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Thrombocytopenia and its Relationship with Bleeding Manifestations in Dengue Patients-A Tertiary Care Hospital Experience

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ABSTRACT

Objective: To explore the extent of bleeding among three different groups of patients based on their blood platelet count and identify the frequency of specific types of bleeding manifestations among the study groups.

Study Design: Comparative prospective study.

Place and Duration of Study: Pak-Emirates Military Hospital, (PEMH) Rawalpindi Pakistan, from Jul to Dec 2019.

Methodology: One hundred patients hospitalized with dengue fever and platelet count of less than 100,000 per microliter of blood were enrolled in the study. They were divided into three groups based on platelet count, i.e., <20,000 (Group-1), 20,000-50,000 (Group-2), and >50,000 (Group-3) per microliter of blood and observed for different types of bleeds and were also categorized as no bleed, single-site bleed and multiple-site bleed.

Results: Group comparisons revealed that no patient from Group-1 versus 3(10.3%), patients from Group-2 whereas 11(19.3%) patients from Group-3 experienced single site bleed (p=0.05). In addition, patients belonging to Group-1 experienced significantly more petechiae as compared to Groups 2 and 3 (92.8% vs 65.5% vs 19.2%, p<0.001). Similarly, gum bleeding and purpura were more commonly observed in Group-1 than in two other groups (50% vs 44.8% vs 14.0%, p 0.001; 85.7% vs 44.8% vs 3.5%, p<0.001, respectively).

Conclusion: Bleeding complications among dengue patients has a positive relationship with platelet count, but some specific bleeds, e.g., melena, hematemesis, hemoptysis and per vaginal bleed, cannot be directly correlated with the number of platelets circulating in the blood.

Keywords: Bleeding, Blood platelet count, Dengue hemorrhagic fever, Dengue infection, Thrombocytopenia.

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INTRODUCTION

Dengue has emerged as the fastest-spreading major global arboviral infection of serious public health concern.[1] According to World Health Organization, a total of 44,000 cases and 75 deaths were reported for dengue fever in Pakistan from July to November 2019.[2,3] Dengue has a wide spectrum of presentation ranging from mild asymptomatic dengue fever (DF) to potentially fatal dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[4,5] These life-threatening complications are attributed to severe thrombocytopenia and a drop in the coagulation factors leading to increased vascular permeability and multiple-organ bleeds.[6]

Recent studies show that all patients with thrombocytopenia do not develop bleeding complications. There are situations where there is no bleeding from any site, regardless of profound thrombocytopenia.[7,8] Thus merely relying on platelet count might not suffice to predict bleeding risk among dengue patients. We need to differentiate dengue hemorrhagic fever (DHF) patients with or without the manifestation of bleeding. Therefore, we need to investigate other potential tests with better positive predictive value (PPV) for the occurrence of hemorrhagic complications.[9]

This prospective comparative study was designed to differentiate between patients with dengue fever who do or do not develop hemorrhagic complications associated with thrombocytopenia. The objectives of our study were to explore the extent of bleeding among three different groups of patients based on their blood platelet count and identify the frequency of specific types of bleeding manifestations among the study groups.

METHODOLOGY

This prospective comparative study was conducted at Pak-Emirates Military Hospital, (PEMH) Rawalpindi Pakistan from July to December 2019. Ethical approval was sought from the Institutional Ethics & Review Board Committee (IRB letter no: A/124 EC 99). The minimum required sample size for

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this study was calculated to be 50 by using the formula n=z2x(p)(1-p)/α2, where the prevalence of dengue in Pakistan was considered to be 2.06%, 10 80% study power and 95% confidence level.

Inclusion Criteria: Patients of either gender, aged 15 years or more, admitted with acute febrile illness, serologically confirmed for dengue virus infection, either by positive NS-1 antigen (ELISA based) or dengue immunoglobulin M (IgM) rapid test, and a platelet count of less than 100,000 per microliter of blood were included in the study.

Exclusion Criteria: Patients who tested positive for dengue IgG antibodies, a history of bleeding tendencies or other underlying diseases that provoke bleeding, including a history of peptic ulcer, chronic liver disease or immune thrombocytopenic purpura were excluded from the study.

All the patients admitted to PEMH with confirmed dengue virus infection were enrolled in the study by convenience sampling. The study participants were divided into three groups based on their platelet counts. Group-1, with a platelet count of <20,000 per microliter, comprised 14 patients, while 29 and 57 patients belonged to Group-2, with a platelet count of 20,001–50,000 per microliter and Group-3, with a platelet count of >50,001 per microliter of blood, respectively. Patients of the three groups were then prospectively observed for the occurrence of bleeding, including petechiae, gum bleeding, purpura, epistaxis, melena, hematemesis, hemoptysis and PV bleeding; the patients were thus categorized as having no bleeding, single-site bleed, and multiple-site (two or more sites) bleed. The patient's demographic and clinical data were retrieved from medical files maintained by nurses in hospital wards.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Qualitative data were summarized using percentages and frequencies, and groups were compared using Chi-square. The *p*-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 100 patients were enrolled in the study with a mean age of 35.5±10.6 years, the majority of which (65%) belonged to the age group of 25–45 years. Overall, 41/100 patients had no bleeding, while 14/100 and 43/100 had single and multiple-site bleeding, respectively. Petechiae (43%) was the most common type of bleeding observed among dengue fever patients, followed by gum bleeding (28%), purpura (27%), epistaxis (17%), melena (5%), hematemesis (3%), hemoptysis (2%) and per vaginal bleed (2%) as shown in Table-I.

Table-I: Summary of Clinical Characteristics of Study Population (n=100)

Characteristics	%
Gender	
Male	73%
Female	27%
Age in years (Mean±SD)	35.5±10.6
Presenting Complaints	
Fever	100%
Vomiting	43%
Myalgia	25%
Joint pain	20%
Platelet Count (per micro liter of blood)	
<20,000	14%
20,001-50,000	29%
50,001-100,000	57%
Type of Bleed	
No bleeding	41%
Single-site bleeding	14%
Multiple-site bleeding	43%
Bleeding Manifestations	
Petechiae	43%
Gum bleed	28%
Purpura	27%
Epitaxis	17%
Melena	5%
Hematemesis	3%
Hemoptysis	2%
Per-vaginal bleed	2%

Group comparisons revealed that 38(66.6%) patients from group 3 had experienced no bleeding, while 11(19.3%) and 8(14.0%) patients experienced single and multiple-site bleeding, respectively (p<0.001). Similarly, in Groups-2, 3(10.3%) patients experienced no bleeding, while 3(10.3%) and 23(79.3%) patients had single and multiple-site bleeding, respectively. Finally, among Group-1, with the least platelet count, all 14(100%) patients experienced multiple-site bleeding complications (p<0.001), as shown in Table-II.

Table-II: Relationship Between Bleeding and Platelet Count (n=100)

Bleeding	Platelet Count per Micro Liter n (%)			*p*-value
	Group-1 <20,000 (n=14)	Group-2 20,001-50,000 (n=29)	Group-3 >50,001 (n=57)	
No Bleeding	-	3(10.3%)	38(66.6%)	<0.001
Single Site	-	3(10.3%)	11(19.3%)	0.005
Multiple Site	14(100%)	23(79.3%)	8(14.0%)	0.018

Group comparisons showed that patients belonging to Group-1 experienced significantly more petechiae than Groups 2 and 3(92.8% vs 65.5% vs 19.2%, p<0.001). Similarly, gum bleeding and purpura were more commonly observed in Group-1 than in two other groups (50% vs 44.8% vs 14.0%, p 0.001; 85.7% vs 44.8% vs 3.5%, p<0.001, respectively). However, in terms of epistaxis, melena, hematemesis, hemoptysis and per vaginal bleed, there was no significant difference in the occurrence of these manifestations among study groups (p=0.789, p=0.418, p=0.397 and p=0.257, respectively) as shown in Table-III.

Table-III: Comparison of Different Bleeding Manifestations Among the Study Groups (n=100)

Bleeding Type	Platelet Count per Micro Liter n (%)			*p*-value
	Group-1 <20,000 (n=14)	Group-2 20,001-50,000 (n=29)	Group-3 >50,001 (n=57)	
Petechiae	13(92.8%)	19(65.5%)	11(19.2%)	<0.001
Gum Bleed	7(50.0%)	13(44.8%)	8(14.0%)	0.001
Purpura	12(85.7%)	13(44.8%)	2(3.5%)	<0.001
Epitaxis	5(35.7%)	10(34.4%)	2(3.5%)	0.567
Melena	-	1(3.4%)	4(7.0%)	0.789
Hematemesis	1(7.1%)	2(6.8%)	-	0.418
Hemoptysis	-	1(3.8%)	1(1.7%)	0.397
Per-Vaginal Bleed	-	2(6.8%)	-	0.257

DISCUSSION

WHO reports that dengue is currently endemic in 128 countries, mostly in tropical and subtropical regions with a 3.9 billion population at risk for infection,[11] and it has been declared as one of the major public health problems in Pakistan.[12] A study conducted by Ahmad *et al.*[13] showed that the prime transfusion season for spreading of virus comprises of later half of the year starting from June to January in Pakistan. During this period, the house index for dengue ranges from 12-18% and 14-29% in pre and post-monsoon seasons, respectively.

The results of our study revealed that thrombocytopenia was directly associated with bleeding manifestations in terms of no bleeding, single and multiple-site bleeding (p<0.001, 0.005 and 0.018, respectively). Similar results were reported by Jayashree *et al.*[8] Bashir *et al.*[14] Azeredo *et al.*[15] Khare *et al.*[16] and Tewari *et al.*[17] where thrombocytopenia showed considerable sensitivity towards predicting bleeding complications of dengue infection. On the contrary, Mourão *et al.*[18] reported no direct relationship between platelet count and bleeding manifestations among dengue patients.

Our study population of <20,000 platelet count per microliter of blood experienced significantly more petechiae, purpura and gum bleeding complications than the other two groups. However, in terms of melena, hematemesis, hemoptysis and per vaginal bleed, no significant difference was observed among the three study groups.

These findings are quite similar to the study by Bashir *et al.*[14] which involved 334 dengue cases, out of which thrombocytopenia was present in 81% of cases. In addition, the most common bleeding manifestations included gum bleeding, purpura and petechiae. In contrast, uncommon complications included hematemesis, hematuria and hemoptysis.

The study by Khare *et al.*[16] involved 58 patients, out of which 36(62.1%) had severe thrombocytopenia, almost half of whom developed bleeding complications. However, the authors established no significant difference in terms of further subdivision of platelet count and bleeding manifestations.

The results of a study conducted by Tewari *et al.*[17] are in-line with our results, in which the researcher examined 443 adult patients diagnosed with dengue infection, thrombocytopenia was seen among 335(67%) of them, and platelet transfusion was required in 46(9.2%) of the patients. In addition, bleeding complications were observed in 36(10.7%) patients, where petechiae were the most common manifestation, followed by hematemesis, melena and epistaxis, as we had observed in our study.

On the contrary, Mourão *et al.*[18] studied 178 dengue patients hospitalized at a tertiary care setup and reported no association between active bleeding and degree of thrombocytopenia at admission overall (p=0.302); however, patients diagnosed with dengue hemorrhagic fever had significantly lower platelet count as compared to dengue fever patients. He also reported that bleeding manifestations among the high-risk hemorrhagic fever group could not be correlated to the number of peripheral platelets. However, it does have an association with an overall clinical condition.

CONCLUSION

Bleeding complications among dengue patients has a positive relationship with platelet count. However, some specific bleeds, e.g. melena, hematemesis, hemoptysis and per vaginal bleed, cannot be directly correlated with the number of platelets circulating in the blood. Therefore, other biomarkers should also be considered to identify the patients at higher risk of bleeding.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

MMS & SN: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

ZU & MS: Conception, study design, drafting the manuscript, approval of the final version to be published.

MSK & DHK: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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