ROLE OF HEMATOLOGICAL INDICES IN PREDICTION OF OUTCOME OF CRITICALLY ILL CHILDREN IN PEDIATRIC INTENSIVE CARE UNITS

By

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ABSTRACT

Introduction: *Early identification of children at high risk of mortality properly is essential for timely changes in the management and enhancement of the clinical outcomes.*

Aim of the study: *This work aims to use some of the simple red blood cells (RBCs), white blood cells (WBCs), and platelet indices present in routine complete blood count (CBC) done to all critically ill patients as a pragmatic marker for outcome in pediatric critical illness.*

Patients and Methods: *This cross-sectional study was conducted on 103 children admitted to the pediatric intensive care unit of El- Sayed Galal university hospital and they were selected by a simple random method during the period from the beginning of December 2020 to the end of April 2021. 53 were males and 50 were female's patient ages ranged from 2 months to 14 years old and including all critically ill children admitted regardless of the underlying disease. The study was approved by the ethical committee of the faculty of medicine, Al-Azhar University. Informed parental consent from one of the parents was obtained before enrollment in this study.*

Results: *The commonest age of admission was from1 to 5 years old, while the highest mortality rate was in children below 1 year old. And the main causes of admission were due to respiratory problems followed by neurological insults. Regarding hematological indices it is noticed that Red blood cells(RBCs) count, hemoglobin, hematocrit (HCT), lymphocytic count, platelet count, and platlecrit (PCT) were higher in survived while Red distribution width (RDW), mean corpuscular volume (MCV), neutrophilic count, neutrophil to lymphocyte ratio (NLR) and large platelet cell ratio(L-PCR) were higher in non-survived and p-value of all were < 0.05 and all of the mean corpuscular hemoglobin(MCH), mean corpuscular hemoglobin concentration (MCHC),total leucocytic count (TLC), monocytes, eosinophils, basophils, mean platelet volume(MPV), platelet distribution width (PDW), showing no significant difference between survived and non-survived. And survived stayed longer in PICUS.*

Conclusion: *This study shows a significant difference between survived and non-survived regarding hematological indices (RBCs count, hemoglobin, hematocrit, MCV, RDW, neutrophil count, lymphocyte count, NLR, platelet count, PCT, L-PCR), so hematological indices is of value in predicting mortality in critically ill children admitted to PICU.*

Keywords: *mortality, PICU, hematological indices, prognosis.*

INTRODUCTION

Early identification of children at high risk of mortality properly is essential for timely changes in the management and enhancement of the clinical outcomes **(Teheux et al., 2019)**.

Although critical care has improved significantly over the last few decades in pediatric patients, the prediction of mortality in a general population of critically ill children has failed to be accurately achieved **(Bai et al., 2014)**.

One of the main measures of the efficiency of the intensive care unit “ICU” is the mortality rate. However, the severity of patients' illnesses, co morbidities, and demographics all strongly affect the mortality rate **(Kao, Priestap, and Donner, 2016)**.

Red distribution width (RDW) is a widely available and low-cost test. Elevated RDW reflects marked anisocytosis that may be caused by any disease involving the destruction or production of (RBCs). Studies have shown that RDW can be used as a mortality predictor in critically ill patients **(Fava et al., 2019)**.

Numerous previous studies have explained the timing of platelet counts and their role in critically ill patients, especially in patients with sepsis. Moreover, the potential effects of MPV and its impacts on mortality in critically ill children are little understood **(Vardon-Bounes et al., 2019)**.

MPV has been considered an index for inflammation, disease activity, and efficacy of anti-inflammatory treatment in several chronic inflammatory disorders, such as inflammatory bowel disease, rheumatoid arthritis, and ankylosing spondyloarthritis **(Korniluk et al., 2019)**.

White blood cells (WBCs) count has been identified as an important systemic inflammation marker. Changes in WBC (neutrophil and lymphocyte) were associated with inflammatory diseases. The neutrophil to lymphocyte ratio (NLR) is a rapid and simple parameter of systemic inflammation and stress, which expresses the severity of the

disease in critically ill patients **(Liu et al., 2019)**.

AIM OF WORK

This work aims to use some of the simple red blood cells (RBCs), white blood cells (WBCs), and platelet indices present in routine complete blood count (CBC) done to all critically ill patients as a pragmatic marker for outcome in pediatric critical illness.

PATIENTS AND MATERIALS

This cross-sectional study was conducted on 103 children of both sexes admitted to the pediatric intensive care unit of El- Sayed Galal university hospital during a fixed period from the beginning of December 2020 to the end of April 2021.

I. Patients:

Inclusion criteria:

- All Critically ill Children admitted to the pediatric intensive care unit (PICU) regardless of the underlying disease.
- Age from 2 months to 14 years old of both sexes.

Exclusion criteria:

- Children below 2 months or above 14 years old.
- Failure to obtain parental informed consent.

II. Methods:

All the studied cases were subjected to the following:

A. Complete detailed history taking with emphasis on age, gender, demographic distribution, and history of illness regarding respiratory, cardiovascular, neurological, and gastrointestinal systems.

B. Complete general and systemic examinations with emphasis on the conscious level, vital signs, colors, and systemic examination regarding respiratory, cardiovascular, neurological, and abdominal systems.

C. **Complete blood count on admission:** by sysmex x5-800 (sysmex corporation, japan) with emphasis on Red blood cells indices including: (Hb, hematocrit, RBCs count, MCV, MCH, MCHC, and RDW).

White blood cells indices including: (total and deferential).

Platelet indices including: (platelet count, MPV, PDW, and P_LCR)

D. Specific investigations: according to situations e.g., Chest X-ray, CT brain, Echocardiology.

E. Close follow up of all patients: till hospital discharge to determine the occurrence of morbidity and mortality

Lastly our studied cases were divided into two groups (survived and non- survived)

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Ethical consideration:

1. Written informed consent was obtained from parents or legal guardians before the study.
2. Approval by the local ethical committee was obtained before the study.
3. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
4. All the data of the patients and results of the study are confidential &the patients have the right to keep it.
5. The patient has the right to withdraw from the study at any time.

Statistical analysis of the data:

Results were collected, tabulated, and statistically analyzed using SPSS version 20. Continuous variables in two groups will be compared using the independent t-test, and if more than 3 groups will be compared, we use the analysis of variance. Continuous variables are expressed as the mean ± standard deviation. Categorical variables will be analyzed by the chi-square test or Fisher's exact test. Pearson correlation analysis to examine the relationship between two continuous variables, and multiple logistic regression analyses will be performed to find independent predictive factors. A P value of less than 0.05 was considered statistically significant.

RESULTS

Our results will be demonstrated in the following tables

Table (1): Sociodemographic characteristics of the study cases

Variables		Survived	Non-survived	P-value
Outcome n (%)		65 (63.10%)	38 (36.89%)	_
Length of stay		11 ± 7	8 ± 4	**0.017[a]***
Age (years)	**Mean± SD**	6.2 ± 4.3	4 ±3.9	**0.011[a]***
Age distribution	**< 1 year**	13 (20 %)	14 (36.84%)	
	1 - <5	16 (24.61%)	12 (31.57%)	
	5 - <10	18 (27.69%)	7 (18.42%)	
	≥ 10	18 (27.69%)	5 (13.15%)	
Gender	**Male n (%)**	35 (53.85%)	18 (47.37%)	0.525[b]
	Female n (%)	30 (46.15%)	20 (52.63%)	
Birth order	**1st**	13 (20%)	11 (28.94%)	
	2nd	17 (26.15%)	8 (21.05%)	
	3rd	16 (24.61%)	5 (13.15%)	0.473[b]
	4th	10 (15.38%)	9 (23.68%)	
	>4th	9 (13.84%)	5 (13.15%)	
Residence	**Urban**	39 (60%)	17 (44.74%)	0.133[b]
	Rural	26 (40%)	21 (55.26%)	

*P is significant is at <0.05 a student t-test; b chi-square test

This table shows that (63%) of admitted cases were survived and (37%) were not survived and there is a significant difference between both groups regarding the length of hospital stay and mean age of studied groups. while no significant difference regarding gender, birth order, and residence.

Table (2): Main Causes of PICU Admissions (Diagnostic Categories)

System	Total (n) %
Respiratory	23 (22.33%)
Neurological	18 (17.47%)
Endocrinal	15 (14.56%)
GIT	16 (15.53%)
Surgical	11(10.67%)
Polytrauma	8 (7.76%)
Renal	7 (6.79%)
Cardiology	4 (3.88%)
Others	1 (0.97%)

This table shows the main causes of admission and shows that the most frequent cause is respiratory diseases (22.33%) followed by CNS insult (17.47%).

Table (3): Mortality Rates in Different Diagnostic Categories

System	Total (n)	Survived	Non-survived	P_value
Respiratory	23	11 (47.82%)	12 (52.17%)	0.41
Neurological	18	9 (50 %)	9 (50 %)	0.19
Endocrinal	15	12 (80%)	3 (20%)	0.52
GIT	16	12 (75%)	4 (25%)	0.34
Surgical	11	8 (72.72 %)	3 (27.27%)	0.81
Polytrauma	8	4 (50 %)	4 (50 %)	0.97
Renal	7	5 (71.42 %)	2 (28.57%)	0.82
Cardiology	4	3 (75 %)	1 (25 %)	0.89
Others	1	1 (100%)	0 (0 %)	0.74

This table illustrates the mortality rates in different diagnostic categories and shows that the commonest diagnostic categories associated with mortality are Respiratory cases (52.17%) followed by neurological and polytrauma and cases by (50%). With insignificant difference between both groups regarding the system affected.

Table (4): Mean values of vital Signs among the studied cases

Variable		Survived	Non- Survived	P-value
SBP	Mean ±SD	108 ± 18	96 ± 22	**0.003***
DBP	Mean ±SD	65 ± 18	55 ± 15	**0.004***
Pulse	Mean ±SD	136 ± 24	140 ± 33	0.480
Respiratory rate	Mean ±SD	39 ± 11	42 ± 11	0.184
Temperature	Mean ±SD	37.3 ± 0.9	37.5 ± 1.2	0.339

SBP systolic blood pressure; DBP diastolic blood pressure

This table shows a significant difference between survived and non- survived regarding both systolic and diastolic blood pressure. While no significant difference in respiratory rate, pulse, and temperature.

Table (5): Comparison between Survivors and Non-survivors Regarding RBC Indices

Variable		Survived	Non- Survived	P-value
RBCs (x 10^{12})	Mean ±SD	4.29 ±0.82	3.75 ±0.97	**0.003***
Hb (mg/dl)	Mean ±SD	10.8± 2.5	9.5± 2.7	**0.015***
HCT (%)	Mean ±SD	31.53 ±6.03	28.71 ±7.63	**0.040***
MCV (fl)	Mean ±SD	73.6 ±9.1	77.7 ±8.5	**0.026***
MCH (PGM)	Mean ±SD	24.55 ±4.04	26 ±3.4	0.065
MCHC (gm/dl)	Mean ±SD	33.51 ±2.55	33.57 ±2.03	0.901
RDW cv (%)	Mean ±SD	15.7 ±2.3	17.8 ±3.9	**0.000***
RDW sd (fl)	Mean ±SD	44.4 ±8.2	55.4 ±15.8	**0.000***

Hb hemoglobin; HCT hematocrit; RBCs red blood cells; MCV mean corpuscular volume; MCH mean corpuscular hemoglobin; MCHC mean corpuscular hemoglobin concentration; RDW CV = Red cell distribution width (coefficient variant);RDW SD = Red cell distribution width (standard deviation) *P is significant at <0.05; student t-test

This table shows a significant difference between survived and non- survived regarding RBCs count, Hb, HCT, MCV, and RDW. While no significant difference in MCH, MCHC.

Table (6): WBC Indices Among the Survivors and Non-Survivors

Variable		Survived	Non- Survived	P-value
TLC	Mean ±SD	14.8 ± 7.1	18.23 ± 11.1	0.058
Neutrophils	Mean ±SD	9.45 ± 6.8	14.5 ± 7.35	**<0.001***
Lymphocytes	Mean ±SD	3.6 ± 1.35	1.9± 1.1	**<0.001***
Monocytes	Mean ±SD	0.95 ±0.25	1± 0.15	0.265
Eosinophils	Mean ±SD	0.76 ± 0.23	0.81± 0.29	0.336
Basophils	Mean ±SD	0.38± 0.10	0.41± 0.09	0.130
NLR	Mean ±SD	1.9± 0.83	7.4± 1.4	**<0.001***

TLC total leukocyte count; NLR neutrophil to lymphocytic ratio *p is significant at < 0.05; student t-test

This table illustrated that Neutrophils were significantly higher in non-survivors than survivors, but lymphocyte count is significantly lower in non-survivors. Also show no significant difference between survivors and non-survivors in TLC, monocytes, eosinophils, basophils. NLR was statistically significantly higher in non-survivors than survivors.

Table (7): Platelet Indices among Survivors and Non-Survivors

Variable		Survived	Non- Survived	P-value
PLT (*10^3 /ml)	Mean ±SD	253 ± 97	190 ± 105	**0.002***
PCT (%)	Mean ±SD	0.27± 0.12	0.09± 0.03	**<0.001***
L-PCR (%)	Mean ±SD	19.7± 5.6	25.3± 12.3	**0.002***
PDW sd (fl)	Mean ±SD	13.37± 5.3	15 ± 5.9	0.151
MPV (fl)	Mean ±SD	8.7 ±1.3	9.1 ±1.6	0.170

PLT; platelet count PCT plateletcrit; P-LCR platelet large cell ratio PDW sd platelet distribution width standard deviation; MPV mean platelet volume; *P is significant at <0.05

This table illustrates that the platelet count and plateletcrit were significantly decreased in non-survivors but the P-LCR is significantly increased in non-survivors. Although PDW and MPV are not significantly different between groups.

DISCUSSION

The primary mission of pediatric intensive care units (PICU) is to improve the survival of critically ill children **(Lu et al., 2015)**.

Complete blood count (CBC) is one of the most frequently used laboratory tests in medicine. It reflects the inherent physiological imbalance of the patient's disease state. Several clinical prediction

models, such as pediatric critical illness score (PCIS), systemic inflammatory response syndrome (SIRS) scores, and pediatric risk of mortality III have incorporated CBC to enhance its predictive performance. But some parameters in the CBC may be overlooked **(Hang et al., 2021)**.

Recently, some parameters in CBC were considered to be reliable indicators in terms of the severity and prognosis of certain diseases **(Li et al., 2017)**.

Our study showed that the mortality rate in our PICU was (37%) while in a study by **Honna et al., (2016)** was (45.7%). also, the highest mortality rate was during the 1st year of life and this correlated with the studies by **Rady et al., (2014)** and **Alsuheel and Shati. (2014)** where the highest mortality rates were found in patients <1 year of age. These facts point to increased vulnerability in this age group and probably a need to be more aggressive in their management to improve outcomes.

Our study showed that the mean length of stay in survived was (11 ± 7) days while it was in non-survived (8 ± 4) days. also, the mean age among the survivors was (6.2± 4.3) years while it was (4±3.9) years in non-survived and showed a significant difference between studied groups regarding the length of stay and mean age of studied groups. While showing no significant difference regarding birth order and residence.

Our study disagreed with the study by **Gadappa et al., (2018)** and **Choi et al., (2017)** where there was no significant correlation of age group with mortality.

In our study male represent (51.46%) of admitted cases while female represents (48.54%). the mortality rate was higher in females than males which consist (52.63%) in females and (47.37%) in males with an insignificant difference.

Regarding gender, only a few studies disagreed with our study and showed significant differences in mortality. **Ala et al., (2012)** and **Rashma et al., (2018)** reported a male preponderance. While in the prospective study performed by **Purbiya et al., (2017)** mortality among girls was higher.

Our study showed that the main causes of admission were respiratory diseases (22.33%) followed by CNS insult (17.47%). and the highest mortality rates were in respiratory cases (52.17%) followed by neurological and polytrauma cases by (50%).

In agreement with our results **Abd El- Hameed et al., 2017** revealed that among 100 children admitted to the PICU, the most common admitted category was those with respiratory diseases 33%, CNS 26%, GIT 17%, sepsis 14%, cardiac or endocrine 4% and those admitted for surgical purposes were at the bottom 2%.

But this was contrasted with the result of **Ramby et al., 2015** who reported that cardiovascular as the commonest admitted category 27%, followed by sepsis 17.4%, respiratory 16.3%, neurologic 12.9%, airway surgery 5.9%, GIT/hepatic 4.7%, renal 3.7%, hematologic/oncologic 3.5%, orthopedic 3.4%, trauma was the least common admitted category 1.3%, and 3.9% were admitted for other purposes.

Our study showed that as regards the mean systolic blood pressure among survived is (108 ± 18) mmHg and non-survived is (96 ± 22) mmHg. Also, mean diastolic blood pressure among survived is (65 ± 18) mmHg and non-survived is (55 ± 15) mmHg showing a significant difference between survived and non-survived regarding both systolic and diastolic. While no significant difference in respiratory rate, pulse, and temperature.

In our study, it Is noticed that Hb level, hematocrit and RBCS count were higher in survived than non- survived, while MCV and RDW are higher in non- survived than survived and all of these values are of significant difference but there is no significant difference in both MCH and MCHC.

Our study agreed with **Gadappa et al., (2018)** as anemia was noted in 57% of patients. A statistically significant correlation between mortality and anemia existed ($p = 0.009$). Similarly, **Hashemi et al., (2017)** reported anemia in 52.7% of the patients; it was more frequent in patients with elevated RDW.

This disagreed with **Sachdev et al., (2018)** where there was no significant difference in the hemoglobin levels between survivors and deaths. Mortality was associated with high RDW but not with hemoglobin levels. This may be due to the involvement of inflammatory processes in the rise of RDW values in critically ill children.

In accordance with our results, the study of **Abd El- Hameed et al., 2017** reported that there was a significant increase in RDW and the frequency of anemia in mortality patients compared with others without mortality, while

showing a significant decrease in Hb and MCV levels in mortality compared to others without mortality.

Increased RDW values reflect greater variability in RBC size, which generally indicates dysfunctional erythropoiesis, shortened RBC lifespan, or premature release of reticulocytes. Recently, there has been increasing awareness of a positive association between RDW and risk of both morbidity and mortality in several disease states, principally in critically ill adults **(Lorente et al., 2014)**.

In agreement with our results **Gadappa et al., (2018)** proved a statistically significant positive correlation between mortality and RDW.

Our study showed a significant difference between studied groups regarding neutrophilic, lymphocytic counts, and NLR while no significant difference between survivors and non-survivors regarding TLC, monocytes, eosinophils, basophils.

White blood cell (WBC) count has been identified as an important systemic inflammation marker. Recent reports demonstrated that the WBC count had an independent ability to predict all-cause mortality (Liu et al. 2019).

Recently research has indicated that the neutrophil to lymphocyte ratio (NLR) is an independent predictor for clinical outcomes for various cancer types, cardiovascular disorders, and ischemic stroke **(Yin Y et al., 2015)**.

Our results were supported by Mathews et al., 2019as they showed that increasing NLR is associated with worsening in the clinical condition and an increase in the mortality in the patients.

Our study showed that platelet count and plateletcrit are significantly decreased in non-survivors but the P-LCR is significantly increased in non-survivors. Although PDW and MPV are not significantly different between groups.

Thrombocytopenia occurring in critically ill patients is the result of hemodilution, increased platelet consumption, increased platelet destruction (immune mechanisms), and increased platelet sequestration. Septicemia-related destruction of platelets increases production and release into the peripheral blood of larger and younger platelets. Later, however, there may be bone marrow suppression **(Gulcu et al., 2013)**.

Our study agreed with **Purbiya et al., (2017)** where

thrombocytopenia was evident in 54% of non-survivors and 9.8% of survivors.

Similarly, the study by **Choi et al., (2017)** platelet count was 3-fold higher in survivors than in non-survivors. Also, **Russul et al, (2012)** reported that thrombocytopenic children have a higher incidence of bleeding and higher mortality.

Gulcu et al., 2013 showed that mean platelet volume (MPV) and platelet distribution width (PDW) were useful in the diagnosis of sepsis, and patients with PDW of more than 18% have a higher risk of death.

Our study disagreed with **Purbiya et al., (2017)** where the mean MPV and PDW were significantly higher in non-survivors ($p< 0.0008$ and $p= 0.0015$) respectively.

This explains why in our study LPCR was higher in non-survivors than survivors with a significance p-value (0.002) although MPV was not a significant p-value (0.170).

CONCLUSION

Haematological indices are simple, rapid, and inexpensive tests. This study shows a significant difference between survived and non-survived regarding some of the haematological indices, so haematological indices are of value in predicting mortality in critically ill children admitted to PICU.

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دور المؤشرات الدموية في التنبؤ بنتائج الأطفال المصابين بأمراض خطيرة في وحدات الرعاية المركزة للأطفال

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التحديد المبكر للأطفال المعرضين لخطر كبير للوفاة بشكل صحيح وسريع أصبح ضروريا من أجل إحداث تغييرات في التعامل مع الحالات في الوقت المناسب وتحسين النتائج السريرية.

الهدف من هذه الرسالة هو استخدام بعض مؤشرات كرات الدم الحمراء وكرات الدم البيضاء والصفائح الدموية كعلامات عمليه للتنبؤ بالحالةالصحية للأطفال المصابين بحالات حرجه في وحدات الرعايةالمركزة للأطفال.

أجريت هذه الرسالة على 103حالة من كلا الجنسين تم حجزهم بوحدة الرعايةالمركزة للأطفال مستشفى السيد جلال الجامعي – جامعه الازهر بالقاهرة خلال الفترة من ديسمبر 2020 الى نهاية شهر ابريل 2021.

توصلت هذه الدراسة الي الاتي:

1. ارتفاع معدل الوفيات بالنسبة للأطفال الأقل عمرا.
2. اهم سبب للحجز بوحدات الرعاية المركزة للأطفال هو امراض الجهاز التنفسي وأيضا كانت امراض الجهاز التنفسي ذات اعلى معدل وفيات.
3. ارتفاع كلا من الضغط الانقباضي والانبساطي بالنسبة للأطفال الناجين عن غير الناجين.
4. عدد كرات الدم الحمراء ونسبه الهيموجلوبين والهيماتوكريت اعلى في الناجين أكثر من غير الناجين بينما كانت متوسط حجم الخلايا ومعدل الاختلاف في الحجم والاشكال بالنسبة لكرات الدم الحمراء اعلى في غير الناجين أكثر من الناجين.
5. نسبه الخلايا متعددة النواه أكثر في غير الناجين بينما عدد الخلايا الليمفاوية يكون اقل بشكل ملحوظ في غير الناجين.
6. وكانت نسبه الخلايا متعددة النواه الى الخلايا الليمفاوية اعلى في غير الناجين من الناجين.
7. ينخفض عدد الصفائح بشكل كبير في غير الناجين أكثر منه في الناجين.

8. ونسبه خلايا الصفائح الكبيرة اعلى في غير الناجين منه في الناجين.