The early predictive value of certain hematological parameters in suicidal cases with acute single paracetamol overdose

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KEYWORDS
Acetaminophen, Liver, NLR, PLR, MLR.

ABSTRACT

Paracetamol-induced hepatotoxicity is one of the most prevalent causes of drug-induced liver injury that may seriously end with fulminant liver failure so early prediction of acute liver injury seems to be helpful. This study aimed to evaluate the early predictive value of some hematological parameters as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR) and red cell distribution width (RDW) in acute single paracetamol overdose. The study was conducted on 40 patients with acute paracetamol overdose presented to the Poison Control Center (PCC) of Minia University Hospital during the period from 1st February 2022 to 31st January 2023 and the patients were classified into 3 groups (mild, moderate and severe) based on the possibility of developing hepatotoxicity. The patient's mean age was 27.75 ± 7.3 years with female predominance (67.5%) and the majority came from urban areas (67.5%). Intentional drug overdose was the only mode of poisoning in all patients. A statistically significant difference was observed as regard the ingested dose which ranged from 5-15 gm. Elevated liver enzymes were recorded among patients of moderate and severe groups in the 2nd and 3rd days of admission. Statistically significant neutrophilia and lymphopenia was recorded with significant increase in NLR, PLR and MLR from the day of admission and during follow up in the moderate and severe groups. The average hospital stay was 4.2 ± 1.5 days and no mortality was recorded. The study demonstrated that NLR, PLR and MLR could act as early predictors of paracetamol-induced acute liver injury.

Introduction

Paracetamol is one of the most widely used analgesics and antipyretics in the world. It is the commonest over-the counter medication which is easily taken without a medical prescription with a wide safety profile at approved therapeutic doses (Schilling et al., 2010). Paracetamol-induced hepatotoxicity is one of the most prevalent causes of drug-induced liver injury (DILI) and acute liver failure either after intentional or unintentional ingestions in different age groups (Roh et al., 2018).

Paracetamol-induced hepatotoxicity is known to be a result of accumulation of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) after drug overdose (Shan et al., 2018). Accumulated amount of non-detoxified toxic metabolite (NAPQI) binds to the cellular biological macromolecules such as proteins, lipids and nucleic acids resulting in mitochondrial dysfunction which considered an important step in hepatotoxicity (Foufelle and Fromenty, 2016).

The measurement of paracetamol plasma level is expensive and often not available in labs. Therefore, alternative methods are needed to predict the severity of

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acute paracetamol overdose. Hematological parameters as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR) and red cell distribution width (RDW) are now commonly used as predictors of acute inflammation because they are easy, fast, and affordable (Shaafi et al., 2022).

Assessing white blood cell differential count, including neutrophils, lymphocytes, monocytes, platelet count, and RDW, can provide valuable information about liver and renal inflammation by estimating ratios like NLR, PLR, and MLR (Craig et al., 2014).

This study aimed to evaluate the early predictive and prognostic value of some hematological parameters as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR) and red cell distribution width (RDW) in acute liver injury after acute single paracetamol overdose.

Patients and methods

The current study was a clinical prospective study which was conducted on 40 patients with acute single paracetamol overdose presented to the Poison Control Center (PCC) of Minia University Hospital during the period from 1st February 2022 to 31st January 2023.

Ethical approval was obtained from The Scientific Research Ethics Committee, Faculty of Medicine, Minia University (approval number: 273-2022). The confidentiality of the patient's data was maintained by using coding numbers.

Inclusion and exclusion criteria:

The study included all male and female patients above 18 years of age with a recent history of acute single paracetamol overdose and presented with a delay time between 1-24 hours. Patients with multiple paracetamol ingestions and those who presented with a delay of more than 24 hours were excluded from the study. Additionally, patients younger than 18 years of age, patients received treatment before arriving at PCC, patients with a previous history of liver or kidney disease, as well as those with a history of co-ingestions of other hepatotoxic or nephrotoxic agents and patients with a history of alcoholism or any drug abuse that may affect liver or kidney functions were also excluded.

The studied patients were classified into 3 groups based on the possibility of developing hepatotoxicity, determined by the concentration of paracetamol after 4 hours following ingestion (PRC) 4h). This time point is significant because it signifies the completion of paracetamol absorption and serves as the starting point for the Rumack-Matthew nomogram. The values were computed using the following equation: (PRC) 4h= (PRC) pl /$2e^{-(0.693/4)t}$ (Waring et al., 2008).

Where (PRC) 4h is the estimated plasma paracetamol concentration 4-hours post ingestion, (PRC) pl is the plasma paracetamol concentration at admission.

Groups:

- Mild group (I): included 18 patients with paracetamol plasma level 4 hrs post ingestion less than 150 µg /mL.
- Moderate group (II): included 14 patients with paracetamol plasma level 4 hrs post ingestion ranging from 150-200 µg /mL.
- Severe group (III): included 8 patients with calculated paracetamol plasma level 4 hrs post ingestion more than 200 µg /mL (Popiolek et al., 2021).

The required data was collected from each patient including socio-demographic data (age, sex, body weight and residence), intoxication data (drug dosage, mode of poisoning, delay time between exposure and hospital admission), and clinical data. Investigations done included serum paracetamol plasma level, liver enzymes (ALT and AST), prothrombin time (PT) and international normalized ratio (INR), complete blood picture with white blood cell differential count. Apart from paracetamol plasma level, all the laboratory tests were repeated daily for all examined patients as a follow up during hospital admission. The assessment of outcome and complications included the duration of hospital stay, the need for ICU admission and in-hospital mortality.

Statistical analysis

The collected data were coded, tabulated and statistically analyzed using SPSS program software version 25. Descriptive statistics were done for quantitative data by mean, standard deviation (SD), minimum and maximum of range and for non-parametric quantitative data by median and interquartile range (IQR) while for qualitative data by frequency and percentage.

Analyses were done between the three studied groups by One Way ANOVA test for parametric quantitative data followed by post hoc analysis between each two groups. Kruskal-Walli's test was done for non-parametric quantitative data between the three groups followed by Mann-Whitney test for non-parametric quantitative data between each two groups. Analyses were done for qualitative data between groups using Fisher Exact test.

Receiver Operating Characteristic (ROC curve) analysis was done for NLR, PLR and MLR on admission for prediction of paracetamol-induced hepatotoxicity and calculate area under the curve (AUC), optimal cutoff point, sensitivity, specificity, positive predictive value, negative predictive value and accuracy. The level of significance was taken at (P value ≤ 0.05).

Spearman's rank correlation was done between the different hematological parameters of the study in different times and case severity. R-values were different in strength as considered weak if (0-0.24), fair (0.25-0.49), moderate (0.50-0.74) and strong if ranged from (0.75 to 1).

Results:

Patient's age ranged from 19 to 45 years the mean age was 27.75 ± 7.3 years. The most affected age was 19-25 years in both sexes. There were noticeably more females (67.5%) than males (32.5%). Female predominance was recorded within the 3 studied groups with a statistically insignificant difference between them. The majority of patients came from urban areas (67.5%). The body weight distribution between the 3 studied groups ranged from 50 to 82 kg with the mean weight about 66.4 ± 7.8 kg (Table 1).

Table (1): Description of ranges and mean values of age and body weight using One Way ANOVA and of sex and residence using Fisher Exact test in the studied patients intoxicated with paracetamol (n: 40 patients).

		Mild (I)	Moderate (II)	Severe (III)	P value			
		n=18	n=14	n=8	3 groups	I vs II	I vs III	II vs III
Age (yrs.)	Range	(19-42)	(18-45)	(19-45)	0.269	0.109	0.649	0.384
	Mean ± SD	26.2±5.9	30.4±7.6	27.6±9				
Sex	Male	4 (22.2%)	5 (35.7%)	4 (50%)	0.359	0.400	0.157	0.512
	Female	14 (77.8%)	9 (64.3%)	4 (50%)				
Residence	Urban	12 (66.7%)	9 (64.3%)	6 (75%)	0.277	0.888	0.671	0.604
	Rural	6 (33.3%)	5 (35.7%)	2 (25%)				
Weight (kg.)	Range	(53-78)	(50-82)	(55-70)	0.435	0.416	0.525	0.210
	Mean ± SD	66±7	68.3±9.7	63.9±5.3				

P<0.01*: highly Significant - P<0.05: Significant - P>0.05: Non-significant. n: number. SD: standard deviation. Yrs: years. Kg: kilogram.

Intentional drug overdose for suicidal purposes was the only mode of poisoning in all examined patients in the present study and all patients were intoxicated through oral intake of paracetamol tablets. A statistically significant difference was observed as regard the ingested dose within the groups which ranged from 5-15 gm. The estimated delay time between overdose ingestion and hospital admission ranged from 3 to 15 hrs with the mean of 7.1±2.2 hrs as illustrated in table (2).

Table (2): Analysis of the mode of poisoning using Fisher Exact test, ingested dose (g) and delay time (hrs) between paracetamol ingestion and hospital admission using One Way ANOVA test in the studied patients intoxicated with paracetamol (n: 40 patients).

		Mild (I)	Moderate (II)	Severe (III)	P value			
		n=18	n=14	n=8	3 groups	I vs II	I vs III	II vs III
Mode of poisoning	Accidental	0 (0%)	0 (0%)	0 (0%)	1	1	1	1
	Suicidal	18(100%)	14(100%)	8(100%)				
	Homicidal	0 (0%)	0 (0%)	0 (0%)				
Ingested dose (g)	Range	(5-7.95)	(7.95-9.2)	(9.55-15)	<0.001*	<0.001*	<0.001*	<0.001*
	Mean ± SD	6.4±0.7	8.6±0.3	11.5±1.7				
Delay time (hrs)	Range	(3-12)	(3-13)	(6-15)	0.539	0.806	0.269	0.403
	Mean ± SD	6.9±2.9	7.2±3.1	8.4±2.9				

P<0.01*: highly Significant - P<0.05: Significant - P>0.05: Non-significant. n: number. SD: standard deviation. hrs: hours. g: gram.

Measured and calculated values of paracetamol plasma levels 4-hours post ingestion showed high results among patients of severe and moderate groups in comparison with patients of mild group with significant P values (<0.001). Elevated liver enzymes (ALT and AST) were recorded among patients of moderate and severe groups in comparison with patients of mild group in the 2nd and 3rd days of admission (Table 3).

Table (3): Analysis of the measured and calculated paracetamol plasma levels using Kruskal-Walli's test and serum levels of ALT and AST using One Way ANOVA test among patients of the studied groups 4-hours post ingestion (n: 40 patients).

			Mild (I)	Moderate (II)	Severe (III)	P value			
			n=18	n=14	n=8	3 groups	I vs II	I vs III	II vs III
Paracetamol level (µg/mL) Measured and calculated 4 hrs. post ingestion		Median IQR	94.5 (80-104.8)	169.5 (162.3-175)	292.5 (237.3-365)	<0.001*	<0.001*	<0.001*	<0.001*
ALT	On admission	Range	(19-55)	(20-45)	(15-45)	0.989	0.891	0.996	0.893
		Mean ± SD	31.3 ± 11.9	31.8±7.7	31.3 ±10.6				
	At day 2	Range	(20-53)	(105-270)	(175-350)	<0.001*	<0.001*	<0.001*	<0.001*
		Mean ± SD	31.8 ± 11.9	171.9±48.4	281.9±59.9				
	At day 3	Range	(18-55)	(175-400)	(250-650)	<0.001*	<0.001*	<0.001*	<0.001*
		Mean ± SD	32 ± 11.6	236.8±61.2	507.5±122.2				
AST	On admission	Range	(19-40)	(20-40)	(20-38)	0.320	0.163	0.361	0.781
		Mean ± SD	25.9 ± 6.3	28.9 ± 5.6	28.3 ± 5.2				
	At day 2	Range	(15-45)	(105-250)	(170-400)	<0.001*	<0.001*	<0.001*	<0.001*
		Mean ± SD	26.9±7.9	174.4±48.8	294.4±77.2				
	At day 3	Range	(20-42)	(175-410)	(370-600)	<0.001*	<0.001*	<0.001*	<0.001*
		Mean ± SD	28.8±6.6	261.1±66.3	488.8±81.3				

P<0.01*: highly Significant - P<0.05: Significant - P>0.05: Non-significant. n: number. SD: standard deviation. IQR: interquartile range. ALT: alanine aminotransferase. AST: aspartate aminotransferase Hrs: hours. µg/mL: microgram/milliliter.

Prothrombin time (PT) prolongation was recorded among patients of the moderate and severe groups on the 2nd and 3rd days of admission. Statistically significant differences were recorded between the three groups starting from the second day. Additionally significant P-values were detected on comparison of values of different times within the same group in moderate and severe groups. Statistical data revealed significant differences between groups as regard international normalized ratio (INR) values with a significant P value after comparison of groups with each other during second and third days of admission. Additionally, paired samples T test found significant P-values on comparison of INR at different times within the same group in moderate and severe groups (Table 4).

Table (4): Statistical analysis of prothrombin time (PT) and international normalized ratio (INR) using One Way ANOVA test in the studied groups intoxicated with paracetamol (n: 40 patients).

		Mild (I)	Moderate (II)	Severe (III)	P value			
		n=18	n=14	n=8	3 groups	I vs II	I vs III	II vs III
PT (sec)								
On admission	Range	(9-12)	(8-16)	(10-15)	0.810	0.539	0.682	0.919
	Mean ± SD	10.6±1.1	12.1±2	12±2.1				
At day 2	Range	(9-13)	(11-19)	(13-23)	<0.001*	<0.001*	<0.001*	<0.001*
	Mean ± SD	11±1.2	14.6±2.2	18.7±3.2				
At day 3	Range	(10-15)	(10-19)	(18-28	<0.001*	<0.001*	<0.001*	<0.001*
	Mean ± SD	11.9±1.6	15.9±2.5	22.8±3.4				
INR								
On admission	Range	(0.5-1.3)	(0.8-1.5)	(0.9-1.6)	0.130	0.651	0.051	0.118
	Mean ± SD	0.98±0.24	1±0.2	1.2±0.2				
At day 2	Range	(0.6-1.5)	(0.8-1.5)	(1-1.9)	0.007*	0.179	0.002*	0.038*
	Mean ± SD	1.05±0.25	1.2±0.2	1.4±0.3				
At day 3	Range	(0.8-1.6)	(0.9-2.2)	(1.1-2.3)	0.001*	0.008*	<0.001*	0.109
	Mean ± SD	1.04±0.25	1.4±0.4	1.7±0.4				

P<0.01*: highly Significant - P<0.05: Significant - P>0.05: Non-significant. n: number. SD: standard deviation. Sec: seconds.

Table (5) illustrates white blood cells differential count which includes relative neutrophils, lymphocytes and monocytes counts. Statistically significant differences were recorded in the form of relative neutrophilia and relative lymphopenia in the moderate and severe groups compared with the mild group from the day of admission and during the follow up. On the other hand, relative monocytes count revealed statistically insignificant changes either on admission or during the follow up.

Table (5): One-way ANOVA analysis of the relative lymphocytes, neutrophils and monocytes counts among the studied groups intoxicated with paracetamol (n: 40 patients).

		Mild (I)	Moderate (II)	Severe (III)	P value			
		n=18	n=14	n=8	3 groups	I vs II	I vs III	II vs III
Relative lymphocyte count (20%-40%)								
On admission	Range	(20-40)	(15-26)	(11-25)	< 0.001*	< 0.001*	< 0.001*	0.131
	Mean ± SD	30.5 ± 8	21 ± 3.5	18.75 ± 5.7				
At day 2	Range	(20-41)	(15-23)	(8-30)	< 0.001*	<0.001*	<0.001*	0.121
	Mean ± SD	30.6 ± 7	19.3 ± 2.5	16.9 ± 6.9				
At day 3	Range	(22-40)	(10-28)	(9-35)	< 0.001*	<0.001*	<0.001*	0.435
	Mean ± SD	30 ± 7	17.4 ± 4.3	17.9 ± 9				
Relative neutrophil count (40%-60%)								
On admission	Range	(43-59)	(50-80)	(50-80)	0.001*	0.008*	<0.001*	0.061
	Mean ± SD	52.9 ± 5	59 ± 8	65.6 ± 11				
At day 2	Range	(40-60)	(52-82)	(67-89)	< 0.001*	< 0.001*	< 0.001*	0.002*
	Mean ± SD	53 ± 6	63.5 ± 9	76.5 ± 8				
At day 3	Range	(45-60)	(62-92)	(73-95)	< 0.001*	<0.001*	< 0.001*	0.001*
	Mean ± SD	53 ± 5.9	70.6 ± 10	84 ± 7.4				
Relative monocyte count (2%-10%)								
On admission	Range	(2-9)	(4-9)	(4-10)	0.366	0.449	0.128	0.079
	Mean ± SD	5.9 ± 2.4	5.8 ± 1.7	7.1 ± 2.2				
At day 2	Range	(4-10)	(4.5-9)	(3.7-9)	0.772	0.241	0.352	0.428
	Mean ± SD	5.9 ± 1.9	6.4 ± 1.5	6.2 ± 1.8				
At day 3	Range	(4-8)	(4-9)	(2.2-8)	0.051	0.197	0.106	0.067
	Mean ± SD	5.8 ± 1.2	6.3 ± 1.7	5.1 ± 1.9				

P<0.01*: highly Significant - P<0.05: Significant - P>0.05: Non-significant. n: number. SD: standard deviation.

Regarding neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), a significant elevation above normal values was recorded from the day of admission and during the follow up among patients of severe and moderate groups compared with patients of mild group. Statistical analysis revealed a significant increase of monocyte to lymphocyte ratio (MLR) in patients of the moderate and severe groups compared with patients of the mild group from the day of admission and during the follow up as demonstrated in table (6).

One-way ANOVA test found insignificant differences in red cell distribution width (RDW) values in all examined patients intoxicated with paracetamol either on admission or during follow up (Table 6).

Table (6): One-way ANOVA analysis of changes in NLR, PLR, MLR and RDW between the studied groups intoxicated with paracetamol on admission and during follow up (n: 40 patients).

		Mild (I)	Moderate (II)	Severe (III)	P value			
		n=18	n=14	n=8	3 groups	I vs II	I vs III	II vs III
NLR (0.43-2.75)								
On admission	Range	(0.9-2.7)	(2.12-3.5)	(3.2-3.9)	<0.001*	<0.001*	<0.001*	<0.001*
	Mean ± SD	1.9±0.59	2.89±0.32	3.54±0.23				
At day 2	Range	(1.1-3.1)	(2.39-3.6)	(3.1-4.5)	<0.001*	<0.001*	<0.001*	0.035
	Mean ± SD	2±0.68	3.14±0.36	3.75±0.52				
At day 3	Range	(0.9-2.8)	(3-4)	(3.5-4.8)	<0.001*	<0.001*	<0.001*	<0.001*
	Mean ± SD	2.01±0.57	3.35± 0.32	4.02±0.43				
PLR (36.63-172.6)								
On admission	Range	(61-171.7)	(119-179)	(115.9-262.7)	0.004*	0.035*	0.002*	0.136
	Mean ± SD	118.8±35.3	159.3±17	181.4±49.9				
At day 2	Range	(53.8-177)	(120-193)	(144.7-218.2)	<0.001*	<0.001*	<0.001*	0.864
	Mean ± SD	119.8±36.7	162.4±19	180.2±24.3				
At day 3	Range	(48.6-197)	(120-220)	(135.2-361.7)	0.006*	0.030*	0.002*	0.196
	Mean ± SD	130.3±42.1	163.6±31.5	205.5±68				
MLR (0.1-0.25)								
On admission	Median	0.17	0.26	0.41	<0.001*	<0.001*	0.001*	0.161
	IQR	(0.12-0.21)	(0.21-0.39)	(0.29-0.5)				
At day 2	Median	0.2	0.26	0.39	0.002*	0.014*	0.003*	0.093
	IQR	(0.14-0.23)	(0.2-0.33)	(0.24-0.49)				
At day 3	Median	0.2	0.26	0.36	0.029*	0.073	0.019*	0.194
	IQR	(0.15-0.25)	(0.22-0.33)	(0.23-0.48)				
RDW (12%-16%)								
On admission	Range	(8-15.8)	(9-14.2)	(12.5-13.8)	0.550	0.986	0.309	0.336
	Mean ± SD	12.6±1.6	12.6±1.5	13.2±0.4				
At day 2	Range	(11-17)	(10-14.5)	(11-14)	0.791	0.500	0.735	0.827
	Mean ± SD	13.1±1.2	12.8±1.5	12.9±1				
At day 3	Range	(10.5-15)	(9-15)	(10.7-14.5)	0.751	0.868	0.534	0.466
	Mean ± SD	12.8±1	12.9±2	12.4±1.3				

P<0.01*: highly Significant - P<0.05: Significant - P>0.05: Non-significant. n: number. SD: standard deviation. IQR: interquartile range. NLR: neutrophil to lymphocyte ratio. PLR: platelet to lymphocyte ratio. MLR: monocyte to lymphocyte ratio. RDW: red cell distribution width.

Table (7) displays a significant positive correlation between the case severity and some hematological parameters (NLR, PLR and MLR) at different times from admission. However, there was insignificant correlation between the case severity and red cell distribution width (RDW) parameter.

Table (7): Spearman's correlation between the severity of cases and various hematological parameters in patients with paracetamol poisoning from day of admission and during follow up (n: 40 patients).

		Severity	
		R	**P value**
NLR	admission	0.790	<0.001*
	day2	0.752	<0.001*
	day3	0.732	<0.001*
PLR	admission	0.482	0.002*
	day 2	0.659	<0.001*
	day3	0.543	<0.001*
MLR	admission	0.685	<0.001*
	day 2	0.556	<0.001*
	day 3	0.425	0.006*
RDW	admission	0.179	0.269
	day 2	0.032	0.843
	day 3	-0.059	0.718

P<0.01*: highly Significant - P<0.05: Significant - P>0.05: Non-significant. R: Spearman's correlation coefficient. NLR: neutrophil to lymphocyte ratio. PLR: platelet to lymphocyte ratio. MLR: monocyte to lymphocyte ratio. RDW: red cell distribution width.

Table (8) and figure (1) present the ROC curve analysis of different hematological parameters on admission to assess early prediction of paracetamol-induced hepatotoxicity. Area under the ROC curve was 0.951 (95% CI = 0.832-0.994, P< 0.001) for neutrophil to lymphocyte ratio (NLR) on admission indicating excellent predictive performance, at a cut-off value above 2.7 with sensitivity 81.82%, specificity 100% and accuracy 90%. For platelet to lymphocyte ratio (PLR) on admission, the area under the ROC curve was 0.759 (95% CI = 0.598-0.880, P< 0.001) indicating fair predictive performance, at a cut-off value above 100 with sensitivity 95.45%, specificity 50% and accuracy 75%. For monocyte to lymphocyte ratio (MLR) on admission, the area under the ROC curve was 0.893 (95% CI = 0.754-0.968, P< 0.001) indicating good predictive performance, at a cut-off value above 0.2 with sensitivity 86.36%, specificity 72.22% and accuracy 80%.

Table (8): ROC analysis of different hematological parameters on admission for early prediction of paracetamol-induced hepatotoxicity (n: 40 patients).

	NLR admission	PLR admission	MLR admission
Optimal cutoff	>2.7	>100	>0.2
AUC	0.951	0.759	0.893
95% CI	0.832-0.994	0.598-0.880	0.754-0.968
P value	<0.001*	0.001*	<0.001*
Sensitivity	81.82	95.45	86.36
Specificity	100	50	72.22
PPV	100	70	79.2
NPV	81.8	90	81.2
Accuracy	90	75	80

P<0.01*: highly Significant - P<0.05: Significant - P>0.05: Non-significant. ROC: Receiver operating characteristic. AUC: area under curve.CI: confidence interval. PPV: positive predictive value. NPV: negative predictive value.

Considering the duration of hospital stay, the average stay was 4.2 ± 1.5 days with a statistically significant difference was recorded among the 3 examined groups. Long duration of stay was recorded among patients of moderate and severe groups with significant P-values (< 0.0001) in comparison with patients of mild group as illustrated in table (9). All examined patients were discharged after successful treatment protocol and no mortality was recorded.

Table (9): Analysis of variations in the period of hospital stay (days) among the studied patients intoxicated with paracetamol by Fisher Exact test (n: 40 patients).

	Mild (I)	Moderate (II)	Severe (III)	P value		
	n=18	n=14	n=8	I vs II	I vs III	II vs III
Hospital stay duration						
- Within 4 days	18 (100%)	6 (42.9%)	1 (12.5%)		<0.0001*	
- More than 4 days	0	8 (57.1%)	7 (87.5%)			
Range	(2-4)	(4-6)	(4-7)	<0.0001*	<0.0001*	0.151
Mean ± SD	3.3±0.7	4.7±0.83	5±1.1			

P<0.01*: highly Significant - P<0.05: Significant - P>0.05: Non-significant. n: number. SD: standard deviation.

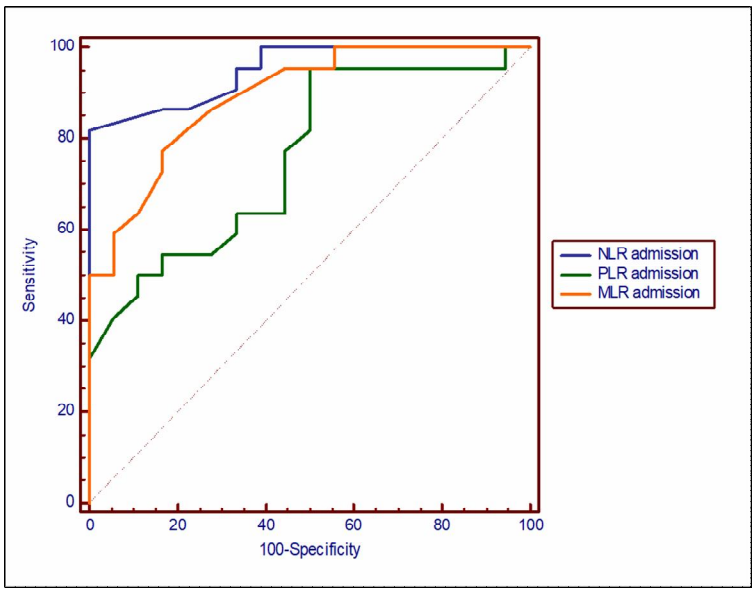

Fig. (1): ROC analysis of hematological parameters on admission for prediction of paracetamol-induced hepatotoxicity.

Discussion:

Paracetamol-induced hepatotoxicity is known to be a state of acute inflammation that may seriously end with fulminant liver failure and need urgent liver transplantation. So, early prediction of acute liver injury seems to be helpful. The objective of this study was to assess the value of neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR) and red cell distribution width (RDW) in predicting acute liver injury in 40 patients with acute single paracetamol overdose presented to the Poison Control Center (PCC) of Minia University Hospital during the period from 1st February 2022 to 31st January 2023.

Regarding socio-demographic variables in the present study, the age ranged from 19 to 45 years while the mean age was 27.75 ± 7.3 years. The most affected age was 19-25 years in both sexes. This is in agreement with Taylor et al. (2013) who found that individuals aged from 15-24 years were significantly more likely to have acetaminophen overdose compared with those aged 45-64 years.

The prevalence of paracetamol poisoning-related hospital admissions has increased among adolescents aged 15-19 years old as well as among young adults aged 20-29 years old according to a study conducted on Australian patients by Cairns et al. (2019). This may be due to the higher incidence of suicidal thoughts in this age group and the easy availability of paracetamol formulations even without medical prescriptions.

Distribution of gender in the present study revealed that paracetamol poisoning was more common in females (67.5%) than males (32.5%) with female to male ratio 2.1:1. Predominance of female in the study is in agreement with Shekunov et al. (2021) who also found a female predominance in their study.

Not coinciding with the current results, another study reported by Friðriksdóttir et al. (2021) showed that accidental overdose was more likely to occur in elderly males over the age of 65 and was

frequently linked with a poor outcome. In a similar way, the study done by Tukur and Bello (2021) to study the gender variations in pharmacokinetics of paracetamol revealed that females appear to have higher plasma paracetamol clearance than males so, men seems to be more susceptible to paracetamol toxicity even at therapeutic levels.

In the current study most cases came from urban areas (27 cases) (67.5%) compared with number of cases from rural areas (13 cases) (32.5%). These results are in accordance with Azekour et al. (2019) who found that acetaminophen poisoning mainly occurred in urban areas more than rural areas.

This might be explained by the fact that among the young individuals living in cities, drug poisoning appears to be a convenient, simple and painless method of suicide. According to the study conducted by Mekaoui et al. (2016), drug poisoning occurs mostly in metropolitan regions since most of rural residents utilize traditional remedies while pharmaceutical drugs are not commonly provided and even avoided.

The results of the current study revealed that there was no impact of body weight on toxicity among all studied patients with a body weight range of 50-82 kg and a mean weight about 66.4 ± 7.8 kg. According to Caparrotta et al. (2018), there was a direct relationship between acetaminophen toxicity and patient's body weight as the incidence of toxicity increased in low body weight patients and even therapeutic doses might cause toxicity if the body weight is less than 50 kg that is not coinciding with the results of the present study.

Intentional drug overdose for suicidal purposes was the only mode of poisoning in the current study and all the patients were intoxicated via consumption of paracetamol tablets. This is in line with a study done by Thusius et al. (2019) about intentional and inadvertent acetaminophen overdoses who found that approximately three-quarters of overdoses (76.3%) were suicidal and the remaining quarter only (23.3%) was accidental.

Similarly, the rate of suicidal and accidental overdoses was determined to be 69% and 25% respectively in a study conducted by Myers et al. (2007) on paracetamol overdose emergency room visits in Canada. Predominance of suicidal mode of poisoning may be explained by the fact that the poisoning requires significant amounts of the drug in relation to the patient's body weight needing intentional intake.

However, a study done by Saab et al. (2016) revealed that accidental intake of paracetamol overdose was the leading cause of acute liver failure in the United States.

Statistically significant difference between groups was found regarding the ingested dose of paracetamol with higher ingested doses were recorded in the moderate and severe groups. It ranged from 5-15 g. The mean ingested doses ± standard deviations were 6.4±0.7, 8.6±0.3, 11.5±1.7 g in mild, moderate and severe groups respectively. Similarly Zyoud et al. (2012) found that an ingested dose more than 8 g was associated with acetaminophen plasma level more than 150 mg/L which was associated with a higher risk of toxicity.

The time span from taking an overdose to being hospitalized appears to be a crucial factor in determining the prognosis and the likelihood of hepatotoxicity. In the present study, there was no significant difference in the delay time among the examined groups. It ranged from 3 to 15 hours, with a mean of approximately 7.3 ± 3 hours.

In a similar way, the study done by Doyon and Kelin-Schwartz (2009) to evaluate

the effectiveness of intravenous NAC administration in early acute acetaminophen poisoning revealed that patients with high toxic doses of acetaminophen developed hepatotoxicity whatever the time of hospital presentation.

Measured and calculated paracetamol plasma levels 4 hrs post ingestion in all studied patients (PRC)4hrs revealed a statistically significant difference between them. These results are in agreement with the study done by Popiolek et al. (2021) which classified patients into 3 groups (mild, moderate and severe) in order to assess the risk factors for hepatotoxicity in adults after paracetamol overdose. Measurement of paracetamol plasma levels on admission for all patients and calculation of (PRC)4hrs also revealed statistically significant differences among the studied groups.

Considerable elevation was detected in liver aminotransferases ALT and AST during the 2nd and 3rd days of admission in patients of moderate and severe groups in comparison with patients of mild group with statistically significant differences between them.

These results are in accordance with Kojidi et al. (2022) who revealed significant elevations in liver enzymes within moderately and severely intoxicated groups with paracetamol compared to mildly intoxicated group. Additionally, according to the case study done by Katzman and Levine (2023) which experienced a progressive elevation of liver transaminases over a period of 4 days in an adult patient who consumed a massive toxic dose of paracetamol despite early treatment with N-acetyl-cysteine.

There were significant changes in the coagulation profile among patients of moderate and severe groups detected during 2nd and 3rd days after overdose intake in the form of prolonged prothrombin time (PT) and elevated international normalized ratio (INR) values.

These findings are lined up with the case study introduced by Arshad and Bangash in (2022) who recorded acute liver injury with acute coagulopathy and highly elevated INR value of 5.5 with jaundice and encephalopathy in a 30-year-old female patient who presented to the emergency department after ingestion of a large dose of acetaminophen (30 g). Additionally, Yoon et al. (2023) recorded another case of coagulopathy with INR >8.7 on admission of a 36-years-old female patient who was experiencing fulminant hepatic failure following large ingested dose of paracetamol (40 g).

On the other hand, these results contradict the findings of Ghannoum et al. (2016), who conducted a case study on an 18-year-old female patient who arrived at the emergency department after consuming 100 grams of paracetamol tablets. Despite experiencing a poor overall condition, agitation, and changes in mental state, the patient's liver function and coagulation profile remained unaffected.

Regarding the white blood cells differential count which included neutrophils, lymphocytes and monocytes, the current results revealed statistically significant changes in neutrophils and lymphocytes counts among patients of the moderate and severe groups compared with patients of the mild group, in the form of increased neutrophils count and decreased lymphocytes count from the day of admission and during the follow up. On the other hand, the monocytes count revealed statistically insignificant changes in the all groups either on admission or during the follow up.

Hematological parameters are significantly impacted by liver diseases whether acute, chronic or acute-on top of

chronic. Neutrophils, lymphocytes, monocytes, and platelets play crucial roles in both the inflammatory and immune systems. Although these components are vital for resolving hepatic injury, they can also contribute to the aggravation of hepatic inflammation and injury. So, their ratios may act as a mirror for the hepatic pathology (Mao and Wu, 2020).

After paracetamol overdose, strong systemic inflammatory and immune responses are developed resulting in dysfunctions, changes and redistribution of immune and inflammatory cells particularly granulocytes as neutrophils, lymphocytes, platelets and monocytes (Antoniades et al., 2012). Different studies revealed that circulating immune and inflammatory cells specially neutrophils, macrophages and lymphocytes are involved in paracetamol-induced hepatic necrosis through massive infiltration within necrotic hepatocytes that ends by aggravation of hepatic necrosis or fortunately may help in hepatic regeneration (Krenkel et al., 2014).

These results are in accordance with the study done by Zahorec (2021) which revealed that neutrophilia and lymphopenia occur as a leucocytic response to inflammation either acute or chronic. As a result, the division of the absolute neutrophil count over the absolute lymphocyte count appears to be an effective strategy for predicting and evaluating the body's inflammatory status.

Neutrophil to lymphocyte ratio is the most often used hematological parameter nowadays in acute inflammatory conditions. It is obtained via division of absolute or relative neutrophil count over absolute or relative lymphocyte count. The present study revealed significant increase in its values in patients with moderate to severe toxicity compared to patients of mild toxicity which was detected from day of admission and during the follow up with a significant positive correlation with the case severity.

The ROC curve analysis of NLR parameter on admission revealed that the area under curve (AUC) was 0.951 which indicated an excellent predictive performance with sensitivity and specificity of 81.82 % and 100 % respectively at a cutoff value of more than 2.7 and an accuracy of 90 %.

During paracetamol-induced hepato – necro -inflammatory process, neutrophil to lymphocyte ratio can provide information about the severity of the hepatocyte necrosis and liver damage in addition to prediction of the outcome through remarkable changes in neutrophils and lymphocytes count during inflammation (Sahani and Das, 2022).

These findings are agreed with those of WenYi et al. (2022) who discovered a significant association between NLR and inflammatory activity of the liver in patients with non-alcoholic fatty liver disease. They also revealed that NLR was a highly accurate predictor of poor outcomes particularly in patients with hepatitis B virus-related decompensated cirrhosis.

Furthermore, Lagadinou et al. (2022), in their research assessing the prognostic value of NLR in liver cirrhosis patients, observed a correlation between increased NLR levels and the occurrence of complications in individuals with liver cirrhosis compared to those with normal ratios.

Contrarily, Meng et al. (2016) studied the predictive role of platelet to lymphocyte ratio and neutrophil to lymphocyte ratio in patients with HCV-related liver infection and found that PLR parameter was superior to NLR in those patients.

Another measured hematological parameter in the existing study was the platelet to lymphocyte ratio (PLR) which is

obtained by division of the absolute platelet count over the absolute lymphocytes count. Platelet count was normal among the 3 studied groups either on admission or during the follow up while lymphocytes count was altered secondary to paracetamol-induced acute liver injury. This alteration was easily reflected in the calculated PLR.

The PLR in this study showed a statistically significant increase during admission and follow up in patients of moderate and severe groups in comparison with patients of the mild group with a significant positive correlation with the case severity.

The ROC curve analysis of PLR parameter on admission revealed that the area under curve (AUC) was 0.759 which indicated fair predictive performance with sensitivity and specificity of 95.45 % and 50 % respectively at a cutoff value of > 100 and an accuracy of 75 %.

These results are in accordance with Zhou et al. (2022) who investigated the relationship between PLR and non-alcoholic fatty liver disease (NAFLD) and discovered a substantial increase in PLR values in patients with non-alcoholic steatosis or steatohepatitis.

In the same way, a study conducted by Yang et al. (2020) to evaluate the effect of systemic inflammatory response (SIR) on carcinogenesis in patients with hepatocellular carcinoma (HCC) and used absolute neutrophil and lymphocyte counts and their ratios to determine presence or absence of SIR. They found that high PLR group of patients had significantly elevated liver enzymes and higher inflammation score which is in agreement with the present results.

Inconsistent with these results, the study conducted by Michalak et al. (2020) to evaluate the role of hematological parameters as NLR and PLR in alcoholic liver cirrhosis (ALC) and alcoholic fatty liver disease and concluded that in acute hepatitis and steatohepatitis, there was a significant increase in the NLR, while the PLR was significantly lowered. They explained this with the evidences indicating that an increase in NLR may coincide with the progression from simple steatosis to steatohepatitis, thereby emphasizing the role of the inflammatory process in raising NLR levels. Decreased values of PLR were observed alongside more advanced liver fibrosis.

Monocyte to lymphocyte ratio (MLR) is another hematological parameter which can be used as a predictor of acute inflammatory disorders nowadays. It is obtained through division of the monocyte count over the lymphocyte count. The present study found negligible alterations in the relative count of monocytes along with a relative decrease in lymphocytes among patients in the moderate and severe groups secondary to paracetamol-induced acute liver injury. Consequently, a statistically notable increase in the values of MLR was observed starting from the day of admission for patients in the moderate and severe groups, with a significant positive correlation with the case severity.

The ROC curve analysis of MLR parameter on admission revealed that the area under curve (AUC) was 0.893 which indicated good predictive performance with sensitivity and specificity of 86.36 % and 72.22 % respectively at a cutoff value of more than 0.2 and an accuracy of 80%.

These findings are in agreement with those of Li et al. (2022) who studied the value of MLR in the prognostic evaluation of hepatitis B virus-related acute on chronic liver failure and found that elevation of MLR is usually associated with severe hepatic inflammation and subsequent decompensation, resulting in high mortality rate.

In the same line with the current results, Wu et al. (2022) studied the immune and inflammatory dysfunctions in patients during early stage of cirrhosis. They recorded significant elevations in MLR among patients with severe hepatic impairment and malnutrition with a cutoff value of MLR more than 0.4.

In contrast, Pomacu et al. (2021) performed a study to investigate the relationship between hematological indicators such as MLR and oxidative stress during liver inflammation. Regrettably, MLR did not reveal a substantial association with all forms of oxidative stress despite hepatic inflammatory condition.

Regarding red cell distribution width (RDW) as a predictor of acute liver damage, it is obtained by division of the standard deviation (SD) of red blood cell volume by the mean corpuscular volume (MCV) then the result is multiplied by 100 to be explained in percentage count. Variations in RDW values associated with paracetamol-induced liver injury are suggested to be due to induced systemic inflammatory response and immune system dysregulation with subsequent release of inflammatory cytokines and oxidative stress. This results in impairment of erythrocyte maturation so immature red cells that enter the peripheral circulation will increase the RDW values (Wang et al., 2019).

The present study found insignificant differences in RDW values among the three examined groups either on admission or during follow-up. Furthermore, there was insignificant correlation between RDW and the severity of the cases.

Aligned with the current findings, Xiang et al. (2022), investigating acute liver damage induced by hepatitis E virus, noted insignificant alterations in RDW values among all studied patients.

These results contradict those of Li et al. (2021) who discussed the increase in RDW as a predictor of severity among patients with drug-induced liver injury (DILI) and observed a positive correlation between elevated RDW values and severity of the case with 86.1% sensitivity and 73.4% specificity.

Average hospital stay was 4.2 ± 1.5 days with a statistically significant difference recorded among the 3 examined groups. Long duration of stay was recorded among patients of moderate and severe groups with significant P-values in comparison with patients of mild group. All patients received the general treatment which included emesis or gastric lavage and activated charcoal administration. Patients of moderate and severe groups received antidotal therapy through intravenous administration of N-acetylcysteine over a period of 21hrs. No mortality was recorded in this study and all patients were discharged after successful treatment protocol.

These results are in accordance with the findings of Zyoud et al. (2011) who examined the length of hospital stay following an acute acetaminophen overdose and discovered a direct relationship between case severity and length of hospital stay.

In contrast to the current results, Baum et al. (2021) studied acetaminophen toxicity and the effect of NAC dosage adjustment on the outcome and duration of hospital stay. They revealed statistically insignificant differences in the duration of hospital stay among the studied groups with median duration 3.6 days.

Conclusion and recommendations:

Easy availability and low cost of paracetamol formulations make their misuse and overdosing a very common method of suicide especially among young adults.

Subsequent paracetamol - induced hepatotoxicity is a critical health problem nowadays. The current study demonstrated that some inflammatory markers such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and monocyte-lymphocyte ratio (MLR) could act as early predictors of paracetamol-induced acute liver injury as they showed remarkable changes from the day of admission and during follow up of patients with acute single paracetamol overdose.

It is advisable to educate the public about the limitations of taking paracetamol and the appropriate daily dosage. It is crucial to prioritize psychological counseling for young adults in order to reduce the incidence of suicide and suicidal thoughts, ultimately saving more lives. Additionally, further research is necessary to assess the effect of acute acetaminophen overdose over the kidney and predictive value of these hematological parameters in paracetamol-induced acute kidney injury (AKI).

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القيمة التنبؤية المبكرة لبعض المعلمات الدموية في حالات الانتحار مع جرعة زائدة حادة من الباراسيتامول

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السمية الكبدية الناجمة عن الباراسيتامول هي واحدة من أكثر أسباب إصابة الكبد نتيجة لتناول الدواء، والتي قد تنتهي بشكل خطير مع فشل الكبد الفوري، لذا يبدو أن التنبؤ المبكر بإصابة الكبد أمر حيوي. تهدف هذه الدراسة إلى تقييم القيمة التنبؤية المبكرة لبعض المعلمات الدموية مثل نسبة العدلات إلى الخلايا الليمفاوية (NLR) ؛ ونسبة الصفائح الدموية إلى الخلايا اللمفاوية (PLR)؛ ونسبة الخلايا الدموية الوحيدة الى الخلايا الليمفاوية (MLR)؛ و عرض خلايا الدم الحمراء (RDW) في حالة التسمم الحاد بالباراسيتامول. اجريت هذه الدراسة على ٤٠ مريضا من المرضى المترددين على مركز علاج التسمم بمستشفى جامعة المنيا في خلال الفترة من أول شهر فبراير ٢٠٢٢ و حتى نهاية شهر يناير ٢٠٢٣ و قد تم تقسيمهم الى ثلاث مجموعات (بسيطة ومتوسطة وشديدة الخطورة). كان متوسط أعمار المرضى ٢٧,٧٥ ± ٧,٣ عامًا مع هيمنة الإناث (٦٧,٥%) وجاء معظمهم من المناطق الحضرية (٦٧,٥%). كان التسمم العمد بالدواء هو الوسيلة الوحيدة للتسمم في جميع المرضى. ولوحظ وجود فارق ذو دلالة إحصائية فيما يتعلق بالجرعة المتناولة التي تراوحت بين ٥-١٥ جم. سُجل ارتفاع في أنزيمات الكبد بين المرضى في المجموعات المتوسطة والشديدة الخطورة في اليومين الثاني والثالث من الدخول. سُجلت زيادة ذات دلالة إحصائية في عدد الخلايا النيوتروفيلية ونقص في الخلايا اللمفاوية وتم تسجيل ارتفاعات ملحوظة في نسبة العدلات إلى الخلايا الليمفاوية ونسبة الصفائح الدموية إلى الخلايا اللمفاوية ونسبة الخلايا الدموية الوحيدة الى الخلايا الليمفاوية ابتداءً من يوم الدخول وخلال فترة المتابعة في المجموعات المتوسطة والشديدة الخطورة. كان متوسط مدة الإقامة في المستشفى ٤,٢ ± ١,٥ يوما ولم يتم تسجيل أي وفيات. أظهرت الدراسة أن NLR و PLR وMLR يمكن أن تكون مؤشرات مبكرة لإصابة الكبد الحادة الناجمة عن الباراسيتامول.