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COMPARISON OF SOME HEMATOLOGICAL AND IMMUNOLOGICAL CRITERIA OF BACTEREMIA AND SUSPECTED PATIENTS

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Abstract:

Three hundred and thirteen blood samples were collected from bacteremia patients , including 146 samples (30 patients samples, 116 samples of out patients) from Azadi Teaching Hospital, 36 samples from the dialysis unit at Kirkuk General Hospital and 126 samples (42 samples of patients, 84 samples of out patients) from the Children's Hospital and 5 samples from the Women's and Obstetrics Hospital in Kirkuk province, for the period from January 24, 2022 to September 10, 2022. The result show as 32(17.87%) positive growth cultures were obtained of Febrile patients, 3(8.33%) of dialysis patients in the dialysis unit and 15(65.21%) of burn and wound patients. Fifty bacterial isolates were obtained, the gram positive Staphylococcus was the highest (28) isolates including; [(11) *S.homoinis*, (4) *S.epidermidis* and (2) isolates each of *S.haemolyticus* and *S.warner* ,and (9) *Staphylococcus spp*], while *Enterococcus faecalis* was one isolate. The gram negetive bacteria were [(11) *Pseudomonas aeruginosa*, (5) *Escherichia coli*, (2) isolates of *Enterobacter cloacae* and followed by one isolate of (, *Acinetobacter spp*. and *Klebsiella spp*.). The hematological criteria in the blood of patients with bacteremia were then studied as no significant difference was observed below the probability level ($P \leq 0.05$) in the mean of WBC, Neutrophils, Monocytes, Lymphocytes, MCHC, MPV, P-LCR, while a significant difference in the mean of RBC, HGB, HCT, MCC, MCH, PLT and PCT was observed in patients with bacteremia than in without bacteremia(suspected)

In the immunological study, no significant difference was observed at the level of $P \leq 0.05$) in the mean of IL-6, Precepsin and Procalcitonin, while a significant difference in the mean of Neutrophil CD64 was observed in patients with bacteremia than in without bacteremia.

Keywords: Bacteremia, Complete Blood count, immunological criteria.

Introduction

Bacteremia is defined as the presence of live bacteria in the bloodstream and can cause mild to life-threatening diseases by activating a series of pro inflammatory substances or causing apoptosis or anti-inflammatory that ultimately disrupt the physiological balance (Liu *et al*., 2014).

Blood in healthy people is characterized by the fact that it does not contain bacteria so the presence of infection can affect the life of the patient and this is the most common cause of bacteremia, as the infection occurs in a certain place in the body and the movement of bacteria in the blood helps it to occur bacteremia (Garnica *et al*., 2021).

Bacteremia is one of the most common causes of death for patients in hospitals and despite health advances mortality rates remain unacceptably high, especially if septic shock appears (Velissaris *et al*., 2021); (Ibraheem, 2011) , which is either primary or idiopathic causes by certain medical procedures that allow bacteria to pass into the blood in healthy patients from places usually colonized by bacteria such as urinary catheterization in the bladder or gastrointestinal endoscopy (colonoscopy) (Garnica *et al*., 2021). Blood stream infection is a growing public health concern worldwide, and represents a serious infection with significant morbidity and mortality rates, especially in children and the elderly (Agyeman *et al*., 2017; Duan *et al*., 2021).

The most frequent infections causing bacteremia are urinary tract (prostatitis, pyelonephritis), respiratory tract (pneumonia), blood vessels (infected catheters), digestive tract (cholecystitis or cholangitis), skin and soft tissues (Cellulitis or myositis), or bone (osteomyelitis) (Garnica *et al*., 2021). The highest relative risks of developing bacteremia are those associated with dialysis, solid organ transplantation and oncological diseases (Bonten *et al*., 2021). Coagulase-negative staphylococci (CoNS) is the most dominant bacteria isolated from newborn blood that causes a high incidence of mortality and pathogenesis (Al-Haqan *et al*., 2020). The most dominant species of bacteremia produced by burns and wounds are *Staphylococcus* spp. (55%), followed by *Pseudomonas* (14.29%), *Enterococcus* (12.24%) and *E. coli* (4%) (Latifi and Karimi, 2017). Staphylococcal bacteria are often isolated from clinical laboratories (Hamad and Al-Ahmer, 2019). The most isolated bacterial types of burn and wound patients were P. aeruginosa (38.6%), E.coli (23.7%), and Klebsiella spp. 12.28%, Staphylococcus spp. 2.19% and spp. Proteus 1.32% (Kareem, 2010).

Boussi *et al*. (2021) study indicated that the most isolated bacteria from the inflammatory bacteremia were *S. aureus* (20.13%), most of which were sensitive to methicillin, followed by the non-coagulase *Staphylococcus* (13.21%) and *Enterococcus* (13.21%), while *Escherichia coli* (10.06%).

At the moment there is a lack of early diagnosis system for bacteremia due to traditional methods such as culture, which takes a long time for the result to appear as well as pseudo-negative results, while molecular techniques need special and expensive equipment, so biomarkers or biometrics such as procalcitonin are useful measures to distinguish between normal and pathological conditions and the gradation of the severity of the disease, a therapeutic guide, follow-up of the therapeutic response and expected progress (Piccioni *et al*., 2021).

The Complete Blood count (CBC) test is an important and easy to perform in the laboratory, which provides a wealth of information on the health status of the individual, and the appropriate interpretation of this test is central to the early detection of many clinical conditions that must be subject to further research by laboratory and clinical analyzes and CBC parameters can be limited to three categories are (WBC), white blood cells (RBC), red blood cells platelets(PLT) (Agnello *et al*., 2021). A number of studies have shown that the monocyte expresses on its surface TLR2 receptors, which are mainly distinguished in detecting the gram positive bacteria (Wisgrill *et al*., 2016; Hegge *et al*., 2019). The absolute value of WBC is clinically significant and is more beneficial than the relative value (percentage) because it refers to the response of the marrow to inflammatory stimuli, and the relative value is useful for assessing which of the WBC white blood cell aggregated are mainly involved in the inflammatory process allowing the diagnosis of pathogens. In general, an increase in the total number of white blood cells indicates the presence of inflammation and infection, as well as the white blood cell count can be normal or in some cases may decrease from sepsis (Agnello *et al*., 2021). Whereas platelets, which are small cells that do not contain a nucleus, wandered in the blood and play the role of mediator in thrombosis blood clotting and hemostasis, In infectious diseases, platelets are involved in the early detection of invasive microorganisms and are recruited at sites of infection and operate either by direct binding to eliminate bacteria, restrict spread or by stimulating the host's immune response (Li et al., 2020). Biological and immunological parameters such as Interleukin 6 (IL-6) are a vital marker of inflammation although it is one of the early responses to sepsis, and its serum levels can be easily measured within a few hours (Gille *et al*., 2021). IL-6 is a multidirectional cytokine that has an effect on both immune regulation and non-immune events in many cells (Hammed et al., 2012). Interleukin-6 plays an important role in the monitoring and evaluation of the severity of the disease and treatment (Al-Haidary, 2007).

Procalcitonin alone or in combination with other biological criteria is a promising tool for knowing and predicting the main cause of sepsis, diagnosing and then treating it, as the biological criteria must be characterized by early and rapid diagnostic susceptibility, as well as procalcitonin is also a biological marker of bacterial infection as it is used to guide antimicrobial therapy, and studies have highlighted bacteremia patients with low procalcitonin and reduce its clinical benefit (Boussi *et al*., 2021). Presepsin is a valuable tool for laboratory work in detecting sepsis, especially when used in combination with other biomarkers and clinical symptoms (Velissaris et al., 2021), and is used neutrophil CD64 (nCD64) as a useful biomarker useful for the detection of bacterium (Patnaik *et al*., 2020).

Materials and Methods

Three hundred and thirteen blood samples were collected, including 146 samples (30 patients samples, 116 samples of out patients) from Azadi Teaching Hospital, 36 samples from the dialysis unit at Kirkuk General Hospital and 126 samples (42 samples of patients, 84 samples of out patients) from the Children's Hospital and 5 samples from the Women's and Obstetrics Hospital in Kirkuk province, for the period from January 24, 2022 to September 10, 2022. The blood samples were divided into three groups:

***The first group of bacteriological study:**

Blood of bacteremia patients were cultured in the brain heart infusion broth and incubated at 37 °C for 24 hours, then cultured on the Blood agar and MacConkey agar and incubated at 37 °C for 24 hours. All isolates were diagnosed depending on Macroscopic and Microscopic characteristics of bacterial cells, then identification by Vitek –2 Compact system and an API staph kit for the gram positive bacteria and the API 20E kit for the bacteria that are gram negative.

*** Hematological Study**

Part of the blood was placed in the anti-blood substance Ethylene diamine tetra acetic acid (EDTA) tubes, mixed and placed in a Count Complete Blood (CBC) device of the Automater Hematology analyzer Genex COUNT-60 to measure the hematological criteria.

*** Immunological Study**

The remnant of blood put on Gell tube to study certain immune criteria in patients with bacteremia and in without bacteremia., including Human Interleukin 6 ELISA Kit, Human Presepsin ELISA Kit, Human Procalcitonin ELISA Kit, and Human Cluster of differentiation 64 ELISA Laboratory. These kits are an enzyme-linked immunosorbent assay (ELISA) test from Bioassay Technology Laboratory Company.

Outpatients have been excluded .

Results and Discussion

Bacteriological study

The results showed the samples grown in the brain heart infusion broth as in Table (1), Distribution of positive growth culture according to the source of bacteremia ,as the number of percentage of positive culture were 32(17.87%) from fibrile , 3(8.33%) from dialysis patients in the dialysis unit, 15(65.21%) from of burn and wound patients. Table (2) shows the number and percentage of *Staphylococcus* isolates from bacteremia patients as follow *[Staphylococcus hominis*, *S. epidermidis* (11) 37.93% and(4)13.79%) respectively, and *S. warneri* and *S. haemolyticus* were (2)6.89%] and *Enterococcus faecalis* was (1)3.44%. While the gram negative bacteria were *Pseudomonas aeruginosa* (11)52.38% and Escherichia coli (5) 14.28 %, *Enterobacter cloacae* (2) 9.52%, *Raoultella terrigena, KlebsiellaSpp.* and *Acinetobacter Spp.* were (1)4.76%.

Table (1): percentage of positive growth culture according to the source of bacteremia .

Source of bacteremia	Total number of samples	Number of positive grown culture	% Percentage
Febrile patients	179	32	17.87
Dialysis patients (dialysis unit)	36	3	8.33
Burns and wounds patients	23	15	65.21

Table (2): Number and percentage of bacterial species isolates from patient with bacterium.

Reaction with gram stain	Genus	Species	Number	Percentage%
Gram positive bacteria	***Staphylococcus***	***warneri***	**2**	**6.89**
		haemolyticus	**2**	**6.89**
		hominis	**11**	**37.93**
		epidermidis	**4**	**13.79**
		Spp.	**9**	**31.03**
	Enterococcus	***faecalis***	**1**	**3.44**

Gram negative bacteria	***Raoultella***	***terrigena***	**1**	**4.76**
	Pseudomonas	***aeruginosa***	**11**	**52.38**
	Enterobacter	***cloacae***	**2**	**9.52**
	Escherichia	***coli***	**5**	**14.28**
	Klebsiella	***Spp.***	**1**	**4.76**
	Acinetobacter	***Spp.***	**1**	**4.76**

Park *et al*. (2022) noted in their study of 158 patients with bacteremia, with 45 (29%) infected with Gram-positive bacteria, 35 (22%) with Gram-negative bacteria, 27 (17%) with fungi and 51 (32%) negative growth culture . While Gille et al., (2021) indicated that 101 patients had 39 blood cultures that were positive growth, 16 (41%) were gram negative, 18 (46.2%) were gram-positive bacteria, and 5 (12.8%) were samples containing both gram positive and negative bacteria . Rasool (2011) noted in his study that the most common people with bacteremia among children were the age group (1 day -1 year) 64.89%.

Salah *et al*. (2021) noted in their study that the main caused bacterial pathogens were the gram positive bacteria ; S. *haemolyticus* (9.1%), *S. epidermidis* (7.1%) and *S. hominis* (5.1%) and pointed out that the Coagulase-negative Staphylococci (CONS) bacteria were the majority of the gram positive bacteria and *S. haemolyticus* were the most among present. While Abbas *et al*. (2014) noted in their study that bacterial isolates from newborns were 21.23% gram positive bacteria followed by gram negative bacilli bacteria and yeasts. Rasool (2011) in his study indicated that the proportion of *S.epidermidis* isolated from bacteremia patients was 54.78%. While de Oliveira *et al.* (2021) in their study which included 200 bacterial isolates of *Staphylococcus* spp. including; 50 were *S. aureus* and 150 were (CoNS) that included species (50 of *S. epidermidis*, 7 of *S.lugdunensis*, 20 isolates each of *S.haemolyticus*, *S. warneri*, and *S.hominis*). pointed out that the Coagulase-negative Staphylococci (CONS) bacteria were the majority of the gram positive bacteria and *S. haemolyticus* bacteria were among the most present

Hematological and immunological criteria for blood samples of patients with bacteremia

Table 3 shows the rate of WBC, Neutrophils, Monocytes and Lymphocytes in patients with bacteremia (11.56± 1.47, 5.11±0.77, 1.32 ±0.41, 5.07±0.54) and in non-infected people it was (11.40±0.88, 5.67 ±0.60, 1.22±0.15, 4.37±0.39) respectively if no significant difference was observed below the probability level (P≤0.05).

Table (3): Hematological criteria (WBC, Neutrophils, Monocytes, Lymphocytes) for the patients with and without bacteremia.

Testes	Infection (Bacterial growth)	Mean ± S.E.	P value
WBC (cell/mL)	Yes	11.56±1.47	0.92
	No	11.40±0.88	
	Yes	5.11±0.77	0.58

Neutrophils (cell/mL)	No	5.67±0.60	
Monocytes (cell/mL)	Yes	1.32±0.41	0.79
	No	1.22±0.15	
Lymphocytes (cell/mL)	Yes	5.07±0.54	0.29
	No	4.37±0.39	

Table (4) shows the mean of RBC, HGB and HCT in the infected patients were (0.16±4.12, 0.54±12.43, 1.64±36.52) respectively and in the non-infected (0.17±4.61, 0.65±15.09, 1.99±44.30) respectively, a significant difference was observed at the level of (P≤0.05).

Table (4): Hematological criteria (RBC, HGB, HCT) for patients with and without bacteremia.

Tests	Infection (Bacterial growth)	Mean ± S.E.	P value
RBC (million/mL)	Yes	4.12±0.16	*0.044
	No	4.61±0.17	
HGB (g/dL)	Yes	12.43±0.54	*0.003
	No	15.09±0.65	
HCT (%)	Yes	36.52±1.64	*0.004
	No	44.30±1.99	

Table (5) shows the MCV and MCH means in the patient with bacteremia were (2.42±88.68 and 0.85±30.33) respectively, and in the patient without bacteremia were (1.53±95.60, 0.46±32.63) respectively, where a significant difference was observed at the level of (P≤0.05), while the MCHC mean was in patients with bacteremia (0.35±34.21) and without bacteremia were (0.23±34.18) and no significant difference was observed at the level of (P≤0.05).

Table (5): Hematological criteria (MCV, MCH, MCHC) for patients with and without bacteremia.

Tests	Infection (Bacterial growth)	Mean ± S.E.	P value
MCV (Fl)	Yes	88.68±2.42	0.014*
	No	95.60±1.53	
MCH (pg)	Yes	30.33±0.85	0.025*
	No	32.63±0.46	
MCHC (g/dL)	Yes	34.21±0.35	0.94
	No	34.18±0.23	

Table 6 shows the mean of PLT and PCT in patients with bacteremia were (41.33±420.29, 0.03±0.35) respectively and without bacteremia were (23.98±275.59 and 0.02±0.25) respectively as they showed a significant difference at the level of (P≤0.05), while the mean (MPV, P-LCR) in patients with bacteremia were (0.34±8.81, 3.11±22.03) respectively and were without bacteremia (0.23±9.36, 2.28±27.35) respectively and no significant difference was observed at the level of (P≤0.05).

Table (6): Hematological criteria (PLT, MPV, PCT, P-LCR) for patients with and without bacteremia.

Tests	Infection (Bacterial growth)	Mean ± S.E.	P value
PLT (thousand/mL)	Yes	420.29±41.33	0.002*
	No	275.59±23.98	
MPV (fL)	Yes	8.81±0.34	0.17
	No	9.36±0.23	
PCT (%)	Yes	0.35±0.03	0.006*
	No	0.25±0.02	
P-LCR (fL)	Yes	3.11±22.03	0.16
	No	2.28±27.35	

Table (7) shows the mean of IL-6, Precepsin and Procalcitonin in patients with bacteremia (20.75±169.10, 19.95±178.64, 156.94±677.15) respectively and without bacteremia , it was (8.42±132.63, 9.98±145.66, 52.47±465.07) where no significant difference was observed at the level of (P≤0.05), while the mean of Neutrophil CD64 was in patients with bacteremia (2.45±27.21) and without bacteremia ,it was (1.11±21.72) where a significant difference was observed at the level of (P≤0.05).

Table (7): Immunological criteria for patients with and without bacteremia.

Tests	Infection (Bacterial growth)	Mean ± S.E.	P value
IL-6 (ng/L)	Yes	169.10±20.75	0.12
	No	132.63±8.42	
Neutrophil CD64 (ng/mL)	Yes	27.21±2.45	0.05*
	No	21.72±1.11	
Precepsin (ng/L)	Yes	178.64±19.95	0.15
	No	145.66±9.98	
Procalcitonin (pg/mL)	Yes	677.15±156.94	0.13
	No	465.07±52.47	

The results showed no significant differences below the probability level (P≤0.05) in the mean of WBC, Neutrophils, Monocytes, Lymphocytes, MCHC, MPV, P-LCR, while a significant difference in the mean of RBC, HGB, HCT, MCV and MCH, PLT and PCT was observed in infected patients than in non infected people.

In the immunological study, no significant difference was observed at the level of P≤0.05) in the mean of IL-6, Precepsin and Procalcitonin, while a significant difference in the mean of Neutrophil CD64 was observed in infected patients than in non infected people.

Chiu *et al*. (2018) noted in his study that the level of hemoglobin is lower in patients with bacterium than in non-infected people and there are significant differences between infected and non infected groups, showing that clinical results related to patients with bacteremia did not show statistically significant differences in the mean of entry and exit of patients or the use of antibiotics in the children's hospital.

Büyükeren *et al*. (2020) noted that hemoglobin and hematocrit values were significantly lower in the group of patients with bacteremia than in the control group, and there was no statistically significant difference between the two groups in relation to white blood cell count. As for platelets, Chang *et al.* (2020) indicated that there were no statistically significant differences in the main characteristics between infected and non-infected with bacterial people, noting there were no significant differences between platelet parameters including Platelet-to-Lymphocyte Ratio (PLR) and MPV/PC between the two groups. While Büyükeren et al. (2020) the patient group had an mean platelet count much lower compared to the control group. From the results we note that the occurrence of a decrease in red blood cells during infections is due to the fact that bacterial infections or the production of bacterial toxins activate and stimulate the adhesion of red blood cells to the epithelial lining of blood vessels, which leads to their decrease or due to the decomposition of red blood cells by bacteria and is inferred by measuring raticulocyte, billirubin and haptoglobin (Ballin *et al*., 2009). High platelets have a variety of etiologies, including inflammatory diseases, infectious diseases and neoplastic tumors (Bleeker and Hogan, 2011). Or it may be due to the fact that children with bacteremia, inflammation-associated cytokines produced by WBC may increase mainly in inflammatory sites that cause a high level of CRP and in turn stimulate thrombocytosis (Tsai *et al*., 2020). In other studies, thrombocytopenia has been reported to be a lack of platelets and this is due either to decreased platelet production or increased platelet circulation rate and this reduces platelet life as the cleared activated platelets are quickly from circulation (Assinger *et al*., 2019). Or that platelets and extracellular neutrophils form (NETs) for bacteria that may lead to the destruction of active leukocytes and thrombocytopenia (Dewitte *et al*.,2017; Fuchs *et al*., 2007; McDonald *et al*., 2017). The differences in studies on the rise or fall of white blood cells are attributed to the method of drawing blood and its difficulty for children, especially if hospitals are not specialized for children, so it is not possible to rely on white cells to predict bacteremia (Lipsett, *et al*. 2019) or may be attributed to the difference in blood sample size, method of measuring white blood cells, time of sampling and severity of infection (Shah and Jha, 2019). The issue of bacteremia and finding predictive criteria remains very difficult and this may be due to the difficulty of obtaining positive samples cultured, lack of knowledge of the patient's condition, treatment period, similar number in terms of age, gendra and source of infection.

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