased risk of ectopic pregnancy rupture. This conclusion is consistent with several other studies.[26,27] Socioeconomic factors, including education, may indirectly affect participants' socioeconomic level, therefore influencing their health-seeking behaviours and access to medical care. The current study found that educational level did not significantly affect the prevalence of ectopic pregnancy or rupture; nevertheless, there was a marked lack of individuals from rural areas in the ruptured ectopic pregnancy group. This discovery may indicate that geographical differences or inequities in healthcare access affect the incidence of ectopic pregnancy rupture, hence supporting the conclusions of previous investigations.[28] Ectopic pregnancy, whether ruptured or intact, is associated with an inflammatory response that affects leukocyte count and its indicators.[29] Our findings validated this hypothesis, since the indices of white blood cells, including neutrophils, lymphocytes, and their ratio (NLR), shown differences between the experimental and control groups. The NLR is acknowledged as a marker of systemic inflammation and has shown a relationship with the degree of tubal damage and the likelihood of rupture in ectopic pregnancy instances.

A marginal increase in MPV was observed in ruptured ETP cases relative to unruptured cases and controls. While MPV has been suggested as a potential marker of platelet activation during inflammation, its diagnostic utility seems constrained due to its low discriminatory capacity in ROC analysis. PDW levels exhibited comparable differences between groups but possessed minimal predictive value for rupture. These indices may indicate underlying inflammation; nevertheless, they should not be solely relied upon for clinical decision-making.[30] PLR was significantly reduced in ETP patients compared to controls, primarily due to proportionately elevated lymphocyte numbers. Previously examined concerning inflammation associated with poor prognoses across several disease states, PLR in our study distinguished ETP from intrauterine pregnancies and demonstrated a significant capacity to predict rupture, positioning it as a promising possibility for future investigation.[8,30] The assessed haematological markers, including PLR, lymphocyte count, neutrophil count, and white blood cell counts, exhibited the highest consistency as distinguishing indices between ectopic and intrauterine pregnancies. Although other signals were statistically obscured, only PLR demonstrated adequate strength in predicting rupture. The results indicate the potential of PLR and NLR as compositional inflammatory markers to enhance existing diagnostic approaches, although additional research is necessary. Numerous studies examined the utility of numerous blood indices in identifying ectopic pregnancy, revealing their effectiveness at different cutoff points, including neutrophil and lymphocyte counts.[31-33] The ROC curve research demonstrated that WBC provides moderate discrimination between ectopic and intrauterine pregnancies. The lymphocyte count demonstrated high sensitivity and specificity, reinforcing its potential as a biomarker. Conversely, MPV and platelet count exhibited subpar performance, demonstrating that they cannot serve as the sole predictors. Our findings corroborate previous research highlighting the need of utilising various haematologic markers for diagnostic prescription.[32,34] The lymphocyte count exhibited strong discriminatory capability, with an AUC of 0.888. The selected cutoff value of 2.340 attained a sensitivity of 82.0% and a specificity of 84.0%, achieving a balanced outcome. The positive predictive value (PPV) and negative predictive value (NPV) were 83.6% and 82.3%, respectively, with an overall accuracy of 83.0%. The findings indicated that lymphocyte count may aid in the diagnosis of ectopic

pregnancies, especially when evaluated in conjunction with other pertinent factors. A study conducted in Turkey in 2023 by Sarıkaya *et al*.[34] yielded analogous results. The NLR measure exhibited limited discriminative capability and may serve as an ancillary marker for diagnosing ectopic pregnancy, albeit with potentially constrained efficacy. This outcome is consistent with the findings of Biswas *et al*.[35]. The NLR demonstrated a moderate efficacy in forecasting tubal rupture, with an area under the curve (AUC) of 0.750. Donmez *et al*.[36] reported that individuals with an NLR ≥ 4 exhibited a 6.9-fold increased risk of rupture.

The platelet indicators, comprising MPV and platelet count, demonstrated inadequate discriminatory capability. While platelet count alone may not be a reliable predictor of ectopic pregnancy, it could nevertheless contribute to the overall diagnostic approach. This discovery aligns with the studies performed by Artunc Ulkumen *et al*.[5]. In contrast, the PLR had significant predictive ability for both ectopic pregnancy and tubal rupture. At a cutoff value of 112.54, the PLR demonstrated potential as a reliable criterion for identifying ectopic pregnancy, exhibiting 92% sensitivity and 82% specificity. At a reduced cutoff value of 88.65, it predicted tubal rupture with 90.0% sensitivity and 85% specificity, which could enhance the accuracy of identifying ectopic tubal pregnancy and inform clinical decision-making. These findings correspond with Kan et al.'s research, which revealed a substantial association between PLR levels and histopathologically verified tubal rupture.[21] Moreover, an earlier study demonstrated that tubal pregnancies with a PLR ≥ 166.6 had a 4.5-fold increased risk of rupture.[36]

In summary, individual haematological markers such as MPV and PDW are inadequate predictors, however combinations of indices like PLR and NLR appear to be effective for detecting ectopic pregnancy and predicting tubal rupture. These indicators may serve as adjuncts to the presently utilised assays, such as β-hCG and ultrasonography, but not as substitutes. Additional extensive research are required to validate these findings and establish suitable clinical thresholds.

Conclusion

The platelet-to-lymphocyte ratio (PLR) has an AUC of 0.815 for predicting tubal ectopic rupture, demonstrating 90% sensitivity and 85% specificity, making it the most effective haematological predictor for this condition. The neutrophil-to-lymphocyte ratio (NLR) was another metric that moderately predicted outcomes (AUC = 0.750; sensitivity 83.3%; specificity 80%). Conversely, mean platelet volume (MPV) and platelet distribution width (PDW) inadequately differentiated between patients and controls (MPV-AUC = 0.456, PDW-AUC ≈ 0.367), therefore possessing restricted clinical use. These findings align with previous reports cautioning against the isolated use of MPV and PDW.[5,16]

Haematological parameters serve as supplementary rather than conclusive indicators. The contemporary standard for diagnosing and managing ectopic pregnancies relies on β-hCG levels and sonographic results, thereafter monitored using transvaginal ultrasound (TVUS).[23] Increased NLR or PLR indices may intensify clinical suspicion and promote more rigorous sonographic monitoring; nonetheless, the determination of rupture risk or intervention should adhere to established standards.[23,24]

Suggestions

1. Prospective, multicenter validation study. Expanded cohorts will confirm acceptable cutoff values for PLR and NLR and evaluate their generalisability across diverse populations.
2. Integration with conventional diagnostics. Future research should evaluate the supplementary significance of PLR and NLR in conjunction with β-hCG trends and TVUS findings.
3. Development of guidelines. If confirmed, thresholds for PLR and NLR may be incorporated into clinical algorithms designed to enhance the early diagnosis of tubal rupture.
4. By implementing these guidelines, doctors and researchers would ascertain whether PLR and NLR can consistently enhance current diagnostic methods and consequently elevate patient outcomes.

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Conflicts of Interest

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Data Availability

The corresponding author will provide further data on justified request.

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