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Quantitative Relationships between Circulating Leukocytes and Certain Enteric Bacterial Infection in Children with Acute Diarrhea

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Abstract

Various pathogenic microorganisms have been implicated as the cause of infectious diarrhea in children as a result of water and food contamination. The study's goal is to determine the reliability of complete blood count (CBC) in peripheral blood of children with acute diarrhea which infected by certain enteric bacteria, with an emphasis on leukocytes (WBCs). A study conducted to examine the pattern of bacterial distribution in children with acute diarrhea's stool, as well as the relationship between the presence of pathogenic bacteria in stool samples and the number of total WBCs and differential leukocyte count in peripheral blood. Samples size includes (76) of health none diarrhea and (174) diarrheal patients, statistical analysis revealed that co-infection by E. coli and Klebsiella sp. was significantly higher (P<0.001) among children which suffered by diarrhea in compare to health individuals. In addition, the logistic regression shows co-infections and infections by Klebsiella sp. (OR: 29.44, 16.288 respectively) more likelihood leads to acute diarrhea compare to E. coli infection alone (P<0.001). Neutrophils/ Lymphocyte ratio (NRL) was (2.412) times higher and neutrophils (1.069) times more in diarrheal group (P<0.001), also the AUC for NRL was 0.833(sensitivity: 81.61 and specificity: 68.42), while for percent of neutrophils was less 0.671 (sensitivity: 46.24 and specificity: 85.71). Concluded that peripheral leukocyte count, particularly the NRL index, is helpful in children with acute diarrhea and additionally that the prevalence of diarrhea is altered by different bacterial infections.

Keywords: *Enteric Bacteria, Acute Diarrhea, Leukocyte Count, NRL Index*

1. Introduction

Over two million people die each year from acute diarrheal illness, which is a major public health concern around the world and primarily affects young children in developing countries (Bryce et al., 2005). Acute diarrhea is the passage of abnormally liquid or unformed stools associated with increased frequency of defecation, with or without fever or vomiting. Diarrhea continues to be a primary cause of paediatric hospitalizations, particularly in children under the age of three years (Guarino et al., 2014, Imanadhia et al., 2019).

These illnesses are particularly prevalent in underdeveloped nations with poor sanitation, hygiene, and access to clean water. These nations also frequently experience underlying issues like hunger, which raise the chance of catching diarrhea. Due to direct medical expenses, job loss, decreased quality of life,

and mortality, these factors may have a major impact on the burden of disease and the economy (Li et al., 2021).

Numerous microorganisms that enter the body through contaminated water or food can cause diarrhea. Etiological agents of acute diarrhea are viruses, parasites and bacteria. Typical bacteria that cause diarrhea mostly in the family of Enterobacteriaceae, which includes Salmonella sp., Shigella Escherichia coli, Klebsiella sp. (Ali et al., 2022, Lin et al., 2021). E. coli and Klepsiella spp. infections frequently result in full recovery, but they can sometimes cause serious, even fatal, consequences. Prolonged exposure, to pathogens can lead to alterations in the gut such as inflammation, damage to the lining of the intestine's reduction, in the height of structures called villi and impaired absorption of nutrients (Prendergast et al., 2015). These problems are more likely to affect elderly adults, pregnant women, small children, and people with compromised immune systems (Imanadhia et al., 2019). E. coli and Klebsiella spp. have some similar chemical and immunological characteristics. Since Klebsiella spp. infections can result in a number of hospital infections, including severe diarrhea in children and newborns, they are a significant issue in paediatric wards (Kobayashi et al., 2021).

Increases in neutrophils and declines in lymphocytes are results of immune response to infections. Circulating leukocyte levels change as a result of the inflammatory response. A recently discovered indication to assess the severity of several disorders, including gastric cancer and enteric infection, is the neutrophils/lymphocytes ratio (NLR). The NLR is a reasonably straightforward, secure, and non-invasive indicator of acute inflammation. (Ramayani and Evalina, Liu and Li, 2019). The objective of this study was to evaluate the correlation between the circulatory leucocytes especially Neutrophil/Lymphocyte Ratio in children with acute diarrhea infected by certain enteric bacteria.

2. Materials And Methods

Socio-demographic information

A cross-sectional investigation was carried out on September 2021 until December 2021. Patients whose guardians had given their consent to participate in the study had their children, ranging in age from 1 month to 12 years, 174 patients' samples (Were taken from various hospitals in the cities of Erbil and Sulaimani), and 76 normal individuals as a control group. Both groups aged was between (1-month to12 years). Following the completion of the questionnaire throughout the interview, the following demographic data was collected: age, sex, feeding type, water used, child whereabouts, and place of residence, socioeconomic status, mother attributes, and characteristics of patients by asking demographic questions in surveys, collecting demographic data at scale, and assisting in the design of a plan to achieve the goal. All of the information was obtained in person from the children's mother after verbal agreement.

General Stool Examination:

Stool samples were randomly collected from children (patients and control group), There were two parts to this test; macroscopic and microscopic inspections. The macroscopic inspection of stool specimens was done immediately to check for any aberrant components (mucus or blood), colour (white, yellow, green, brown, or black), form (for "soft," or liquid), and size (large, small, or none at all). While the stool sample underwent microscopic examination to show RBCs, pus cells, monilla, bacteria, protozoa, fatty droplets, and incomplete digested substances.

Stool Culture for bacteria

Healthy and patients who had diarrheal symptoms and signs had their stools sampled. The various media (MacConkey agar, Blood agar, and Mannitol salt agar) were inoculated with a 20-ul loop of feces and incubated at 37°C for 16 hours. A typical colony on MacConkey agar was picked for the purpose of isolation of E. coli and Klebsiella spp it was streaked once more with eosin methylene blue (EMB) for additional confirmation by the development of metallic sheen green. It is intended to distinguish between Gram-negative of the family Enterobacteriaceae, which contains a large number of genera that are chemically and genetically related to one another. A total of diarrheal stool samples was collected from patients. A loop of stool was inoculated on eosin methylene blue (EMB), and incubated at 37°C for 16 hours; no bacteria grew on it, except E.coli and Klebsiella spp. Methyl red method tests are used to differentiate between E.coli and Klebsiella spp. as a biochemical test bacterium to be tested in inoculated into glucose phosphate broth containing glucose and a phosphate buffer and incubated at 37

C^o for 48 hours. Over the 48 hours, the mixed-acid-producing organism must produce sufficient acid to overcome the phosphate buffer and remain acid. The medium's pH is tested by adding 5 drops of Methyl red (MR) reagent. The development of the red color is taken as positive. MR-negative organisms produce a yellow color. E. coli: Positive; Klebsiella spp.: Negative. (Dennis et al., 2004).

Blood specimen collection

The same children whose stool was collected also provided blood samples, which were then transferred to anticoagulant-tested tubes and sent to a laboratory for (CBC test) examination. Complete blood counts were carried out using Mythic 22 device.

Statistical Analysis

The Statistical Package for Social Science (SPSS) Version 25 and Graphpad Prism 8 were used to analyse the data. Results presented as the mean SD. Independent T tests used to compare group mean differences in order to determine statistical differences. We calculated odds ratio differences and 95% confidence intervals (CI) using logistic regression models. To determine the sensitivity and specificity of parameters, use the ROC curve and AUC as well. The data presented using straightforward frequency distribution tables for each variable along with both descriptive analytical tests. The means, standard deviations (SD), and ranges for various parameters were calculated. Statistical significance was defined as p value less than 0.05 (Amrhein et al., 2019).

3. Results and Discussion

Table 1 illustrate general information on the data, which includes age groups. Most age participant in a toddler and preschool (41.2%) and least in infant (26%). From both groups the abundant blood type was O^+ (43.6%) compare to other blood groups. Fortunately, the gender (male and female) approximately has balanced, and other information was explained in the table 1 such as mother education and occupation, family income. Data analysis revealed that in general stool analysis, mostly semi-solid (56.8%) and followed by watery stool (34%) and just one case was bloody diarrhea. Pus cell found in 159 (63.6) samples and the remainder includes (36.4) pus cell not founded. Another stool examination, which is important in this investigation, is a bacterial examination, E. coli seen in 39 (15.6%) out of 250 samples, and Klebsiella sp. in (41.2%), coinfection of pervious bacteria was (43.2). The clinical signs and symptoms were clearly mentioned in the table 2, which includes abdominal cramp (36.8%), bowling (14.4%), vomiting (58.8%) and fever, which was (76.4%).

T test analysis for bacterial infections and types between diarrhea and non-diarrhea groups shows a highly significant differences ($P<0.001$), coinfection in diarrhea group higher in compare to the health groups, then followed by Klebsiella sp., E coli infection was a lower level in patients stool sample and highest in control group, figure 1. Logistic regression analysis revealed that infection by Klebsiella spp. 16.288 more likelihood causes diarrhea compare to reference (E. coli) P value < 0.001(OR: 16.288 CI: 16.132-43.256), while coinfection (Klebsiella spp. and E.coli) significantly 29 time as a factor of causative agent of diarrhea compare to reference $P<0.001$ (OR:29.44, CI: 10.698-81.023), as shown in table (3). White blood cells which done via haem-analyser automate machine, show the ratio of leukocytes count generally differ between groups. Figure-2 demonstrated that total leukocyte counts and neutrophils significantly increased among diarrhea patients ($P<0.001$) in compare to healthy individuals, moreover amount of monocyte declined significantly in patients ($P<0.05$).

NLR index shows dramatically increased among children which suffered by diarrhea ($P<0.001$), finally amount of lymphocytes seen none significantly variation between healthy and patient groups ($P>0.05$). None diarrhea was a baseline reference, NRL 2.4 times more in acute diarrhea (95% CI: 3.3723-4.222), moreover, and neutrophils percentage 1.069 likelihood more in diarrhea group (95% CI: 1.037-1.103). The NRL and neutrophils proposed cut-off (Criterion) were used as leukocyte indices of diarrhea-infected patients who were infected with Enterobacteriaceae and healthy people. According to the sensitivity, specificity, area under the curve (AUC), and characteristic (ROC) curves, NRL was more sensitive than neutrophils % (81.61, 46.24), while neutrophils percent was more specific than NRL % ($P<0.001$), and the area under curve of ROC of NRL was (0.833) and for neutrophils was (0.671).

Table 1: Socio-Economic Characteristics of Study Samples

Variable	Level	Frequency	%
Groups	None Diarrhea	76	30.4
	Diarrhea	174	69.6
Age groups	Infant	65	26
	Toddler and preschool	103	41.2
	School Age and Above	82	32.8
Blood groups	+	73	29.2
	B+	35	14
	AB+	25	10
	O+	109	43.6
	A-	1	0.4
	AB-	4	1.6
	O-	3	1.2
Gender	Male	127	50.8
	Female	123	49.2
Mother Education	Illiterate	23	9.2
	Read and Write	34	13.6
	Primary School	41	16.4
	Secondary School	67	26.8
	Institute	39	15.6
	College and Above	46	18.4
Mother Occupation	Employed	58	23.2
	Unemployed	40	16
	Self-employed	4	1.6
	House Wife	148	59.2
Family Income	Sufficient	116	46.4
	Barely Sufficient	96	38.4
	Insufficient	38	15.2

Table 2: Stool characteristics with related sign and symptoms

Variable	Level	Prevalence	%
Appearance of Stool	Watery	85	34
	Semi-liquid	142	56.8
	Mucoid	22	8.8
	Blood Diarrhea	1	0.4
Colour	Yellow	135	54
	Greenish Yellow	9	3.6
	Brown	78	31.2
	Yellowish Brown	15	6
	White	13	5.2
Pus cell	seen	159	63.6
	Not Seen	91	36.4
E. histolytica	seen	22	8.8
	Not Seen	228	91.2
Monelia Stool	Few	67	26.8
	Nil	183	73.2
Bacteria	E. coli	39	15.6
	Klebsiella sp.	103	41.2
	Co-infection	108	43.2

How long diarrhea lasts	Within 2 days	140	56
	Within 1 week	94	37.6
	More than 1 week	16	6.4
Cramps	Founded	92	36.8
	Not Founded	158	63.2
Blowing	Founded	36	14.4
	Not Founded	214	85.6
Vomiting	Founded	147	58.8
	Not Founded	103	41.2
Fever	Founded	191	76.4
	Not Founded	59	23.6

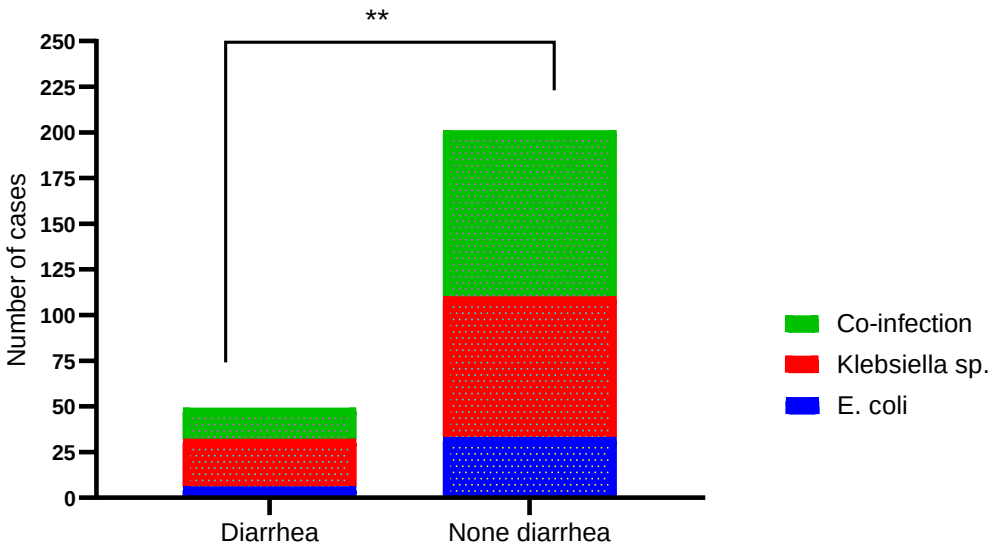

Figure 1: Frequency and types of baccteria between groups

Table 3: Types of bacterial infection among patients and control groups

Types of bacterial Infections	None Diarrhea	Diarrhea			95% C.I.	
	No.	No.	P value	Odd ratio	Upper	Lower
E. coli	33 (84.6%)	6 (15.4%)	Reference	1		
Kleibsella spp.	26 (25.2%)	77 74.8%	0.001	16.288	16.132	43.256
Co-infection	17 (15.7%)	91 (84.3%)	0.001	29.44	10.698	81.023

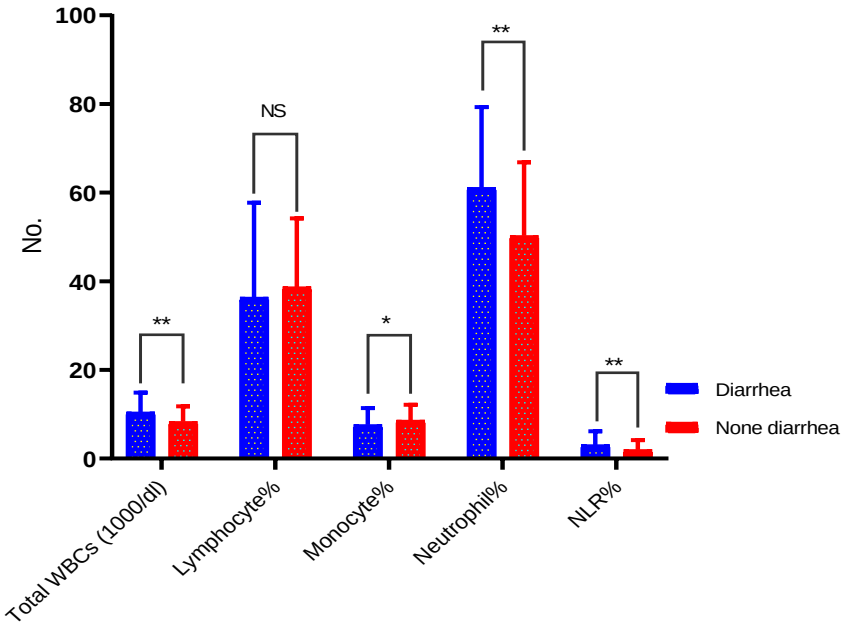

Figure 2: Distrbution of Leuckocytes between groups

Table 4: Means of Leukocyte indices and odd ratio between groups

Items	Groups	Mean	SD	P value	OR	95% C.I.	
						Lower	Upper
Total WBCs	None Diarrhea	8.3276	3.507	Reference	1		
	Diarrhea	10.3914	4.438	0.195	1.180	0.918	1.516
Lymphocyte%	None Diarrhea	38.6763	15.584	Reference	1		
	Diarrhea	36.3506	21.329	.630	1.009	0.974	1.045
Monocyte%	None Diarrhea	8.642	3.548	Reference	1		
	Diarrhea	7.569	3.782	0.39	0.927	0.863	0.996
Neutrophil %	None Diarrhea	50.1842	16.710	Reference	1		
	Diarrhea	61.0609	18.138	0.001	1.069	1.037	1.103
Neutrophil /Lymphocyte ratio	None Diarrhea	1.9911	2.208		1		
	Diarrhea	3.0612	3.085	0.09	2.412	3.3723	4.2220

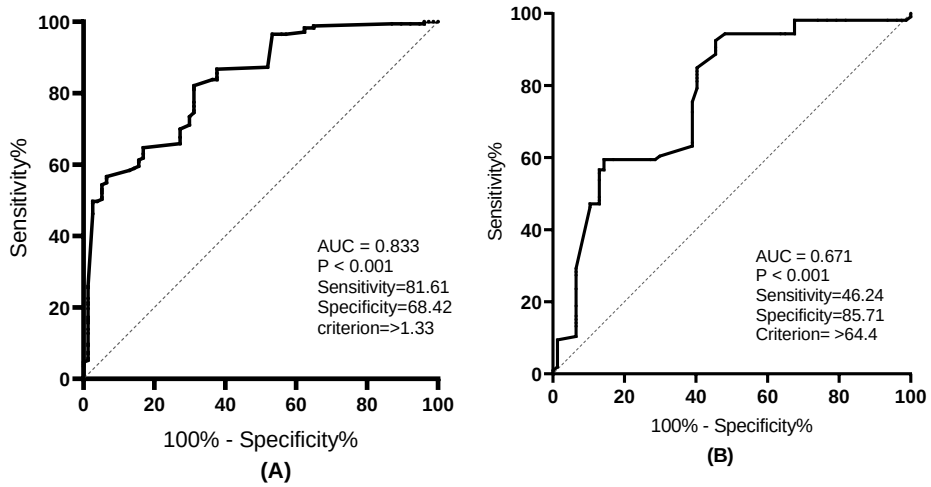

Figure 3: Receiver operating characteristic (ROC) curve explain and the Area under curve (AUC), sensitivity and specificity of (A) Neutrophil to Lymphocyte % ratio, (B) Granulocyte % .

Analysis of the information showed that, in general, semi-solid and watery (56.8%, 34%) stools repectively, with just one episode of bloody diarrhea. Pus cell was discovered in 159 and 36.4 samples did not include pus cell. A bacterial analysis of the feces is another examination that is crucial to this study, (15.6%) of the samples included E. coli, and 41.2% contained Klebsiella spp., with a coinfection rate of 43.2%. Due to their widespread prevalence in both hospital and community settings, intestinal parasites and bacteria, particularly enteropathogenic Escherichia coli (EPEC), are significant causes of recurrent diarrhea in infants and children around the world (Abdulqader et al., 2022).

In the present study cramps (36.8%), bowling (14.4%), vomiting (58.8%), and fever were among the clinical signs and symptoms. Demers-Mathieu et al. (2019) reveals in their investigation the signs and symptoms of viral gastroenteritis include watery diarrhea, stomach pain, nausea, or vomiting, and, on occasion, fever which mostly in viral infection. The source of drinking water and the implementation of hygienic conditions are very important variables for human health; using contaminated water may be the cause of high infection rates (Al-Ubaydi et al., 2019). Consequently, the form of diarrhea caused by confections made with multiple types of microbes may occasionally be severe. When the pathogenic agent is bacteria, E. coli is thought to be the most common cause, particularly in pediatric diarrhea (Gambushe et al., 2022). According to the gender and age, the total rate of infected males was higher than females were male (50.2%), (49.8%), males have a higher infection rate than females because they are more exposed to environmental factors and have direct contact with the source of the microbes, Regarding to the relationship between infection ratewith gender and age. ages of >6 mostly infected by bacteria (Jameel and Essa, 2021).

Previous research has focused on finding serum markers that can distinguish between viral and bacterial causes of children acute diarrhea and the severity of infections. The ability to distinguish between bacterial and viral gastroenteritis in emergency situations, however, has not been established using serum markers alone (Miyagi, 2023). The leveles of total leukocyte count and neutrophils % significantly higher among acute, also monocyte significantly declined ($P<0.05$) meanwhile lymphocyte ratio none significantly declined ($P>0.05$) in compare to healthy indidviduals. These results agree with other investigation done by Ali et al. (2022), he demonstrated that infection by bacteria which leads to diarrhea hematological parameters such as total white blood, and platelet sinificantly increaased.

Leukocyte counts have been used to identify infectious disorders in the past. The neutrophils that are devoured during bacterial infections are in great quantities. From the time of infection until recovery, there are rapid fluctuations in count of white blood cells and left-shift data that represent the severity of the bacterial illness (Zhang et al., 2022). The results show NRL ratio 2.4 time more as well as

neutrophils percentage 1.069 times more in dairrhea. ROC curve revrealed that NRL was more senstive indicate for differentiation between acute diarrhea by bacterial infections and healthy none diarrhea persons (AUC: 0.83, sensitivity:81.61, sensitivity: 68.42), (AUC:0.671, sensitivity:46.24, sensitivity: 85.71). The NLR is a simple measure that may be calculated using a complete blood count. NLR has previously been demonstrated to predict poor outcomes in cancer patients, as well as viral and bacterial infections (Zahorec, 2001, Cho et al., 2009).

Despite a large number of evidences confirmed an association between NLR and mortality, the relationship between NLR and outcomes of acute diarrhea patients was rarely investigated. The pathophysiological process of infection and sepsis includes both extensive activation and malfunction of the immune system. NLR is an indication of systemic inflammation because it demonstrates a balance between neutral and lymphoid cells (Angus and Van der Poll, 2013). On the one hand, a low level of circulating neutrophils raises hospital mortality. Patients with reduced NLR frequently have neutropenia, which is a risk factor for bacterial infection, and are unable to fend off following severe sepsis and septic shock (Legrand et al., 2012).

Increased neutrophils are an inflammatory response, especially when triggered by a bacterial infection. Lymphocytopenia has also been described as a bacterial infection diagnostic sign. Concluded that, the NLR is expected to have greater discriminative capacity for predicting bacterial infection than neutrophilia or lymphocytopenia alone. The study's most important finding was that NLR may be a valuable indicator for identifying acute diarrhea.

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