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Research Article

Utility of Neutrophil/Lymphocyte Count Ratio in Critically Ill Children

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Abstract

Background: Neutrophil to lymphocyte ratio (NLR) has been used in adult patients as a predictor of mortality. However, few studies have assessed their utility in pediatric patients.

Objective: To assess role of NLR in diagnosis of sepsis andpredicting prognosis among critically ill children.

Methods: This was a prospective observational study conducted on 133 children admitted to pediatric intensive care unit (PICU) of a tertiary center. Patients were evaluated on admission by routine laboratory biomarkers, including NLR, in addition to clinical risk score. Patients were followed up till hospital discharge. The primary outcome was PICU mortality.

Results: 133 patients were recruited. 47.4% had sepsis; 7.5% had non-infectious systemic inflammatory response syndrome (SIRS) and 45.1% had no SIRS. No significant differences in NLR was observed between sepsis, non-infectious SIRS, and non-SIRS [median and IQR: 2.5 (1.25 - 4.4), 4.3 (1.4 - 13.9), 1.7 (0.92 - 4.2) respectively; p = 0.087]. No significant differences were found among the three groups regarding lymphocytic count, absolute neutrophilic count, white blood cell count (WBC), and platelet count. No significant difference in NLR was observed between survivors and non-survivors [median and IQR: 2.3 (1 - 4.4) vs. 2.3 (1.2 - 4.8); p = 0.65]. Conversely, WBC, platelet count, lymphocytic count, and serum albumin were significantly lower, while CRP was significantly higher among non-survivors. Multivariate logistic regression analysis revealed that mechanical ventilation and platelet count are independent predictors of mortality.

Conclusion: NLR is not useful for diagnosis of sepsis or prediction of prognosis of critically ill children. Mechanical ventilation and platelet count are more useful for that purpose.

Keywords: *Neutrophil/Lymphocyte Ratio; Critically Ill Children; Pediatric*

Introduction

Critical illness is a heterogeneous group of disorders that share a risk of organ dysfunction, long-term morbidity, and mortality [1]. According to the American Academy of Pediatrics, there are different criteria for children who need admission in pediatric intensive care unit (PICU), including patients with severe life-threatening, or unstable cardiovascular disease, neurologic disease, endocrine or metabolic disease, gastrointestinal disease, postoperative patients requiring frequent monitoring and patients with life-threatening or unstable renal disease [2].

Approximately 80% of the patients admitted into intensive care units survive the acute event, and most remain in this unit briefly. However, a subgroup does not recover sufficiently quickly to become independent and from then they recover slowly. These patients are called chronically critically ill (CCI) patients who comprise 5 to 10% of the patients admitted into intensive care units [3].

The outcome of critically ill children recovering from life threatening diseases in intensive care situations has improved owing to advancing diagnostic and therapeutic methods. Clinicians recognized the importance of identifying patients with the highest risk of mortality among those admitted to PICU, and of proper monitoring and appropriate intervention and treatment [4].

Pediatric critical illness can profoundly disrupt child health and development and negatively affect family function and well-being. Although PICU mortality is declining, agrowing number of survivors develop deficits that persist beyond hospital discharge [5].

Neutrophils are the most abundant white blood cell, constituting 60 - 70% of the circulating leukocytes. They defend against bacterial or fungal infection. They are usually first responders to microbial infection; their activity and death in large numbers form pus [6].

Neutrophil to lymphocyte ratio (NLR) is used as a marker of subclinical inflammation. It is calculated by dividing the number of neutrophils by number of lymphocytes, usually from peripheral blood sample, but sometimes also from cells that infiltrate tissue, such as tumor [7].

As the physiological immune response of circulating leukocytes to various stressful events are often characterized by an increase in neutrophil counts and a decline in lymphocyte counts, so the ratio of the both is used as an additional infection marker in clinical ICU practice [8].

Objective of the Study

The objective of the present study was to assess the role of neutrophil / lymphocyte ratio in diagnosis of sepsis and prediction of prognosis among critically ill children.

Subjects and Methods

The design of the study: In this prospective study, we enrolled 133 critically ill children admitted to a 10-bed PICU at Menoufia University Hospital, Egypt, from February 2019 to August 2020. The Scientific and Ethical Committee approved the study protocol of Menoufia University, and informed consent was obtained from parents before enrolling their children in the study. Critically ill children in the PICU aged 1 month to 18 years were included in this study. Exclusion criteria were 1) age less than one month or more than 18 years and 2) Any children with aplastic anemia or received immunosuppression drugs and oncology patients with bone marrow depression and 3) inability to follow up for the first 30 days after discharge.

The PICU patients: The included patients were diagnosed according to the International Pediatric Sepsis Consensus Conference, characterizing, sepsis, non-infectious SIRS, and non-SIRS [9]. Sepsis is a systemic response to an infectious stimulus characterized by two or more of the following, resulting in infection: (a) a temperature of more than 38°C or less than 36°C, (b) pulse rate > 90 beats/minute, (c) breath rate > 20 breaths/minute or $PaCO_2$ < 32 mm Hg, and (d) white blood cell count (WBC) of > 12000/mm^3 or < 4000/mm^3, or > 10% immature (band) formation in a total blood count.

The outcomes of the study: The primary outcome measure was PICU mortality during hospital admission or during the 30-days follow up period after hospital discharge. The length of stay (PICU and hospital), need and duration of mechanical ventilation (MV) were secondary outcomes.

The Method of the study: We collected the complete history of all children including in this study, including age, sex, admission data, and length of stay in the PICU and the inpatient department. Vital signs, anthropometric measurements, and examination of all body systems were also assessed. PICU scoring systems were applied, including the 1) Pediatric risk of mortality score (PRISM) 2) Pediatric index of mortality-2 (PIM2), and 3) Pediatric sequential organ failure assessment scale (pSOFA). The PRISM score was calculated within

24 hours of admission for each patient, using 14 clinical and laboratory variables. Values for these variables were entered into the PRISM application (http://www.sfar.org/scores2/prism2.php), which calculates the expected death rate [10]. PIM2 is a more rapid technique for which scores are estimated within 1 hour of in-person contact with the patient, and scores correspond to a predicted mortality rate [11]. The pediatric Sequential Organ Failure Assessment Scale (pSOFA) is used to assess organ dysfunction. Depending on the patient's baseline risk level, a pSOFA score of 2 or greater corresponds to a 2- to 25-fold greater risk of death than patients with pSOFA scores was less than 2 [12].

Arterial blood gases, random blood glucose and complete blood count (CBC) were analyzed (Pentra ABX 80 analyzer; Horiba, Paris, France). C-reactive protein (CRP), hepatic function (alanine aminotransferase and aspartate aminotransferase) were determined using a kinetic UV-optimized IFCC method (LTEC Kit, England). Renal function (blood urea and serum creatinine) was determined colorimetrically (Diamond Diagnostic kit, Germany). Blood culture, chest X- radiography, brain CT and other laboratory or radiological analyses were performed as needed.

The procedure: Neutrophil to lymphocyte ratio (NLR) was measured once from blood samples withdrawn from all patients (within 24 hours of PICU admission).

Statistical analysis: Data were statistically analyzed using SPSS (version 19, SPSS Inc, Chicago, Illinois). Descriptive statistics included arithmetic medians and interquartile ranges (IQRs) of quantitative data and numbers and percentages of qualitative data. Analytical statistics included the Chi-square (χ^2) test, Student's t-test, Mann-Whitney test and Fisher's exact test. We used logistic regression models to determine the ability of NLR to predict mortality. Receiver operating characteristics (ROC) analysis was performed for the diagnostic and prognostic powers of the NLR, and other variables. P-values < 0.05 were considered significant.

Results

Table 1 showed demographic and clinical data of survivors and non-survivors. Non-survivors had significantly higher frequency of severe sepsis, mechanical ventilation need, multiple organ dysfunction syndrome (MODS), and acute respiratory distress syndrome (ARDS) compared with survivors. Mechanical ventilation duration, PRISM, and pSOFA scores were also significantly higher among non-survivors.

Variable	Survivors (n = 105)	Non-survivors (n = 28)	P-Value
Age, month	24 (8 - 72)	18 (7.3 - 117)	0.88
Male sex	52 (49.5%)	11 (39.3%)	0.34
Weight, Kg	12 (7 - 18)	9.3 (6.6 - 22)	0.71
Height, cm	85 (63.5 - 109.5)	79 (63.5 - 116.8)	0.92
BMI	16.3 (14.8 - 18.5)	16.2 (14.1 - 18.9)	0.59
Malnutrition	48 (45.7%)	18 (64.3%)	0.08
Category - Severe Sepsis - Sepsis - Non-infectious SIRS - Non-SIRS	 7 (6.7%) 40 (38.1%) 6 (5.7%) 52 (49.5%)	 12 (42.8%) 4 (14.3%) 4 (14.3%) 8 (28.6%)	<0.001* 0.08
Shock on admission	29 (27.6%)	10 (42.9%)	0.12
MODS	28 (26.7%)	21 (75%)	<0.001*
ARDS	1 (0.9%)	10 (35.7%)	<0.001*

MV	23 (21.9%)	25 (89.3%)	<0.001*
MV duration	0 (0 - 4.5)	4 (0 - 16)	<0.001*
Nosocomial infection	17 (16.2%)	15 (53.6%)	<0.001*
PRISM mortality risk%	2 (1.4 - 4.2)	3.7 (1.8 - 10.4)	0.012*
PIM2 mortality risk%	2.3 (1.7 - 6.2)	5.4 (1.8 - 14.6)	0.057
pSOFA	5 (4 - 6)	6 (5 - 9.8)	0.002*

Table 1: *Demographic and clinical data of survivors and non-survivors.*

**Statistically significant; Data is presented as median (interquartile range) or number (%); BMI: Body Mass Index; SIRS: Systemic Inflammatory Response Syndrome; MODS: Multiple Organ Dysfunction Syndrome; ARDS: Acute Respiratory Distress Syndrome; MV: Mechanical Ventilation; PRISM: Pediatric Risk of Mortality; PIM2: Pediatric Index of Mortality2; pSOFA: Pediatric Sequential Organ Failure Assessment Score.*

Laboratory data of survivors and non-survivors is shown in table 2. CRP was elevated in non-survivors versus survivors. WBC, platelet count, lymphocytes, and albumin level were lower in non survivors comparing to survivors.

Variable	Survivors (n = 105)	Non-survivors (n = 28)	P-Value
CRP, mg/dL	16 (5 - 48)	32.5 (12.3 - 87.5)	0.013*
Hemoglobin, g/dL	10.7 (9.4 - 12.2)	10.3 (8.9 - 10.9)	0.10
WBC, 1000/uL	13.1 (9 - 17.7)	9.9 (5.9 - 15.9)	0.044*
Platelets, 1000/uL	298 (181 - 383.5)	202.5 (130.5 - 330.3)	0.027*
Creatinine, mg/dL	0.4 (0.3 - 0.6)	0.5 (0.3 - 0.7)	0.25
ALT, U/L	24 (15 - 51)	37 (19 - 77)	0.063
Albumin, g/dL	3.8 (3.3 - 4.2)	2.7 (2.2 - 3.1)	<0.001*
Bilirubin, mg/dL	0.4 (0.2 - 0.7)	0.4 (0.23 - 1.35)	0.56
Base excess	-5.3 (-8.6 - -2.2)	-4.7 (-11.1 - 0.15)	0.68
ANC, 1000/ml	7.6 (4.8 - 12.1)	5.3 (2.9 - 9.4)	0.14
NLR	2.3 (1 - 4.4)	2.3 (1.2 - 4.8)	0.65
Lymphocytes, 1000/uL	3.3 (1.9 - 5.6)	2.1 (1.4 - 3.6)	0.022*

Table 2: *Laboratory data of survivors and non-survivors.*

**Statistically significant; CRP: C-Reactive Protein; WBC: White Blood Cell Count; ANC: Absolute Neutrophilic Count; ALT: Alanine Amino-transferase; NLR: Neutrophil/Lymphocyte Ratio.*

Correlation of neutrophil/lymphocyte ratio (NLR) with other variables. NLR was positively correlated with PRISM score, ANC, and WBC. NLR was negatively correlated with lymphocytes (Table 3).

Univariate and multivariate logistic regression analyses for the prediction of mortality by different variables are shown in table 4. Univariate logistic regression analysis showed that high PRISM, and pSOFA scores, MV need, ARDS, severe sepsis, higher CRP level, lower levels of Platelet count and albumin were significantly associated with mortality. Multivariate logistic regression analysis showed that MV requirement, and lower platelet counts were the most significant independent risk factors for mortality.

Variable	NLR	
	Rs	p-value
Age	0.20	0.025*
Weight	0.19	0.028*
PRISM	0.19	0.025*
PIM2	0.14	0.10
pSOFA	0.065	0.46
PICU stay	-0.08	0.39
MV duration	0.057	0.51
Vasoactive infusion days	0.06	0.46
ANC	0.70	<0.001*
Lymphocyte count	-0.59	<0.001*
Hemoglobin	0.08	0.38
WBC	0.26	0.002*
Platelet count	0.02	0.83
Base excess	-0.12	0.19
CRP	0.12	0.17
Creatinine	0.12	0.18
ALT	-0.05	0.59
Albumin	-0.18	0.08
Total bilirubin	-0.13	0.12

Table 3: Correlation of neutrophil/lymphocyte ratio (NLR) with other variables.

*Statistically significant; PICU: Pediatric Intensive Care Unit; PRISM: Pediatric Risk of Mortality; PIM2: Pediatric Index of Mortality2; pSOFA: Pediatric Sequential Organ Failure Assessment Score; MV: Mechanical Ventilation; CRP: C-Reactive Protein; WBC: White Blood Cell Count; ANC: Absolute Neutrophilic Count; ALT: Alanine Aminotransferase.

Univariate logistic regression analysis		
Variable	**Odds ratio (95% CI)**	**p-value**
PRISM	1.07 (1.01 - 1.13)	0.015*
pSOFA	1.30 (1.12 - 1.5)	0.001*
MV	29.7 (8.2 - 107.3)	<0.001*
ARDS	57.8 (6.9 - 479.3)	<0.001*
Severe sepsis	10.5 (3.6 - 30.7)	<0.001*
CRP	1.01 (1.002 - 1.019)	0.019*
WBCs	0.99 (0.95 - 1.037)	0.67
Platelets count	0.996 (0.99 - 1.0)	0.028*
Albumin	0.24 (0.12 - 0.48)	<0.001*
Lymphocytic count	0.89 (0.76 - 1.06)	0.19
Multivariate logistic regression analysis		
Variable	**Adjusted odds ratio (95% CI)**	**p-value**

PRISM	0.99 (0.91 - 1.09)	0.88
pSOFA	0.92 (0.71 - 1.20)	0.53
Mechanical ventilation	31.4 (5.9 - 156.4)	<0.001*
Albumin	0.88 (0.59 - 1.30)	0.53
CRP	1.01 (0.99 - 1.03)	0.08
Platelet count	0.994 (0.98 - 0.999)	0.028*
ARDS	9.1 (0.93 - 89.1)	0.058
Severe sepsis	3.4 (0.74 - 15.5)	0.12

Table 4: *Univariate and multivariate logistic regression analysis for prediction of mortality by different clinical variables.*

**Statistically significant; CRP: C-Reactive Protein; WBC: White Blood Cell Count; OR (95% CI): Odds Ratio and 95% Confidence Interval; PRISM: Pediatric Risk of Mortality; pSOFA: Pediatric Sequential Organ Failure Assessment score; MV: Mechanical Ventilation; ARDS: Acute Respiratory Distress Syndrome; OR (95% CI): Odds Ratio and 95% Confidence Interval.*

ROC curve analysis showed CRP had the largest area under the curve for prediction of mortality followed by platelets and lymphocytes, then albumin. NLR failed to predict mortality with poor sensitivity and specificity (Table 5 and figure 1A and 1B).

Variable	AUC (95% CI)	P value	Cutoff level	Sensitivity	Specificity
CRP, mg/dL	0.65 (0.54 - 0.77)	0.012*	≥ 21.5	71.4%	54.3%
WBC,1000/uL	0.37 (0.24 - 50)	0.044*	≥ 38.6	7.1%	99%
ANC,1000/uL	0.41 (0.28 - 0.54)	0.14	≥ 31.7%	10.7%	99%
Lymphocytes, 1000/uL	0.64 (0.52 - 0.76)	0.022*	≤ 2.2	57.1%	71.4%
NLR	0.53 (0.41 - 0.65)	0.64	≥ 1.8	64.3%	46.7%
Platelets,1000/uL	0.64 (0.53 - 0.75)	0.027*	≤ 213.5	57.1%	66.7%
Albumin, g/dL	0.62 (0.52 - 0.72)	0.052	≤ 3.2	82.1%	55.8%

Table 5: *ROC curve analysis for prediction of mortality by different biomarkers.*

**Statistically significant; CRP: C-reactive protein; WBC: White Blood Cell Count; ANC: Absolute Neutrophilic Count; NLR: Neutrophil/Lymphocyte Ratio; AUC (95% CI): Area Under the Receiver Operating Characteristic Curve and 95% Confidence Interval.*

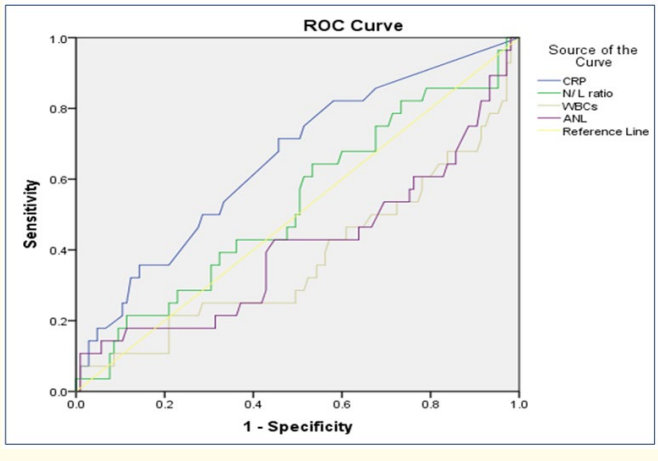

Figure 1 A: *ROC curve analysis for prediction of mortality by WBCs, ANC, NLR and CRP.*

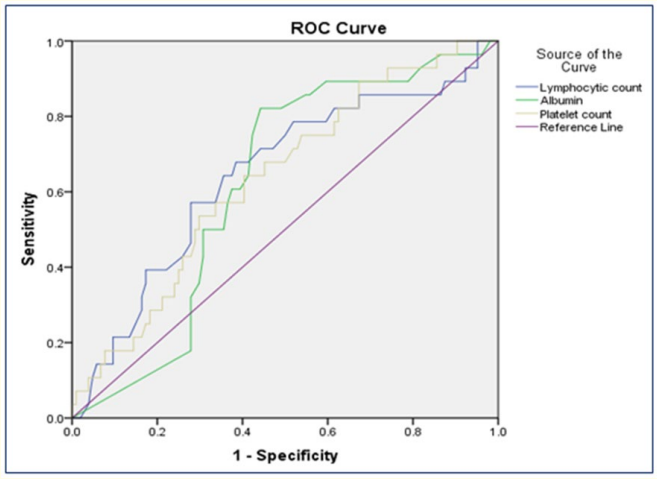

Figure 1B: *ROC curve analysis for prediction of mortality by platelets, lymphocytes and albumin.*

Discussion

Critically ill children are in need of biomarkers for diagnosis of sepsis and prediction of prognosis. However, most new biomarkers are expensive and not commercially available. This problem is more prominent in resource-limited countries. That is why we aimed in the present study to evaluate the potential role of NLR among critically ill children, an issue which has been addressed by few pediatric studies.

In our study, we found that NLR is not useful for diagnosis of sepsis among critically ill children. Our results are consistent with some previous adult studies [13,14]. While the majority of pediatric studies [15,16]. Neonatal study [17] and adult studies [18,19] tended to demonstrate the contrary. Discrepancy between our results and the latter studies might be explained by the fact that our study was conducted in a tertiary center and many patients had been referred from other centers after receiving antibiotic therapy. Additionally, the small sample size might have masked the diagnostic role of NLR.

Besides the diagnostic value of NLR, we evaluated NLR for a possible prognostic role. We found no significant difference between survivors and non-survivors in NLR which is consistent with a previous study of critically- ill children [20]. Another adult study [21] demonstrated that NLR has no effect on 28 - day mortality in intensive care patient. On the contrary, Duffy., *et al*. [22] has reported higher rates of mortality among patients admitted to PICU with high NLR values and Mathews., *et al*. [23] reported that rise in NLR helps in predicting the mortality in the pediatric intensive care.

The best Cutoff for prediction of mortality by NLR varied among studies. Yao., *et al*. [24] reported a cutoff > 6.24 (sensitivity: 81.08%; specificity: 69.17%). Durmus., *et al*. [25] reported a lower cutoff > 5.1 (sensitivity: 75%; specificity: 62%). Shimoyama., *et al*. [26] reported a cutoff > 3.28 (sensitivity: 62.5%; specificity: 66.7%) while in our study NLR failed to predict mortality with poor sensitivity and specificity.

We found a positive correlation of NLR with PRISM as well as other biomarkers implying that NLR might not be totally devoid of prognostic utility. This finding suggests that NLR could be utilized to increase the accuracy of PRISM score or other prognostic scores in PICU.

The mortality rate in our study sample was noted to be 20.3% which is higher compared with the PICU mortality in developed world [20-27] which appears to be attributed to our poor diagnostic and therapeutic resources. This high mortality rate might have affected the prognostic value of NLR since some patients who were expected to live according to NLR actually died, which decreased the utility of NLR.

Our results found that CRP level was significantly higher in non-survivor group and, consequently, more prognostically useful. This result is consistent with some previous studies [28,29]. Siddiqui., *et al.* [30] and El-Ella., *et al*. [31] reported that median CRP wasn't associated with mortality.

In our study; we found that lymphocytic count was significantly lower among non-survivors which are close to the results reported by previous pediatric study [32] which showed that mortality of ICU patients is associated with lymphopenia. Interest in the prognostic value of lymphocytic count has increased in recent months in association with COVID-19 pandemic [33]. For instance, Liu., *et al.* [34] found that the decrease of lymphocytic count was related to the progress of COVID-19 disease.

Of note, we reported that serum albumin was significantly lower among non-survivors which is consistent with other pediatric studies [32-35] that reported hypoalbuminemia at admission to a PICU is associated with higher mortality, longer duration of mechanical ventilation, and lower probability of ICU discharge.

In addition, platelet count was significantly lower among non survivors in our study consistent with another pediatric study [36] which reported that thrombocytopenic children have higher incidence of bleeding, longer ICU stay and a higher mortality. Akca., *et al*. [37] agreed with our results that thrombocytopenia is common in PICU. Patients requiring cardiopulmonary resuscitation or with circulatory shock, coagulopathy, sepsis and with more severe disease have higher risk of developing thrombocytopenia. Thrombocytopenic patients have a higher risk of bleeding. Drop in platelet counts > 27% and thrombocytopenia were independently related to mortality. Serial measurements of platelet counts are better predictors of pediatric intensive care outcome than one-time values. Any drop-in platelet counts even without thrombocytopenia needs an urgent and extensive evaluation.

Ghoneim., *et al*. [38] reported that thrombocytopenia in patients with community acquired pneumonia is associated with more severe pneumonia, severe sepsis, septic shock, need for ICU admission, need for invasive MV, and poor outcome.

Multivariate logistic regression analysis for prediction of mortality in our study revealed that mechanical ventilation and platelet count are independent predictors of mortality. Many studies have demonstrated that mechanical ventilation is associated with complication; the weaning period may comprise up to 40% of MV days [39,40]. Epstein [41] reported that weaning from MV is difficult for 30% of patients, and such patients showed a higher mortality rate and that study agreed with our results regarding mechanical ventilation as independent predictor of mortality in PICUs.

Conclusion

Neutrophil to lymphocyte ratio (NLR) is not useful for diagnosis of sepsis or prediction of prognosis of critically ill children. Mechanical ventilation and platelet count are more useful for that purpose.

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Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Disclosure

The authors declare no conflicts of interest related to this work.

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Informed Consent

Informed consent was obtained from the parents (or legal representative).

Author Contributions

Conceptualization, Nagwan Saleh, Fady El-Gendy; Formal analysis, Nagwan Saleh and Muhammad El- Mekkawy; Funding acquisition, Nagwan Saleh, Fady El-Gendy, Muhammad El- Mekkawy, and Eman Barbary; Investigation, Eman Barbary, Nagwan Saleh; Methodology, Nagwan Saleh, Fady El-Gendy, Muhammad El- Mekkawy, and Eman Barbary; Resources, Nagwan Saleh, Fady El-Gendy, Muhammad El-Mekkawy, and Eman Barbary; Supervision, Nagwan Saleh, Fady El-Gendy, Muhammad El- Mekkawy, and Eman Barbary; Writing - review and editing, Nagwan Saleh. All authors have read and agreed to the published version of the manuscript.

Ethical Approval

All procedures performed in the study were in accordance with the ethical standards of the Menoufia University and Faculty of Medicine.

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