International Journal of Medical and Health Research
www.medicalsciencejournal.com
ISSN: 2454-9142
Received: 17-02-2023, Accepted: 06-03-2023, Published: 20-03-2023
Volume 9, Issue 2, 2023, Page No. 1-6

Comparison of platelet indices and coagulation profile as an early indicator for lowering the risk of mortality and morbidity

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Abstract
Introduction: The coagulation pathway represents a balance between the procoagulant pathway. Platelets, in addition to the coagulation pathway, play a pivotal role in hemostasis and thrombosis. Any disturbance of these pathways as a result of various diseases can inhibit the protective mechanism abilities of these pathways. There are overall 10 parameters that can help in evaluating the platelet and coagulation profile of patients which helps in the diagnosis and management.
Aims and Objectives: To assess and compare coagulation profile and platelet indices as a reliable early indicator of the severity of diseases like dengue, PIH, CLD, and CKD to decrease morbidity and mortality.
Methods: This is a cross-sectional study done on 201 patients attending OPD and IPD of CSSH Meerut from December 2020 to June 2022, requiring laboratory and serological investigation.
Results: Mean platelet count was found to be least in dengue and highest in diabetic patients and when mean platelet count was compared according to a different diagnosis, a significant difference was found with a p-value of 0.007. The coagulation parameters were also found deranged in various conditions with the values of PT and aPTT being highest in dengue and Pt values least in PIH whereas the values of aPPT were least in pyrexia of unknown origin.
Conclusion: This study gives a guideline for the investigation to be done in cases of various diseases which can alert the doctor regarding the severity of the disease, so that appropriate and timely management can be initiated, which can help in reducing mortality and morbidity among patients.

Keywords: coagulation profile, platelet indices, mortality and morbidity

Introduction

The regular coagulation pathway indicates a balance between the procoagulant pathway which is responsible for the formation of a clot and the anti-coagulant pathway which describes the mechanisms inhibiting the same beyond the injury site. Any irregularity of such a system may occur in the perioperative period or during severe illness, which may be secondary to various factors resulting in a tendency to either thrombosis or bleeding [1]. The coagulation profile is investigated through various tests such as Bleeding Time (BT), Clotting Time (CT), Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), and platelet count [2].

The Platelets are the cytoplasmatic bits of bone marrow megakaryocytes, having a diameter of 3-5 µm and a volume of 4.5–11 fL [3]. Platelets are active blood specks whose primary function, along with the coagulation factors, is hemostasis, or the prevention of bleeding. Platelets interact with each other and with leukocyte and endothelial cells, probing the vascular bed for sites of injury, where they become activated. When stimulated, platelets transform their shape by increasing their surface area thereby rapidly secreting the bioactive molecules stored within their alpha and dense granules [4]. Furthermore, they play an important role in hemostasis and thrombosis. The vast scientific evidence has established that platelets contribute to the inflammatory process, microbial host defense, wound healing, angiogenesis, and remodeling [5].

Lately, over the last few decades, unique platelet indices like MPV, PDW, and PCT have been researched and investigated as prospective platelet activation markers [6]. Platelet volume, a hallmark of platelet function and activity is measured as mean platelet volume (MPV) by hematology analyzers. MPV also can be used as an independent predictor of bleeding. It is a substitute marker of bone marrow activity; a high MPV specifies an increased megakaryocytic activity. A low MPV points towards marrow suppression and an increased risk of bleeding [7]. The interconnection of platelet count and MPV with bleeding and severity of the disease can potentially predict outcome [8]. Nevertheless, platelet activation alters the morphology of these cells, which can be assessed based on MPV (6.00-11.00µm³) and PDW (11-18%), an additional platelet parameter is plateletcrit (PCT), which is the volume engrossed by platelets in the blood as a percentage (0.150-0.500 %), is a reliable measurement of platelet biomass as it combines the MPV with the platelet count. [9] PCT relies solely on the platelet number. PCT is one of the important screening tools for detecting platelet abnormalities. Coagulation parameters and platelet indices are disturbed in several diseases like chronic liver disease, pre-eclampsia, eclampsia, sepsis, dengue, and diabetes mellitus.

As the coagulation profile and platelet indices are fluctuant in many diseases and are associated with increased mortality and morbidity, the present study was conducted to compare coagulation profile and platelet indices in patients coming to the tertiary care center.

Materials and Methodology

A cross-sectional study with a sample size of 201 patients (104 males and 97 females) in the age group ranging between 18 years and more than 60 years reporting to both the outpatient department (OPD) and Inpatient department (IPD) requiring laboratory investigations including serological investigations from December 2020 to June 2022 were included in this study.

Inclusion criteria

1. Patients age more than 18 years.
2. Both male and females subject in which CBC and Coagulation profiles are being done.

Exclusion criteria

1. Pediatric age group
2. The patient is on antiplatelet drugs and anticoagulant therapy
3. Patients who are critically ill (having malignancy)

Methodology

EDTA (CBC) sample was run on a hematology analyzer (Figure 1), which utilizes photometry and electrical impedance phenomenon to analyze various blood parameters. Platelet parameters of the patients were collected from routine laboratory blood investigations. The sodium citrate sample (for the Coagulation study) was run on Semi Automated Coagulation Analyzer (Figure 2) and various coagulation parameters were recorded. A manual platelet count obtained on routine peripheral smear findings of the respective cases was done. A peripheral blood smear was observed for uniform distribution of platelets. The serological tests were performed by using Leishman Stain. The values recorded were tabulated and compared to the normal reference values (Tables 1 and 2) and statistically analyzed.

Fig 1: Horiba Pentra XLR- CBC Analyzer

Fig 2: STA Compact Max Coagulation Analyzer

Table 1: Normal Reference values for the platelet count

Platelet Indices	>18 years
Platelet (× 10^3 / mm^3)	150–500
MPV (fl)	6.0-11
PCT (%)	0.150-0.500
PDW (%)	11-18

Table 2: Normal Reference Values of the coagulation profile

Coagulation Profile Parameters	>18 years
PT(sec)	11.4-14.6
aPTT(sec)	26.3-29.5
BT(min)	1-7
CT(min)	4-11
Fibrinogen(mg/dl)	200-400
D-Dimer(µml)	0.1-0.49

Statistical Analysis

Data collected were tabulated in an excel sheet and the means and standard deviations of the measurements per group were used for statistical analysis using SPSS 22.00 for windows; SPSS inc, Chicago, USA. For each assessment point, data were statistically analyzed using one-way ANOVA, and the level of significance was set at $p < 0.05$.

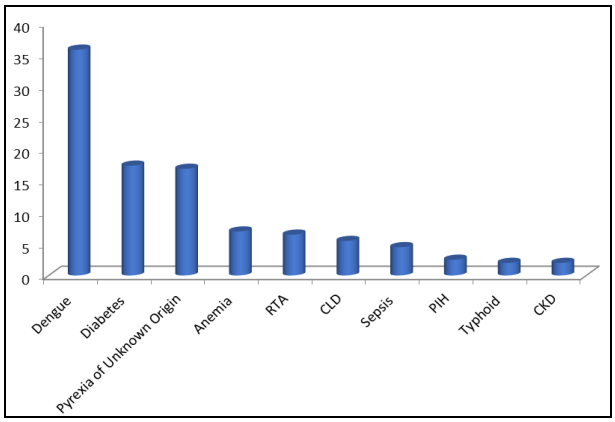
Results

The results of the present study revealed 51.7% and 48.3% of the subjects were male and female respectively. Maximum subjects were from the age group of 18-30 years (35.82%) followed by >41-50 years (18.91%) (Graph 1). Minimum subjects were from the age group of 31-40 years (13.43%) followed by 51-60 years (14.43%) (Graph 2).

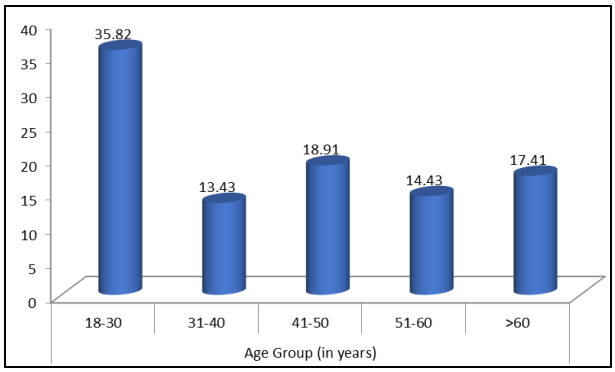
Out of 201 subjects, the most common diagnosis was dengue (35.82%) followed by diabetes (17.41%), 6.97% of the subjects were suffering from anemia and pregnancy-induced hypertension was found in 2.49% of the subjects. (Table 3)

Mean platelet count was found to be least in dengue (Figure 3), and pancytopenia subjects followed by anemia (Figure 4) and CLD (Figure 5). The highest mean platelet count was reported in diabetes followed by pyrexia of unknown Origin. When the mean platelet count was compared according to a different diagnosis significant difference was found. (Table 4)

Mean MPV was found to be least in dengue followed by anemia subjects. The highest MPV was reported in CKD subjects. When mean MPV was compared according to a different diagnosis, an insignificant difference was found as $p>0.05$. Mean PDW count was found to be least in dengue followed by anemic subjects and pyrexia of unknown Origin subjects. The highest mean PDW was reported in CKD subjects followed by typhoid and CLD subjects. When mean PDW was compared according to a different diagnosis, a significant difference was found. Mean PCT was found to be comparable among all the different diagnoses as $p>0.05$. Mean PT count was found to be least in PIH subjects followed by anemia. Highest mean PT was reported in dengue followed by sepsis and CLD subjects. When mean PT was compared according to a different diagnosis, a significant difference was found. (Table 5) Mean aPPT count was found to be least in Pyrexia of Unknown Origin subjects followed by RTA. The highest mean aPPT was reported in dengue followed by CLD subjects. When mean aPPT was compared according to a different diagnosis, a significant difference was found. (Table 6)



Graph 1: Diagnosis among the study subjects



Graph 2: Age distribution among the study subjects

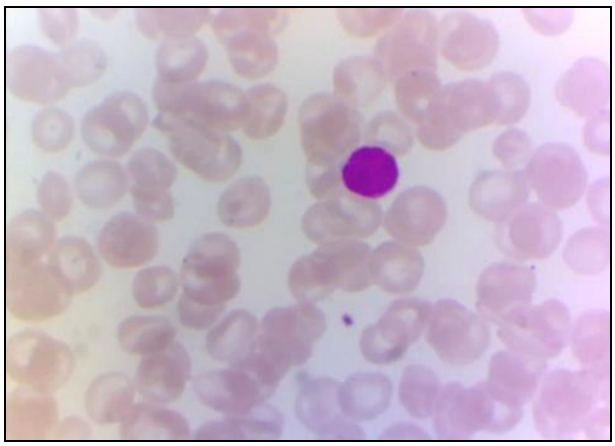


Fig 3: Decrease in Platelet count in Dengue (Leishman stain)

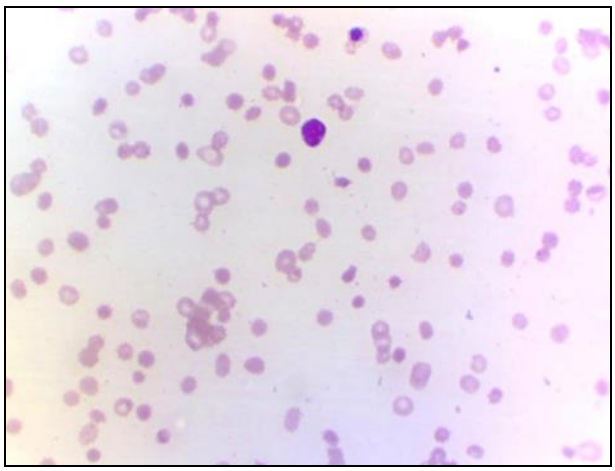


Fig 4: Low Platelet count in Microcytic Anemia (Leishman stain - 400X)

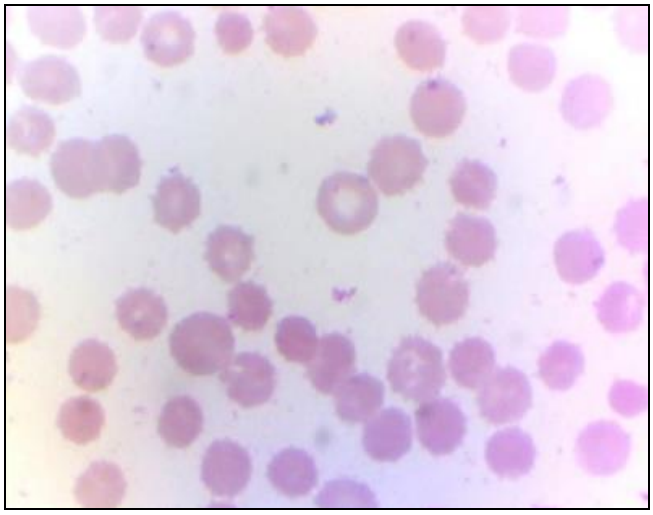


Fig 5: Decreased Platelet count with spur cells in Chronic liver disease (Leishman stain -1000X)

Table 3: Distribution of sample based on the diagnosis

Diagnosis	N=201	%
Dengue	72	35.82
Diabetes	35	17.41
Pyrexia of Unknown Origin	34	16.92
Anemia	14	6.97
RTA	13	6.47
CLD	11	5.47
Sepsis	9	4.48
PIH	5	2.49
Typhoid	4	1.99
CKD	4	1.99

Table 4: Comparison of platelet count (Normal:150-500) according to diagnosis

Diagnosis	Mean	SD	Anova test	p value
Anemia	79.50	35.994	7.31	0.007*
CKD	108.75	44.041		
CLD	88.73	55.225		
Dengue	17.39	87.788		
Pyrexia of Unknown Origin	218.94	79.654		
PIH	138.44	108.768		
Diabetes	241.17	65.909		
RTA	187.77	55.753		
Sepsis	114.56	50.792		
Typhoid	106.67	37.859		

Table 5: Comparison of PT (Normal:11.4-14.6) according to diagnosis

Diagnosis	Mean	SD	Anova test	p value
Anemia	16.98	2.28	6.86	<0.01*
CKD	23.13	9.29		
CLD	24.61	7.55		
Dengue	26.81	9.19		
Pyrexia of Unknown Origin	18.62	3.57		
PIH	15.85	2.78		
Diabetes	18.46	2.31		
RTA	17.79	2.69		
Sepsis	26.36	15.97		
Typhoid	20.40	5.75		

Table 6: Comparison of aPPT (Normal:26.3-29.5) according to diagnosis

Diagnosis	Mean	SD	Anova test	p value
Anemia	30.33	3.04	8.18	<0.01*
CKD	34.42	16.12		
CLD	40.48	20.19		
Dengue	41.04	7.04		
Pyrexia of Unknown Origin	23.79	4.36		
PIH	26.94	5.38		
Diabetes	31.47	10.76		
RTA	25.22	5.26		
Sepsis	38.07	13.58		
Typhoid	30.60	.78		

Discussion

The idea of blood coagulation dates back to the 1960's It was Ratnoff, Davie, and Macfarlane who described the "waterfall" and "cascade" theories outlining the vital principle of a cascade of proenzymes leading to activation of downstream enzymes [10]. Hemostasis is the arrest of bleeding, derived from the Greek word, heme meaning blood, and stasis meaning to stop [11]. Thrombo-hemorrhagic balance is maintained in the body by the interactions between coagulation and the fibrinolytic system also between platelets and the vessel wall. The results of our study demonstrated 51.7% and 48.3% of the subjects were male and female respectively. These were in concordance with the study done by Melak Aynalem *et al* [12] that revealed similar gender distribution i.e. out of 384 study participants; 210 (54.7%) of them were male. Almost similar results have been seen in other studies conducted in India and other countries. Nehara HR *et al* [13] carried out a study on 200 patients and found that 132 (66 %) were males and 68 (34 %) were females. Mehta SR also showed male preponderance (63%) to females (37 %) [14]. Prashant Patel *et al* [15] in their study too stated that liver disease was found to be more in males.

The results of our study showed mean platelet count to be least in dengue followed by pancytopenia subjects followed by Anemia and CLD. The highest mean platelet count was reported in diabetes followed by pyrexia of unknown origins. These results corroborated with those of Shailja Khansili *et al* [16] who reported that the maximum number of dengue patients 72 (36%) had platelet counts between 51000 and 1 lakh per cubic mm. 48 patients (24 %) had platelet counts of more than 1 lakh per cubic mm; 59 patients (29.50%) had a platelet count of between 21,000 and 50,000 per cubic mm; while remaining 21 patients (10.50%) had platelet counts less than 20,000 per cubic mm. The results were similar to a study done by Navya BN *et al* [17] which had maximum patients, 42 % with platelet counts between 51,000 and 1 lakh per cubic mm; 24 % had platelet counts between 21,000 and 50,000 per cubic mm; 20 % had platelet counts more than 1 lakh per cubic mm and least, 14 % had platelet counts less than 20,000 per cubic mm. In this study, thrombocytopenia was present in Pregnancy-induced hypertension (PIH) women. The low platelet count was related to immune-mediated destruction, platelet aggregation, and consumption, which occurs to be due to endothelial damage. Platelet activation leads to increased generation of thromboxane A2 and serotonin release, which leads to increased vasoconstriction and aggregation of platelets. Our study correlates well with the study by Chaudhary S *et al* [18] and Jambhulkar *et al* [19]. Mishra DP *et*

al [20] in their study similarly found that there is a significant increase in the number of patients with low platelet count with increased severity of the disease.

The results of our study showed mean MPV to be the least in dengue followed by anemia subjects and the highest MPV was reported in CKD subjects. When mean MPV was compared according to a different diagnosis, an insignificant difference was found as p>0.05. It showed similarity with the study done by Bashir AB *et al* [21] that showed a maximum number of dengue patients, 82 % having MPV between 9 and 13 fl, 17.4 % with MPV < 9fl, and 0.6 % patients with MPV more than 13 fl [9]. According to Shailja Khansili *et al* [16], 149 patients (74.50 %) had mean platelet volume (MPV) between 9 and 12.95 fl while 51 patients (25.50%) had MPV more than 12.95 fl and none had MPV more than 12.95 fl. Vijay Kumar Meena *et al* [22] in their study showed that dengue-positive cases were associated with low MPV(<13fl). MPV was also higher in diabetes (11.20) which was similar to the study done by Purnima *et al*. MPV has a major role in assessing complications of diabetes.

When mean PDW was compared according to a different diagnosis, a significant difference was found. Mean PDW count was found to be least in dengue followed by anemic subjects and pyrexia of unknown origin subjects. The highest mean PDW was reported in CKD subjects followed by typhoid and CLD subjects. In a study by Shailja Khansili *et al* [16], 144 patients (72%) had platelet distribution width (PDW) more than 14 fl; 56 patients (28%) had PDW between 9 and 14 fl and none had PDW less than 9. This was similar to the study done by Nehara HR *et al* [22] had 78% of patients with PDW more than 14 fl and 22% PDW between 9 and 14 fl. Navya BN *et al* [17] study also had a maximum number of patients, 92 % with PDW more than 13 fl and 8% of patients with PDW less than 13 fl. Bashir AB *et al* [21] study had 67.7% of patients with PDW between 9 and 14 fl; 27.8 % had PDW more than 14 fl and 4.5 % patients had PDW less than 9 fl. Vijay Kumar Meena *et al*[22] in their study showed that dengue-positive cases were associated with high PDW(>17fl) values in 62% of cases.

Mean PT count was found to be least in PIH subjects followed by anemia. Highest mean PT was reported in dengue followed by sepsis and CLD subjects. When mean PT was compared according to a different diagnosis, a significant difference was found.

Similarly, Tiruneh Adane *et al* [23] in their study showed that there is a high magnitude of prolonged PT in dengue fever patients. Similarly, Mishra DP *et al* [20] in their study showed that no cases had prolonged PT in control as well as mild preeclampsia groups. S. Gurdoy *et al* [24] in their study too revealed the elevation of PT in CLD subjects. Similarly, Tarun P. Kotadiya *et al* [25] in their study stated that in viral hepatitis, PT was prolonged in 75% of cases. In obstructive jaundice, 80% of cases show an increase in PT.

Mean aPPT count was found to be least in Pyrexia of Unknown Region subjects followed by RTA. The highest mean aPPT was reported in dengue followed by CLD subjects. When mean aPPT was compared according to a different diagnosis, a significant difference was found. APTT and PT represent the intrinsic and extrinsic pathways of the coagulation system. The elevation of PT and APTT might be caused by the downregulation. The non-structural protein 1 (NS1) of the dengue virus can bind with both thrombin and prothrombin. Which leads to the inhibition of prothrombin activation. This explains the changes in APTT which occur early before antibodies are formed. Coagulopathy is denoted by prolongation of APTT and shows an abnormality in the intrinsic pathway that can last for a few days during the disease course.

Prolongation of APTT in DF patients is due to a lack of intrinsic pathway probably due to impaired synthesis of coagulation factor or by an increase in consumption of some factors [23]. Similarly, Tiruneh Adane *et al* [23] in their study revealed that there is a high magnitude of increase in APTT in dengue fever patients. Tarun P. Kotadiya *et al* [25] described that aPTT has a significant role in cirrhosis. Bleeders showed prolongation of aPTT in 80% and non-bleeders show 15% cases. In viral hepatitis, decreased number of cases i.e. 22.5% rise in aPTT. In obstructive jaundice, 55% of cases show an increase in aPTT. In the present study, aPTT among the PIH women was found to be 26.94 which was a little higher than the normal value. Mishra DP *et al* [2] found, no prolongation of aPTT among mild preeclampsia, but the severe preeclampsia and eclampsia group had prolonged aPTT which correlated well with the study by Chaudhary S *et al* [18], Chaware S A *et al* [26] and Lakshmi CV *et al* [27]. Mean PT and aPTT were high in diabetic subjects and correlated well with the study done by H Pahim *et al* [28]. It aids in predicting long-term complications in such patients. This study gives a guideline for an investigation to be done in cases of various diseases which can alert the doctor regarding the severity of the disease, so that appropriate and timely management can be initiated, which can help in reducing mortality and morbidity among patients.

Conclusion

Platelet indices are a useful tool in dengue infection. Platelet count, PDW, MPV, and plateletcrit are useful in monitoring dengue fever. A decrease in MPV, and PCT and an increase in PDW are significant. Platelet indices play a significant role in predicting early diagnosis and severity of dengue in endemic areas. These parameters can help in the early and timely management of dengue and can reduce both mortality and morbidity in such patients. In advancing liver cirrhosis, the prolongation of PT and APTT indicates damage of liver parenchyma resulting in decreased production of coagulation proteins which increases the risk of bleeding tendencies, that can be detected before these ensue. The coagulation profile aids in predicting long-term complications in CKD patients. Hemodialysis done, in such patients have an advantageous effect, which can be overcome with monitoring of platelet indices and coagulation profile. From the study of platelet indices, it may be concluded that there is a mild decrease in platelet count in PIH and a significant reduction of platelets in preeclampsia and eclampsia patients when compared to normotensive pregnant patients. Thus, we concluded that platelet indices and coagulation profiles can be used as a reliable early indicator of the severity of diseases like dengue, PIH, CLD, and CKD. These are simple and easy routine tests that can be performed in every hospital and can help to timely diagnose and treat these patients, by doing so we can reduce the morbidity and mortality associated with these diseases.

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