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Evaluation of some immunological parameters for patients infected with bacteremia in ICU-Mosul city hospitals

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Abstract
The study was conducted on patients admitted to intensive care units (ICU) in Mosul city hospitals (Ibn Sina teaching hospital, Mosul general hospital and AL-Salam teaching hospital) in Nineveh Governorate/Iraq. 90 blood samples both of sexes and for different age groups ranging from (21-90) years were collected through this study, 24 blood samples were collected from healthy people used as a control group for the period between the first of July and December of 2022.

The present study aimed to: Isolation and identification of bacteremia in ICU patients by using the Vitek-2 compact system and study of some immunological parameters (IgM, IgG and hs-CRP) in ICU patients with and without bacteremia**.** The results of the current study indicated that 66(73.33%) blood samples revealed negative cultures and 24(26.67%) blood sample revealed positive cultures consisting of 14(58.34%) Gram-positive bacteremia were predominant, and 10(41.66%) Gram-negative bacteremia. The results of ELISA found high level of IgM, IgG and hs-CRP in serum of bacteremia patients compared with healthy control group high significant difference P-value (<0.001). Also mean level of IgM, IgG and hs-CRP in serum of non-bacteremia patients group compared with healthy control group high significant difference P-value (<0.001).

Keywords: ICU patients, bacteremia, antibiotics, sensitivity, resistance, immunological parameters

Introduction

The main objective of the respiratory system is to facilitate the process of air exchange, carrying oxygen and transporting it through the respiratory system, and removing carbon dioxide (Hsia *et al*., 2016**)** [15]. The respiratory system was described as one of the organs most susceptible to infection with microbes, being in direct contact with the atmospheric air and the external environment, as it begins with the nostrils and ends downward with the lung alveoli. It is divided into two parts, the upper respiratory tract (URT) and the lower respiratory tract (LRT), (Pawlina, W., & Ross, M. H. 2018) [24]. Each of these areas also plays an important role in defending the respiratory tract against infection, the mucociliary blanket of the sinuses, middle ear, and tracheobronchial tree clears particulate matter and contains immunoglobulin and other antimicrobial substances, if particles reach the alveoli, resident macrophages ingest organisms; polymorphonuclear leukocytes and monocytes are recruited once the lung becomes inflamed (Mahon *et al*., 2015) [21]. Hospitalization-acquired pneumonia is one of the most frequent infections in critical patients. It is primarily associated with mechanical ventilation leading to severe illness and high mortality (Perez *et al.*, 2021) [25]. Community-acquired pneumonia by *Streptococcus pneumonia* and other pathogens is a focus of infection in patients with community-acquired bacterial meningitis, invasive disease by these pathogens is preceded by nasopharyngeal colonization, after which the bacteria are able to pass the mucosal barrier, invade the bloodstream and eventually cross the blood-brain barrier to cause meningitis (Figueired *et al*., 2020).Blood stream infections (BSIs) refer to presence of microorganisms(bacteria, viruses, fungi and parasites) in blood, which are a threat to every organ in the body; however as bacteria account for the majority of BSIs and it is called bacteremia (Apurba, S.S., & Sandhya, B.K. 2019a) [5, 6].

Worldwide, bloodstream infections (BSIs) with Gram-Positive and Gram-Negative bacteremia which are a major health problem, constitute an important cause of morbidity and mortality in clinical settings (Habyarimana *et al* 2021**)** [13]. However, BSIs remain undiagnosed due to limited diagnostic laboratory facilities resulting in poor clinical outcomes and the increasing risk of antimicrobial resistance (Leal, *et al* 2019) [18]. identify risk factors of BSIs lead to describe epidemiological patterns for early onset bacteremia (EOB) and late onset bacteremia (LOB), (Lee, *et al* 2020) [19].

Materials and methods

Collection of blood samples

90 blood samples were collected from patients admitted to intensive care unit in Mosul city hospitals (Ibn Sina teaching hospital, Mosul general hospital and AL-Salam teaching hospital) in Nineveh Governorate/Iraq after their diagnosis by specialist doctor and 24 blood samples were collected from healthy people used as a control group, both of sexes and for different age groups ranging from (21-90) years. Approximately 10ml of venous blood was withdrawn by researcher himself using plastic medical syringes.

Methodology procedure and techniques used in our study

Figure (1) below illustrates methodology of procedure assay of our study and techniques used in the diagnosis of microorganisms and measurement of immunological parameters.

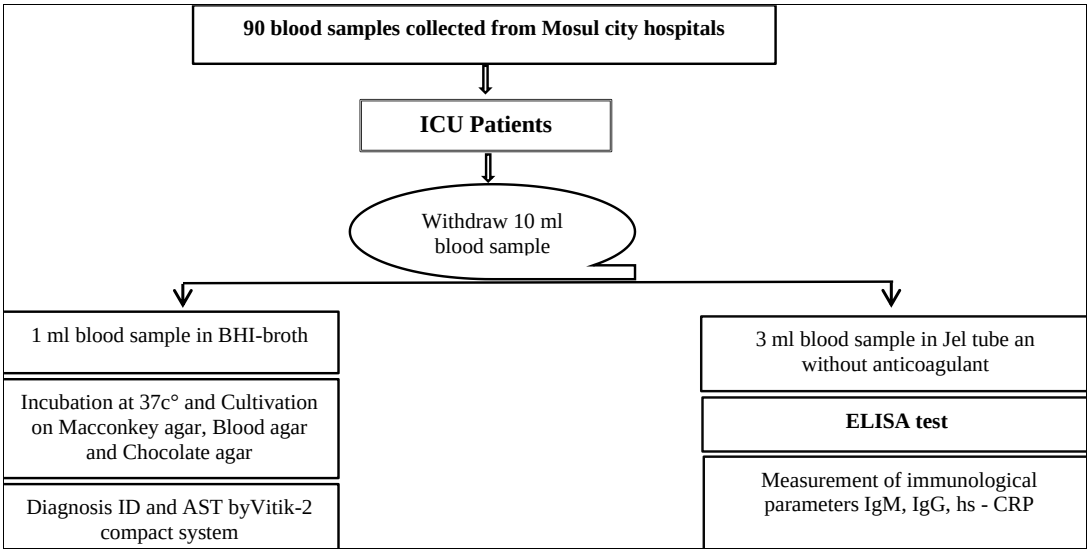

Fig 1: methodology of procedure assay

Isolation and Identification of Gram-Positive and Gram-Negative Bacteremia

All the appeared bacterial colonies on the specific culture media were identified by gram stain, biochemical tests (Catalase and Oxidase test) (Granato *et al.*, 2019) [12], VITEK 2compact system was also used utilizing ID-GNB and ID-GPB cards (BioMerieux, France) (Bagudo *et al.*, 2020) [8].

Results and discussion

The demographic characteristic of the study

According to Figure (2) below, the results of our study may differ with local and international previous studies, it is difficult for the results of our study to agreed for several reasons, including the difference in the size of the clinical sample, geographic and climatic differences, the immune response of population groups, microbiologic techniques in pathogen isolation, in addition to the application of primary health care programmes, medical staff working in intensive care units and infection control programs. The current study included 114 blood samples as a total of (90 blood sample) taken from ICU patients and 24 blood sample taken from healthy control group), patients group including (40 male and 50 female patients), while healthy control group including (12 male and 12 female) this is demographic characteristic of the study group as shown in Figure (2) below.

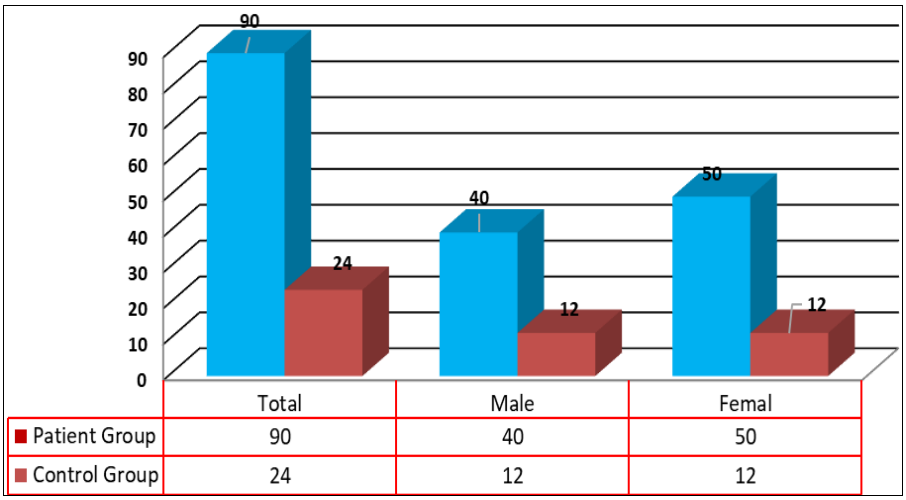

Fig 2: The demographic characteristic of the study.

Distribution of the patients group according to sex

Figure (3) illustrates 90 blood samples were collected from patients confirmed to be infected with the Gram-positive and Gram-negative Bacteremia and those hospitalized in ICU in Mosul city hospitals in Nineveh Governorate/Iraq after their diagnosis by specialist doctor. It is found that 24 blood samples are positive culture (male=9, female =15), and 66 blood samples revealed negative cultures without growth (male= 31, female=135), for different age groups ranging from (21-90) years, The result of current study showed that the incidence of bacteremia for both sexes of the study group was 24(26.67%) while the percentage of non-bacteremia of the study group was 66(73.33%). The results of our study may agree with previous studies in close proportions such as local and international studies (Al-Saadi, 2011 [4]; Akbar, 2000) [3]. The result also showed that the incidence of bacteremia for females (62.5%) higher than the incidence of bacteremia in males (37.5%). Our results indicated the presence of bacteremia which were also obtained by other investigators (Komori *et al.*, 2020) [17]. Distribution of the patients group with bacteremia and non-bacteremia according to sex as shown in Figure (3) below.

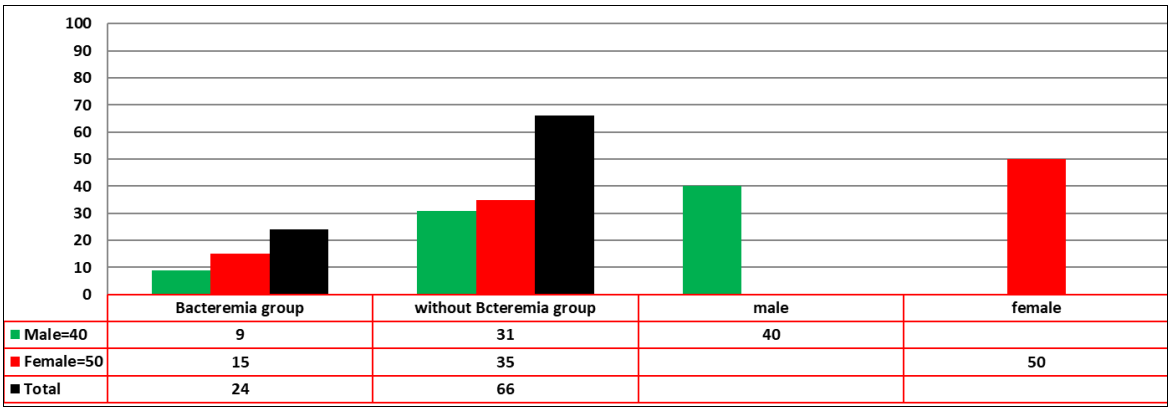

Fig 3: distribution of the patients group according to sex

Statistical Analysis

Statistical analysis for immunological parameters were performed using independent t-test (two tailed) and Mann-Whitney *U* test. Descriptive statistics were calculated for all variables

Immunological Parameters

Level concentration of (IgM, IgG and hs-CRP) in Patients with Bacteremia group and Control Group

Table 1: and figure (4,5) below showed the level concentration of immunological parameters (IgM, IgG and hs-CRP) in patients with Bacteremia group compared to healthy control group.

Parameters	Patients with Bacteremia group (Men ± SD)	Control Group (Men ± SD)	P-value
IgM	620±1075 pg/ml	40.9±22.5	0.001**
IgG	0.121±0.454 pg/ml	0.00±0.00	0.001**
hs-CRP	7.59±1.10 mg/l	0.963±0.907	0.001**

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

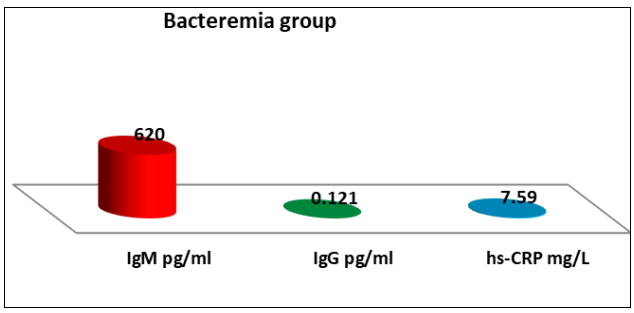

Fig 4

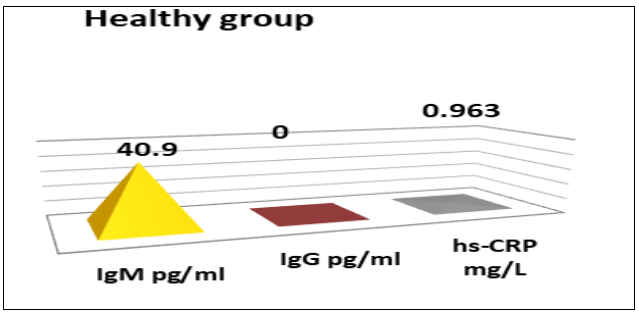

Fig 5

The results that expressed in table (1) mentioned above, show the relationship between bacteremia and immunological parameters studied in ICU patients, high level of IgM, IgG and hs-CRP found in serum of bacteremia patients group compared with healthy control group high significant difference (P-value < 0.001). The mean of IgM and IgG of patients with bacteremia compared to healthy control group were reached to (620±1075; 40.9±22.5 pg/ml), (0.121±0.454; 0.00±0.00 pg/ml) respectively.

Immunoglobulins (Igs) and cells of the innate and adaptive immune systems play a critical role in a host's response to sepsis. The aim of this study was to investigate the possible differences in the levels of IgM, IgG and hs-CRP in relation to the microbiological and clinical responses of ICU patients with sepsis or septic shock based on clinical manifestation (Aretha *et al* 2021) [7]. The changes in total of immunoglobulines concentrations may

reflect exposure to environmental triggers, such as viral infections, bacterial infections, hypertension, shortness of breathing (SOB), heart failure (HF) or insulinopenia prior to clinical disease onset (Gorus *et al*.,1998) [11]. Because of recurrent infections to ICU patients and continuous exposure to pathogens, immune system can be defensed by secretion the primary and secondary response markers (i.e. IgM and IgG respectively) in order to defense against the infections (Abbas *et al*.,2021) [1]. Microbial products stimulate granulocytes, macrophages and NK cells to produce cytokines, these cytokines promote and regulate humoral and cell-mediated immune responses (CMI) and inflammation. It released from T-cells stimulate B cell to produce antibodies (Apurba, S.S., & Sandhya, B.K. 2019b) [5,6]. Humoral or antibody mediated immune response (AMI) provides protection to the host by secretion antibodies that can bind and neutralize microbial antigens circulating free or present on the surface of the host cells and in the extracellular spaces but have no role against intracellular antigens. Cell-mediated immune response provides protection to the host against intracellular microbe as well as virus-infected cells, tumor cells or transplanted cells and respond to antigen presented by antigen presenting cells (APCs), (Rahi, 2003) [26].

hs-CRP as indicated in the statistical analysis of table (1`) above, the mean of hs-CRP of patients with bacteremia was substantially higher (P < 0.001) than the healthy control group, which reached to(7.59±1.10 mg\L) compared with healthy control group (0.963±0.907mg\L. Changes of hs-CRP levels can be useful in the diagnosis of bacterial infection (Adnet *et al*., 1996) [2]. In which hs-CRP levels were substantially greater in ICU patients with bacteremia than in healthy control group this means that even when their temperature is normal or not. Respiratory and heart diseases patients are always infected, inflamed, and have immune system dysfunction. Some critical illness patients have a high CRP level, indicating that they were infected with bacteria or that they were inflamed by the disease itself (Han *et al*., 2007). Agreement with previous study demonstrated that the CRP levels in the blood have been linked to the severity of infection, also it is study showed CRP is a valuable biomarker for monitoring therapy response (Cho and Choi, 2014).

Level concentration of (IgM, IgG and hs-CRP) in Patients without Bacteremia group and Control Group

Table 2: and figure (6) below showed the level concentration of immunological parameters (IgM, IgG and hs-CRP) in group of patients without bacteremia compared to healthy control group

Parameters	Patients without Bacteremia group (Men±SD)	Control Group (Men±SD)	P-value
IgM	384±713 pg/ml	40.9±22.5	0.001**
IgG	0.333±1.11 pg/ml	0.00±0.00	0.001**
hs-CRP	7.86±1.69 mg/l	0.963±0.907	0.001**

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

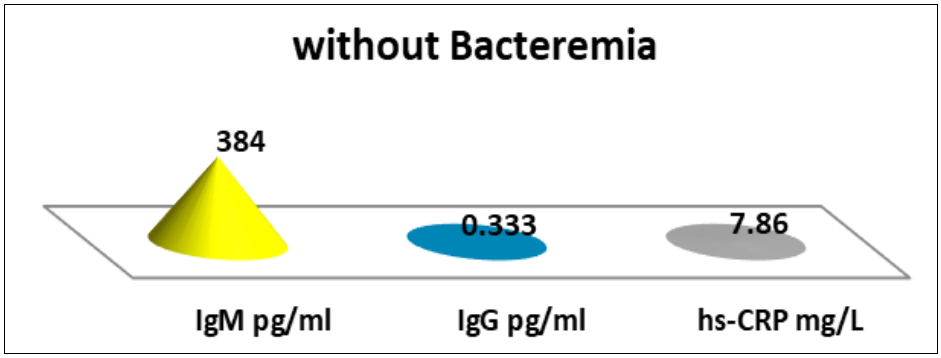

Fig 6

The results that expressed in table (2) mentioned above, show the relationship between patients without bacteremia group in ICU and healthy control group, high level of IgM, IgG and hs-CRP found in serum of patients without bacteremia compared with healthy control group high significant difference (P-value < 0.001). The mean of IgM, IgG and hs-CRP of patients without bacteremia compared to healthy control group were reached to (384±713; 40.9±22.5 pg/ml), (0.333±1.11; 0.00±0.00 pg/ml) and (7.86±1.69; 0.963±0.907 mg\L) respectively.

ICU patients in our study were classified by pulmonologists and cardiologists based on their chronic diseases, including asthma, chronic obstructive pulmonary disease, pneumonia, and congestive heart failure, as well as disease-related risk factors such as hypertension, diabetes, advanced age and smoking addiction.

With reference to the mentioned above, the clinical manifestations in patients included coughing, sneezing, wheeze, high temperatures, shortness of breath, chest pain and fluid accumulation in the lung, all of which are positive indications that patients suffer from microbial infection like viral infection which lead to co-infections (secondary bacterial infections) inhabiting the lung and mucous membranes in the upper and lower respiratory tracts. Some patients appeared to have high indicators of an elevated white blood cells with fever, perhaps they already had bacteremia such as Brucella, Mycobacterium tuberculosis and Haemophilus influenzae or other type of fastidious bacteria which need special culture media with high requirements for growth, however the researcher was unable to retrieve or recovery it on the basic culture media. Hence with each breath, the respiratory system is continuously challenged by harmful pathogens and foreign materials, therefore pulmonary immune system responds and plays a vital role in protecting pulmonary tissue or delicate structures of gaseous exchange against invasion from bacterial lung diseases. The epithelial cells of the upper respiratory tract secretes mucus via mucus glands and goblet cells, which traps foreign material including bacteria, this mucus is then swept towards the larynx, stimulating a cough reflex to eliminate trapped foreign materials (Muruganandah, V., & Kupz, A.2022a) [22, 23]. A range of antibacterial peptides are also secreted to providing immunity against microbes by inhibit bacterial growth (Johnstone, K. F., & Herzberg, M. C.2022) [16].

Bacteria that escape from innate immune responses into the lower respiratory tract are met with a wide range of innate immune responses at the terminal bronchioles and alveolar airspaces. The epithelial cells can initiate inflammatory responses once bacterial invasion is detected through several pathways including pattern recognition receptors (PRRs). Alveolar macrophages and dendritic cell (DCs) are poised to phagocytose local bacteria. Neutrophils are recruited to sites of high bacterial load via a range of chemical signals. Non-specific immunoglobulin produced by B cells and from previous immune responses can also assist with

opsonophagocytosis during early infection (Muruganandah, V., & Kupz, A.2022b) [22, 23]. So the statistical analysis of table (7) revealed that there were high significant differences (P< 0.001) in the concentration of IgM, IgG and hs-CRP in patients without bacteremia compared to healthy control group.

Conclusions

We found that Gram-positive bacteremia were predominant more than Gram-negative bacteremia especially *S. aureus* are still the classical causative agents of BSIs in Mosul city hospitals. We found high level of IgM, IgG and hs-CRP in serum of bacteremia and non-bacteremia patients group compared with healthy control group high significant difference P-value (<0.001).

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