ASSOCIATION OF AGE, GENDER AND PLATELET INDICES WITH BLOOD CULTURES AND ISOLATED BACTERIA IN SEPSIS

Aamna Latif*, Rabia Latif, Uzma Ishaq***, Sara Ali Zaidi****, Nimra Anwar*****, Jahanzeb Malik******

*Regional blood Centre, Islamabad Pakistan
**College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia
***Healthways Lab, Rawalpindi Pakistan
****Armed Forces Institute of Pathology (National University of Medical Sciences), Rawalpindi Pakistan
*****Army Medical College (National University of Medical Sciences), Rawalpindi Pakistan
******Rawalpindi Institute of Cardiology, Rawalpindi Pakistan

ABSTRACT

Objectives: Present study explored the association of sepsis with patients' age, sex and platelet indices [Platelet Count (PC), Mean platelet volume (MPV), MPV/PC)] with blood cultures and isolated bacteria.

Material and Methods: Adult patients (18-70 years old) with clinically diagnosed "sepsis" and had at least one blood culture and complete blood count performed during January to September 2020 were included in this cross-sectional study conducted at a tertiary care hospital in Pakistan. Data was collected regarding patients' age, sex, platelet indices, blood culture and bacterial profile.

Results: In 150 patients (79.3% females and 20.7 % males), Staphylococcus aureus was the most frequently isolated pathogen (52%) followed by Pseudomonas aeruginosa (12%). Chi-square test failed to reveal any association of gender (χ2 0.33, p 0.6); age (χ2 3.17, p 0.20); PC (χ2 0.1, p 0.9); MPV (χ2 2.36, p 0.30); MPV/PC (χ2 0.02; p 0.9) with blood culture results. No association was found between gender (χ2 0.68, p 0.4); age (χ2 2.99, p 0.84); PC (χ2 0.8, p 0.8); MPV (χ2 0.98, p 0.75); and MPV/PC (χ2 0.27; p 0.6) with isolated bacteria. Binary logistic regression showed that culture results and bacterial profile outcome cannot be predicted based on gender, age, PC, MPV or MPV/PC (p 0.50, 0.95, 0.83, 0.12, 0.84 and p 0.16, 0.12, 0.28, 0.43, 0.39 respectively).

Conclusion: The predominant bacteria in our subjects was Staphylococcus aureus, followed by Pseudomonas aeruginosa. Blood culture results and bacterial profile are not associated with and cannot be predicted based on age, gender and platelet indices.

Key Words: Blood culture, Mean platelet volume, Pathogens, Platelet count, Sepsis.

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INTRODUCTION

Sepsis is a common and complicated dysregulated inflammatory host response to a systemic infection resulting in organ malfunctioning [1]. The incidence of sepsis is rising worldwide due to an increasing elderly population, antibiotic resistance, and better diagnostic facilities [2].

Blood culture plays the most significant role in diagnosing and treating sepsis. Targeted antimicrobial therapy is possible only after identification of the sepsis-causing organism [3]. However, blood culture test is costly, and its results are delayed for 5-7 days. Furthermore, culture-negative sepsis is common [4-6] that may lead to unnecessary antibiotic therapy, extended hospital stays, and emergence of resistant pathogens. The epidemiology of sepsis varies with the geographic location, age, and gender [7,8]. For example, Salmonella Paratyphi is the predominant organism isolated from blood samples in Africa while *Salmonella* Typhi is commonly found in Asia. Both serotypes differ in their antibiotic sensitivity pattern significantly [7]. Hence, knowledge of local epidemiology may assist clinicians to make right diagnosis and start treatment well before getting the results of blood culture. In developing countries like Pakistan who lack a proper hygiene and healthcare system, an initial treatment is generally commenced based on the patient's clinical symptoms instead of blood culture results. Therefore, an up-to-date knowledge of the sepsis epidemiology in a locality and its associated factors may improve sepsis's prognosis and outcome. One of the factors that might be associated with sepsis is Mean Platelet Volume (MPV) and Platelet Count. Platelets play a critical role in sepsis. Interaction with pathogens may produce platelet adhesion, activation, aggregation, and release of platelet- derived mediators to clear the pathogens [9]. MPV is commonly raised [10] and PC is often reduced in sepsis [11]. However, the

Correspondence: Dr Aamna Latif, Consultant Haematologist, Regional Blood Centre, Islamabad Pakistan.

Email: **aamnalatif6@gmail.com**

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association of these parameters with blood culture results and microbial profile in sepsis have not been investigated.

The objective of this study was to detect the predominant bacteria involved in sepsis in patients from a tertiary care hospital in Rawalpindi Pakistan, and to explore the association of patients' age, sex, and platelet indices (PC, MPV, MPV/PC) with blood culture results and microbial profile.

MATERIAL AND METHODS

Ethical approval for this cross-sectional study was obtained from the Institutional Review Board at Fauji Foundation Hospital, Pakistan (a tertiary care hospital of 811 beds). Informed consent form was signed by each study participant.

Study population: Adult patients (18-70 years old) with clinically diagnosed "sepsis" and having at least one blood culture and complete blood count performed during January 2020 to September 2020 were included in study. Personal data about age, sex, antibiotic status, comorbidities, and drug history was recorded. Patients who fulfilled the inclusion criteria were excluded if they were on antibiotics, antiplatelet drugs or immuno-suppressants, or if they were suffering from immune thrombocytopenia, Bernard Soulier syndrome, ischemic heart disease, myeloproliferative disorders, and chronic liver disease.

Sample size calculation: Sample size for this cross-sectional study was calculated using the formula [12]. $N = (Z^2 * P (1 - P))/d^2$ where N = Sample size; Z = 1.96 for 95 % Confidence Interval (from probability tables); P (Prevalence of culture-positive sepsis cases) = 40 %; d (relative precision) = 20 % of the P. Value of P was found from a pilot study in which 6 out of 15 septic patients fulfilling the inclusion criteria were found to be culture positive. Putting all the values in the equation gave the sample size equal to 144 which was rounded off to 150.

Sepsis definition: For clinical diagnosis of "sepsis", FFH follows the diagnostic criteria developed by the Society of Critical Care Medicine and American College of Chest Physicians in 1991 and revisited in 2001[13]. Sepsis was defined as a systemic response to infection. It is indicated by two or more of the following conditions.

Temperature >38°C or <36°C

HR > 90 beats/min

RR > 20 breaths/min or PaCO2 <32 mmHg (<4.3 kPa)

WBC > 12000 cells/mm3, < 4000 cells/mm3, or > 10 % immature (band) forms

Study variables: Independent variables were age, gender, and Platelet Indices (PC, MPV, MPV/PC) Dependent variables were Blood Culture Results and Microbial Profile

Platelet Indices: 2.5 ml venous blood was collected in vacutainers containing EDTA (ethylene diamine tetra acetic acid), mixed properly and transferred to the hematology lab. Later, all samples were analyzed on an automated hematology analyzer (SYSMEX XT 1800i system), which uses impedance technology (electrical resistance detecting method) to measure platelet count and MPV. When the diluted suspension passes through the small aperture, each cell changes the resistance of the electrical current between two electrodes on both sides of the aperture. Electrical impedance is proportional to the volume of the particle traversing the aperture, and so this method can give estimated cell size and count.[14] The analyzer calculates the platelet volume by analyzing the platelet distribution curve, which is calculated from a log transformation of the platelet volume distribution curve, to yield a geometric mean for this parameter in impedance technology systems[15]. All samples were processed within an hour of sampling to prevent time-dependent EDTA-induced deformation of platelets that can produce inaccurate platelet parameters. Extreme care was taken during collection, handling, and processing of the samples to avoid preanalytical errors. PC and MPV values were recorded and MPV/PC ratio was calculated.

Blood culture results and Bacterial Profile: 20 ml of blood was collected under aseptic conditions, by venipuncture; and 10 ml blood each was put in an aerobic and an anaerobic culture bottle. Bottles were clearly labeled with the patient ID, date, time, and site of collection. Before inoculating the culture bottles, their septums were wiped with 70% alcohol swabs. Bottles were shaken to avoid blood clotting and then transported to the Microbiology laboratory of the hospital, where the blood cultures were processed according to the laboratory protocol. Briefly, blood culture bottles were incubated at 35-37°C and regularly checked two times a day for evidence of microbial growth, such as turbidity, hemolysis, coagulation, pellicles, formation of any gas/white grains/floccular deposits. If a sign of growth was identified, a small amount of broth was removed aseptically with a Pasteur pipette, and a Gram-stained smear was analyzed by microbiologist to identify the pathogens. This was followed by making subcultures on suitable media. Even in the absence of any growth signs, subcultures were performed routinely after 18-24 hours of incubation on chocolate

agar to detect those pathogens that flourish without any noticeable change in the broth.

Data stratification: To explore the association of study variables with blood culture results/microbial strain, variables were stratified as following; Age (18-40 years and 41-70 years), Gender (male and female), PC (≥ 150 x 109/L and < 150 x 109/L), MPV (raised and not raised), MPV/PC Ratio (<0.05 and ≥0.05). Thrombocytopenia was defined as PC < 150 x 109/L. The normal reference range for MPV was 8.3 fL to 13.2 fL in our lab. For MPV based stratification, a cut-off value of 10.35 fL was used [16]. For MPV/PC Ratio based stratification, an MPV/PC cut-off value of 0.05 fL/(109/L) showing 60% sensitivity and 73% specificity in receiver operating characteristic curve was used [17]. SPSS version 20 was employed to analyze the data. Datasets were first checked for missing values and outliers. Frequencies were obtained by descriptive statistics. A Chi square (χ^2) test and a Binary Logistic Regression Analysis test were carried out to identify the factors associated with blood culture results. In Binary Logistic Regression analysis, the presence or absence of microorganisms was taken as a dependent variable and the rest of all variables as covariates/predictors. P values < 0.05 were considered significant.

RESULTS

Majority of the septic patients coming to Fauji foundation hospital during that period were of female gender (79.3%) and having PC ≥ 150 x 109/L (68.67%). Blood cultures were positive in 33.33 % patients only. Among those who were found culture positive, S. aureus was the most frequently isolated pathogen (52%) followed by P.aeruginosa (12%) (Table-I). None of the study variables was found to be associated with blood culture results and microbial profile (Table-II & III). Binary logistic regression showed that culture results' and microbial profile outcome cannot be predicted based on age, PC, MPV or MPV/PC Ratio (Table-IV). The predominant microbial strain in our subjects was Staphylococcus aureus, followed by Pseudomonas spp (Table V & VI).

Table-I: Frequency distribution of study variables.

S #	Variables	Number (%)
1.	*Gender*	
	Male	31 (20.7)
	Female	119 (79.3)
2.	*Age (years)*	
	18-40 years	67 (44.67)
	41-70 years	83 (55.33)
3.	*Platelet Count (PC)*	
	≥ 150 x 10^9/L	103 (68.67)
	< 150 x 10^9/L	47 (31.33)
4.	*Mean Platelet Volume (MPV)*	
	Raised (≥10.35 fL)	71 (47.3)
	Not raised (<10.35 fL)	79 (52.7)
5.	*MPV/PC Ratio [fL/(10^9/L)]*	
	< 0.05	59 (39.3)
	≥ 0.05	91 (60.7)
6.	*Blood Culture*	
	Culture-Negative	100 (66.67)
	Culture-Positive	50 (33.33)
	Gram-Positive	33 (22)
	Gram-Negative	17 (11.33)
7.	*Microbial Strain in Culture*	
	Staphylococcus aureus	26 (52)
	Pseudomonas	6 (12)
	MRSA	4 (8)
	E. coli	3 (6)
	Burkholderia cepacia	3 (6)
	Bacillus	2 (4)
	Klebsiella pneumoniae	2 (4)
	Streptococcus pyogenes	1 (2)
	Acinetobacter baumannii	1 (2)
	Enterobacter	1 (2)
	Stenotrophomonas maltophilia	1 (2)

Table-II: Association of study variables with Blood Culture Results.

Variables	Groups	Culture Negative *(Number)*	Culture Positive *(Number)*	Chi square (χ^2)	P value
Gender	Male	22	9	0.325	0.56
	Female	78	41		
Age	18-40 years	46	21	0.216	0.64
	41-70 years	54	29		
Platelet Count (PC)	≥ 150 x 10^9/L	69	34	0.015	0.9
	< 150 x 10^9/L	31	16		
Mean Platelet Volume (MPV)	Raised (≥10.35 fL)	43	28	2.260	0.13
	Not raised (<10.35 fL)	57	22		
MPV/PC Ratio fL/(109/L)	< 0.05	40	20	0.000	1.0
	≥ 0.05	60	30		

Table-III: Association of study variables with Blood Microbial Profile.

Variables	Groups	Gram- Positive *(Number)*	Gram-Negative *(Number)*	Chi square (χ^2)	P value
Gender	Male	7	2	.678	.410
	Female	26	15		
Age	18-40 years	11	10	2.99	.084
	41-70 years	22	7		
Platelet Count (PC)	≥ 150 x 10^9/L	22	12	.079	.778
	< 150 x 10^9/L	11	5		
Mean Platelet Volume (MPV)	Raised (≥10.35 fL)	19	9	.098	.754
	Not raised (<10.35 fL)	14	8		
MPV/PC Ratio fL/(10^9/L)	< 0.05	13	8	.271	.603
	≥ 0.05	20	9		

Table-IV: Binary logistic regression analysis of blood culture results (culture positive or negative) and blood microbial profile (gram- positive or gram-negative) with study variables.

Blood Tests	Study variables	P value	Odds Ratios	95% Confidence Interval	
				Lower	Upper
Blood Culture Results	Gender	.502	1.370	.546	3.438
	Age	.948	1.001	.979	1.023
	Platelet Count (PC)	.830	1.000	.998	1.002
	Mean Platelet Volume (MPV)	.122	.789	.584	1.066
	MPV/PC Ratio	.842	1.138	.318	4.070
Blood Microbial Profile	Gender	.156	.244	.035	1.709
	Age	.117	.968	.929	1.008
	Platelet Count (PC)	.283	.997	.992	1.002
	Mean Platelet Volume (MPV)	.432	.779	.418	1.452
	MPV/PC Ratio	.392	.095	.000	20.893

Table-V: Distribution of gram-positive strains in relation to study variables

Variables	Subgroups	*Staphylococcus aureus (Number)*	*MRSA (Number)*	*Bacillus (Number)*	*Streptococcus pyogenes (Number)*
Gender	Male	4	1	2	0
	Female	22	3	0	1
Age	15-40 years	9	1	0	1
	41-70 years	17	3	2	0
PC	≥150 x 10^9/L	19	2	2	0
	<150 x 10^9/L	7	2	0	1
MPV	Raised (≥10.35 fL)	14	1	2	1
	Not raised (<10.35 fL)	12	3	0	0
MPV/PC Ratio fL/(10^9/L)	< 0.05	11	2	0	0
	≥0.05	15	2	2	1

PC: Platelet Count; MPV: Mean Platelet Volume; MRSA: Methicillin-resistant Staphylococcus aureus

Table-VI: Distribution of gram-negative strains in relation to study variables.

Variables	Sub groups	*Enterob-acter (Number)*	*E. coli (Number)*	*Pseudo-monas (Number)*	*Klebsiella pneumoni-ae (Number)*	*Stenotroph-omonas maltophilia (Number)*	*Burkholde-ria epacia (Number)*	*Acinetoba-cter baumannii (Number)*
Gender	Male	1	1	0	0	0	0	0
	Female	0	2	6	2	1	3	1
Age	15-40 years	1	3	3	0	1	1	1
	41-70 years	0	0	3	2	0	2	0
PC	≥150 x 10^9/L	0	2	4	1	1	2	1
	<150 x 10^9/L	1	1	2	1	0	1	0
MPV	Raised (≥10.35 fL)	1	2	3	1	1	2	0
	Not raised (<10.35 fL)	0	1	3	1	0	1	1
MPV/MPC Ratio fL/(10^9/L)	< 0.05	1	2	1	1	0	3	0
	≥0.05	0	1	5	1	1	0	1

PC: Platelet Count; MPV: Mean Platelet Volume; E. coli: Escherichia coli

DISCUSSION

Our study did not find any association of blood culture results and microbial profile with age, gender, and platelet indices. In our study population, sepsis was more common in females (79%), contrary to the published studies that reported male predominance in sepsis (59% - 72%) [18,19,20]. Compared to males, female patients' turnover is higher in FFH because of entitlement of ex-military service men's families in this hospital. This might be the reason of female gender predominance in our study and it may not represent true incidence of sepsis in general population gender wise.

Thrombocytopenia was present in 31% of the septic patients in our study. This agrees with Claushuis *et al*.,[11] who reported thrombocytopenia in 37.7% septic patients. Vardon- Bounes *et al*., [21] summarized etiology of sepsis-induced thrombocyte-penia as decreased production, increased consumption/ sequestration, and immune-mediated destruction [22]. MPV was raised in 47.3% of the patients. Rise in MPV values has been observed in several inflammatory conditions and attributed to the increasing concentration of proinflammatory cytokines chiefly IL-6 that causes an increase in the size of megakaryocytes, which results in large size platelets production [23]. Variations in MPV values could be due to the variations in PC as MPV is highly correlated to PC [24] and platelet activity [25]. Gao *et al*.,[10] reported significantly higher MPV in survivors compared to non-survivors' patients in septic shock. Blood culture was positive in one-third (33%) of the septic patients only. This shows that there is a limited chance of identifying pathogens in blood cultures. This agrees with published literature which mentions less than 50% septic patients as culture positive [4,5,6]. Our results are contrary to Kethireddy *et al*.,[26] who conducted a large-scale study involving 8670 cases of septic shock in three countries (KSA, Canada and USA) and reported culture positive cases being 69.4%. Subjects in the study of Kethireddy *et al*. [26] were having either severe sepsis or septic shock whereas we included patients with all forms of sepsis. This might be the reason behind higher ratio of culture positive cases in Kethireddy's study compared to ours. Another reason of variability in culture positivity across different hospitals may occur probably due to the differences in the time from collection of blood to incubation. Gram positive bacteria were the most prevalent in our study participants. This agrees to Hanaganahalli *et al*. [27] who reported 72.4% gram-positive and 27.6% gram-negative bacteria in neonatal sepsis and Djordjevic *et al*.,[28] who reported 16.6% gram-positive and 3.8% gram-negative and 46.9% polymicrobial species. There were some studies in which gram-negative organisms were predominant. Chatterjee *et al* [29] and Babu *et al* [30] reported prevalence of gram-negative bacteria as 73.4% and 54% respectively.

CONCLUSION

Our study concludes that the blood culture results and microbial profile are not associated with and cannot be used to predict sepsis based on age, gender, platelet indices. Gram-positive bacteria are common in our hospital. The predominant microbial strain was *Staphylococcus aureus* regardless of the age, gender, and platelet indices, followed by the *Pseudomonas aeruginosa*. The study was limited to 150 patients only, at a single center which may preclude generalizability. The epidemiology of sepsis patients might be different in other hospitals. All our patients were adults (18-70 years old). The

epidemiology may be different in other age groups such as pediatric and geriatric.

AUTHOR CONTRIBUTION

Aamna Latif: Participated in study design, data acquisition, data analysis, drafting and submission of the final manuscript.

Rabia Latif: Participated in critical review and submission of the final manuscript.

Uzma Ishaq: Participated in data acquisition.

Sara Ali Zaidi: Participated in data analysis.

Nimra Anwar: Participated in data analysis

Jahanzeb Malik: Participated in study design and critical review of the article.

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