

**Etiological Profile of Thrombocytopenia in Central Kerala and Pseudo Thrombocytopenia: A Diagnostic Pitfall in Automated Analysers**Feby T Francis<sup>1</sup>, Magdalene K F<sup>2</sup>, Antony Peter<sup>3</sup><sup>1</sup>Assistant Professor, Department of Pathology, Government Medical College, Palakkad<sup>2</sup>Professor, Department of Pathology, Government Medical College, Palakkad<sup>3</sup>Assistant Professor, Department of Pathology, Government Medical College, Palakkad

Received: 21-03-2023 / Revised: 22-04-2023 / Accepted: 25-05-2023

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Conflict of interest: Nil

**Abstract:**

**Background:** Thrombocytopenia is fall of platelets to below 150,000/micro L. It produces clinical symptomatology when the count falls below 100,000/micro L. Early detection and initiating suitable corrective measures avoids life threatening situations. Wide spread use of automated analysers could result in the diagnosis of pseudo thrombocytopenia/spurious thrombocytopenia resulting in a major diagnostic pitfall. In the post COVID pandemic years there were several case reports of COVID patients developing antibody against EDTA leading to platelet aggregates, hence spuriously low platelet count in automated analysers. Detection of pseudo thrombocytopenia is very important nowadays as it can avoid unnecessary interventions and treatment.

**Aim and Objectives:** To identify the etiological factors of thrombocytopenia, calculate the incidence of spurious thrombocytopenia and evaluate their causes; to establish the importance of peripheral smear examination in managing thrombocytopenia.

**Materials and Methods:** The study was undertaken at a tertiary care centre in central Kerala, India between August 2022 and February 2023; 07 months. Random Blood samples shown platelet counts <150000/micro L in haematology analyser were taken. Peripheral smear examination of such samples was undertaken to exclude the presence of platelet clumps. Incidence of pseudo thrombocytopenia was calculated. Etiological and epidemiological spectrums of thrombocytopenia were identified in correlation with other haematological parameters including bone marrow findings. Spurious thrombocytopenia samples were analysed separately and classified according to clinic-pathological diagnosis.

**Results:** A total of 1000 samples assessed using automated haematology analyser, using EDTA anticoagulant vacutainers shown platelet counts <1,50,000/micro L were analysed. Detailed etiological analyses including history, laboratory investigations, bone marrow study in necessary cases were done. Viral infection constituted for the 45.7% of the total blood samples showing thrombocytopenia's, followed by bacteriological infections constituting to 18.6% of the total cases. Parasitic infection like malaria constituted for 64/1000 (06.4%), alcoholic liver disease constituted for 57/1000 (05.7%), pregnancy was the cause in 51/1000 (05.1%), drug intake in 68/1000 (06.8%) patients and Leukaemias in 94/1000 (09.4%) patients. Among the 1000 cases 21 cases (2.1%) were diagnosed to have platelet clumps in peripheral smear examination (spurious thrombocytopenia/ pseudo thrombocytopenia). When these samples were examined using sodium citrate anticoagulant only 4 cases showed platelet clumps.

**Conclusion:** Prevalence of pseudo thrombocytopenia (02.10%) among 1000 patients with thrombocytopenia is significant. Among the true thrombocytopenia patients viral infections were the commonest cause. The other causes were Alcoholic liver disease, malarial parasitic infection and Leukaemias.

**Keywords:** COVID, Infection, Platelet, Pseudo Thrombocytopenia, Leukaemia, Thrombocytopenia.

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**Introduction**

Thrombocytopenia is defined as a platelet count below the lower limit of normal (i.e. <150,000/micro L [150 x 10<sup>9</sup>/L] for adults). Degrees of thrombocytopenia can be further subdivided into mild (platelet count 100,000 to 150,000/micro L), moderate (50,000 to 99,000/micro L), and severe (<50,000/micro L) [1]. It may result in poor clot formation and is

associated with a higher risk of bleeding [2]. The severity of thrombocytopenia ranges from an incidental finding otherwise undetected to severe life-threatening bleeding. So the early detection of the cause of thrombocytopenia followed by proper treatment may prove to be lifesaving. A bone marrow examination is a helpful and affordable diagnostic method in haematological practice. Both

neoplastic and non-neoplastic haematological conditions are identified using the aid of a bone marrow aspiration. This additionally, is used for the classification of anaemia, and the assessment of several cytopenias and unidentified pyrexia [3]. Common causes of thrombocytopenia included acute myeloid leukaemia, acute lymphoblastic leukaemia, megaloblastic anaemia, viral and bacterial infections, Immune thrombocytopenic purpura, and myelofibrosis. Pregnancy can cause thrombocytopenia physiologically. [3, 4, 5, 6, 7 and 8] Most of the hereditary causes of thrombocytopenia showed giant platelets in peripheral smear examination except Wiskott-Aldrich syndrome showing micro platelets. [9] Among infections COVID-19 accounts for a major portion of cases of thrombocytopenia for the last three years. Studies have shown that 35-40% of COVID patients present with mild to severe degree of thrombocytopenia. [10 and 11] Gestational thrombocytopenia (GT; defined as a platelet count below  $150 \times 10^9/L$ ) occurs in 04.4% to 11.6% of pregnancies, accounting for about 75% of all cases of thrombocytopenia in pregnancy. Platelet counts in many women show a gradual downward trajectory beginning in the second trimester, which is most likely from hemodilution related to an increase in plasma volume during pregnancy and possibly increased platelet clearance as mean platelet volumes, platelet volume distribution width, and platelet-derived cyclooxygenase products rise. A subset of women with GT develop a more significant decline in platelet count and a reduction in antithrombin III, suggesting a discrete pathogenesis that lies on a continuum with the haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome and acute fatty liver of pregnancy (AFLP) and that may be associated with a higher risk of recurrence in subsequent pregnancies. [12 and 13] Pseudo thrombocytopenia is caused by platelet clumping in vitro, which may be induced either by antibody-mediated agglutination, the most important causes of which are ethylene-diamine-tetra-acetic acid (EDTA) - dependent agglutination and platelet satellitism, or aggregation secondary to platelet activation resulting from improper blood sampling techniques or delayed mixing with anticoagulant in the test tubes (i.e., pre-analytical errors). [14] This phenomenon can typically be identified by reviewing the peripheral blood smear (PBS), using a different anticoagulant than dipotassium ethylene-diamine-tetra-acetic acid (EDTA) for blood collection, or maintaining the sample at around 37 °C before testing. [15] Reported for the first time in 1969 [14], pseudo thrombocytopenia (PTCP) has been increasingly described in patients suffering from various disorders and more recently even in patients with coronavirus disease 2019 (COVID-19) [16,17]. The widespread use of

automatic instruments for the analysis and counting of blood cells in clinical laboratories on the one hand has enabled the recognition of this phenomenon, but on the other hand has decreased the frequency of microscopic observation of blood films, which is the only procedure that can demonstrate the presence of platelet clumps with certainty [14]. The present study aims to identify the etiological factors of thrombocytopenia, calculate the incidence of spurious thrombocytopenia and evaluate their causes; to establish the importance of peripheral smear examination in managing thrombocytopenia.

### Materials and Methods

The present cross sectional study was undertaken in department of Haematology, in a tertiary care centre in central Kerala. An Institution ethics committee approval was taken and a consent form approved by it was used for this study.

**Inclusion criteria:** Patient's blood samples shown as platelet counts below  $1, 50, 000/\text{micro mol L}$  in automated analysers were included.

**Exclusion criteria:** Patients who could not be followed up with peripheral smear examination and patients in whom proper clinical history and details were not available were excluded from study. This was a Prospective analysis of the patients whose blood samples were reported as thrombocytopenia with automatic analyzers. Patients in whom the Peripheral smear examination was done alone were included in the study. The entire research procedure was in accordance with the ethical standards of the responsible committee on human experimentation. Informed consents were taken from the participants. Institutional Ethical Committee approval was taken. Sample size was calculated using the standard formula and a total of 1048 cases of thrombocytopenia were considered and from that 1000 cases satisfying the criteria were included in study.

### Methodology

Clinical data was collected for each case in a proforma: age, gender, signs and duration of clinical symptoms were noted. Laboratory investigation reports were collected from medical record library and lab registers. Fresh blood samples of the patients were taken in EDTA anticoagulant vacutainer tubes. Each sample was stained with Leishman stain for peripheral smear examination as per standard guidelines. A fresh 4ml sample was withdrawn in an ethylene diamine tetra acetic acid (EDTA) VIAL and peripheral smear was prepared with fresh blood. Leishman's stain was poured on the slide and waited for 2 minutes.

This was allowed for the fixation of peripheral blood film in methyl alcohol. A double quantity of

buffered water was added drop wise over the slide and mixed for 5 minutes. After washing it in water for 1-2 minutes, the slide was air dried and then examined in an oil immersion lens. [18] The patients were worked up systematically and findings were documented. All patients with platelet count below 1,50,000/micro L were subjected to peripheral smear examination.

Patients showing platelet clumps in smear were classified as pseudo thrombocytopenia. True thrombocytopenia cases having giant platelets and WBC inclusions were classified as hereditary thrombocytopenia. Samples having schistocytes were investigated with liver functions tests, coagulation profile and D dimer to exclude TTP/HUS.

Those patients showing blasts, Pelger – Huet anomaly, nucleated RBCs etc were subjected to leukaemia / MDS work up. Presence of lymphocytosis, atypical lymphocytes, neutrophilia and toxic granules indicated the presence of infection. ESR, CPR, CXR, blood cultures and virology tests were done to confirm the diagnosis. [19] After detailed clinical and laboratory assessment, all cases of true thrombocytopenia were classified according to aetiology.

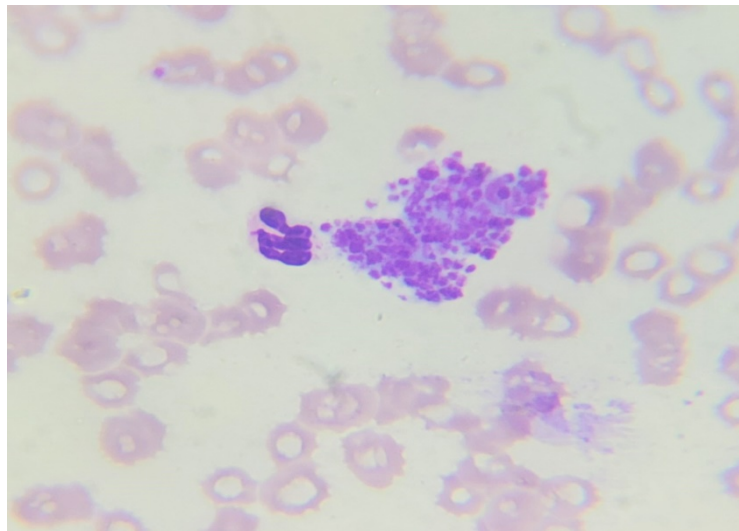
Patients showing platelet clumps were followed up with repeat blood count in automated analyser and repeat peripheral smear after taking fresh sample in sodium citrate vacutainers and checked whether the clumps disappeared in sodium citrate anticoagulant. 21 cases of spurious thrombocytopenia were analysed separately with fresh samples in different anticoagulant and repeat peripheral smear and other investigations.

**Statistical Analysis**

The results obtained along with patient details were entered in Microsoft excel and further analysis done using frequency measurements and cross tabulations using Statistical package for Social Science (SPSS) software version 17.0 where indicated.

**Results**

Sample size was 1000. All cases were having platelet count  $\leq 1,50,000/\mu\text{l}$  of blood and all were undergone peripheral smear examination. 21 out of 1000 cases were having platelet clumps in peripheral smear (spurious thrombocytopenia/pseudo thrombocytopenia), [Image 1]



**Figure 1: Photomicrograph of peripheral smear showing platelet clumps**

True thrombocytopenias were classified in mild, moderate and severe form (Table 1). There were 21/1000 (02.10%) of spurious thrombocytopenias in the study (Table 1).

**Table 1: Showing the Frequency distribution of thrombocytopenia (n-1000).**

Type of Thrombocytopenia	Number	Percentage
Mild	482	48.2%
Moderate	270	27.0%
Severe	227	22.7%
Spurious thrombocytopenia	021	02.1%
Total Number	1000	100%

Age and gender distribution of the patients was as follows (Table 2). Of the 1000 cases, majority of cases were males (60%) as compared to females (30%). The age distribution ranges from 05 years to 78 years with peak incidence among patients between 41-60 ages ranges; 302/1000 (30.20%). (Table 2)

**Table 2: Showing the Gender and age distribution of thrombocytopenia patients (n-1000)**

Age	Frequency (%)	Male	Female
≤10	046 (4.60%)	25 (02.5%)	021 (02.10%)
11-20	178 (17.80%)	109 (10.90%)	069 (06.90%)
21-40	257 (25.70%)	154 (15.40%)	103 (10.30%)
41-60	302 (30.20%)	152 (15.20%)	150 (15.00%)
>60	217 (21.70%)	163 (16.30%)	054 (05.40%)
Total number	1000 (100%)	603 (60.03%)	397 (39.70%)

Majority of the patients presented with fever as the main symptom. Some patients presented with more than one symptom. It was followed by abdominal pain, breathlessness, body ache, headache, sore throat, loss of appetite, cough and increased bleeding (Table 3).

**Table 3: Showed the Presenting complaints of patients with thrombocytopenia (n-1000)**

Symptoms	Number Of Patients
Fever	686 (68.6%)
Abdominal Pain	504 (50.4%)
Breathlessness	452 (45.2%)
Body Ache	444 (44.4%)
Headache	387 (38.7%)
Sore Throat	304 (30.4%)
Loss Of Appetite	288 (28.8%)
Cough	89 (08.9%)
Bleeding	79 (07.9%)
Weight Loss	66 (06.6%)
Asymptomatic	34 (03.4%)

Clinical signs of patients with thrombocytopenia were analysed and found that most of the patients presented with pallor and jaundice. Other signs were hepato-splenomegaly, lymphadenopathy, pedal edema and altered sensorium (Table 4).

**Table 4: Clinical signs of thrombocytopenia patients**

Signs	Number Of Patients
Pallor	385 (38.5%)
Jaundice	280 (28%)
Pedal Oedema	187 (18.7%)
Hepatosplenomegaly	106 (10.6%)
Altered Sensorium	043 (4.3%)
Lymphadenopathy	069 (6.9%)
Petechiae, Echymosis	044 (4.4%)
No Obvious Clinical Signs	112 (11.2%)

Etiological analysis of thrombocytopenia patients were done with proper history, examination of patients, referring of medical lab records, radiological and lab investigations.

Final results are shown in the following table (Table 5). Viral infection constituted for the 457/1000 (45.7%) of the total blood samples showing thrombocytopenia's, followed by

bacteriological infections constituting to 156/1000 (15.6%) of the total cases.

Parasitic infection like malaria constituted for 44/1000 (04.4%), alcoholic liver disease constituted for 57/1000 (05.7%), pregnancy was the cause in 51/1000 (05.1%), drug intake in 68/1000 (06.8%) patients and Leukaemias in 94/1000 (09.4%) patients (Table 5).

**Table 5: Showing the Etiological profile and their frequency of thrombocytopenia in the study (n-1000)**

Aetiology	Frequency	Total Number
<b>Viral infections-</b>		
Dengue- 16.00%	160	457 (45.7%)
COVID-19- 12.20%	122	
Influenza- 06.40%	064	
HIV- 05.32%	052	
Hepatitis B- 01.16%	016	
Hepatitis C- 01.1%	011	
Chickungunya- 01.90%	019	

Measles- 01.30%%	013	
Bacterial infections		
Streptococcus- 05.70%	57	
Staphylococcus- 04.40%	44	
E coli- 02.40%	24	156 (15.60%)
Tuberculosis- 03.10%	31	
Malarial infection- 04.40%	44	44 (06.40%)
Alcoholic liver disease- 05.70%	57	57 (05.70%)
Pregnancy- Gestational thrombocytopenia- 03.10%	31	51 (05.10%)
Preeclampsia/HELLP- 02.00%	20	
Drug intake		
Chemotherapy- 02.00%	20	
Heparin- 01.30%	13	64 (06.40%)
Rifampicin- 01.10%	11	
Quinine- 01.0%	10	
Ceftriaxone- 01.0%	10	
Myelo-dysplastic syndromes	13	13 (01.3%)
Leukaemia		
AML- 05.20%	52	94 (09.4%)
ALL- 02.10%	21	
CML- 01.10%	11	
ITP- 01.10%	10	--
Megaloblastic anaemia- 04.30%	43	43 (04.30%)
Spurious thrombocytopenia- 02.10%	21	21 (02.10%)
Total	1000	100%

All the 21 cases of spurious thrombocytopenia were evaluated separately. All cases were studied to know the etiology. Among them most common cause was COVID 19 infection (**Table 6**).

**Table 6: Showed the Etiological profile of pseudo thrombocytopenia in the study (n-21).**

Etiology	Frequency
Covid 19	09 (42.85%)
Pregnancy	05 (23.80%)
Lymphoma	01 (04.76%)
Autoimmune Diseases	02 (09.52%)
No Disease Identified	04 (19.04%)
Total	21 (100%)

All these patients were undergone repeated blood collection in citrate anticoagulant vacutainers. Except 04 cases all showed normal platelet count and disappearance of platelet clumps in peripheral smear.

### Discussion

Thrombocytopenia is defined as a condition where platelet count drops below the lower limit of normal (i.e. less than 150,000/micro L [150 x 10<sup>9</sup>/L] for adults). In this study the common causes of thrombocytopenia were analysed among the south Indian population. In addition the incidences of different infective, myelo-proliferative disorders and normal physiological conditions that may cause thrombocytopenia and pseudo thrombocytopenia in regular blood samples received in the Haematology department were analysed. The total study sample size was 1000 patient blood samples among them 21 patients were found to be spurious

thrombocytopenias. The samples of these patients were rechecked on peripheral smear examination, which was confirmed. When true thrombocytopenias were studied separately, it was found that thrombocytopenias were more in the male population (60%) compared to females (40%). These results correlated with the other similar studies which stated that the females were recorded with higher mean platelet count, compared to their male counterparts even in normal random population [20, 21]. There were studies in the literature which speculated that iron deficiency in menstruating woman stimulated the production of platelets [22, 23] which could be the cause for lower prevalence of thrombocytopenia among the women. Predominant age group incidence of thrombocytopenias was 40-60 years according to this study. But other studies stated that a progressive decline in platelet count was observed with advanced ageing [20, 21]. This disparity could

be due to the fact that majority of the patients reporting to this Tertiary Hospital were among the ages of 40 to 60 years. There were 979 patients presenting with true thrombocytopenia in the present study's observation and among them predominant causes were due to viral infections (45.7%), followed by bacterial infections in 15.60%, malarial parasitic infection in 04.40% of the patients. Alcoholic liver disease constituted for 57/1000 (05.7%), pregnancy was the cause in 51/1000 (05.1%), drug intake in 68/1000 (06.8%) patients and Myelo-dysplastic syndromes in 94/1000 (09.4%) patients (Table 5). D. Verma et al in their study stated that acute leukaemia was the most common cause followed by dimorphic anaemia and megaloblastic anaemia [3]. Gupta et al in their study found that ITP was the most common cause of thrombocytopenia, followed by megaloblastic anaemia and iron deficiency anaemia [4]. Among 457 patients of viral infections in the present study, 160/1000 (16.00%) patients were diagnosed with dengue infection followed by COVID infection in 122/1000 (12.20%), influenza in 06.40% and HIV in 05.32% of the patients. Although there are studies which revealed infections as a cause of thrombocytopenias, none of them showed viral infections as the most important cause [3, 4]. Further studies are to be done for further clarification about the etiological profile of thrombocytopenia after the post COVID pandemic years. Among 94 leukaemia patients presented with thrombocytopenia, 05.20% of the patients were diagnosed as AML followed by ALL in 02.10% patients. The observations made in the present study correlated with other study by few authors [3, 24, 25]. All patients with acute lymphoblastic leukaemias were under chemotherapy which explained the reason for thrombocytopenia [26, 27]. Although CML typically presented with thrombocytosis, thrombocytopenia usually occurs after Imatinib therapy taken during accelerated phase of CML [28]. Among the 64 cases of drug induced thrombocytopenias, majority were patients undergoing chemotherapy (02.00%). Other drugs found to be used were heparin in 01.30%, rifampicin in 01.10%, quinine in 01.0% and ceftriaxone 01.0%. A Study conducted by Weycker et al showed that 09.7% of patients undergoing chemotherapy showed thrombocytopenia ranging from 06.1% for regimens containing cyclophosphamide to 13.5% for regimens containing gemcitabine [29]. Several studies showed that heparin induced thrombocytopenias (HIT) can occur in up to 05% of patients exposed to heparin products and up to 50% of such patients developed thromboembolic complications resulted in a mortality rate of up to 30% (30, 31, 32). There were several studies which reported that rifampicin also caused thrombocytopenia [33, 34]. In the present study the incidence was 01.10%. In the

present study, a significant portion (04.40%) was constituted by malarial infection which is in accordance with worldwide literature [35, 36, 37, and 38]. Some studies quote that thrombocytopenia was more common with Plasmodium falciparum infection [37, 38]. There were only few proposed theories of mechanisms for such thrombocytopenia developing in malarial parasitic infection which included increase in consumption and destruction of platelets and suppression of thrombopoiesis. More studies are needed to reveal the actual mechanisms involved. [39, 40] 57 patients (05.70%) among the total 1000 in the study had alcoholic liver diseases. Thrombocytopenia due to alcoholism was not well documented and under reported and under researched in reality. Assessment of thrombocytopenia among alcohol users were mainly performed on small groups with fewer than 100 subjects until recent years [41, 42]. Incidence of thrombocytopenia in chronic liver diseases are said to be up to 76% according to some studies and lower platelet counts are associated with greater severity of portal hypertension [43].

Out of the 51 cases (05.10%) of pregnant patients, 20 were diagnosed to have preeclampsia/HELLP syndrome and the rest of the 31 cases (03.10%) were diagnosed as gestational thrombocytopenia. According to literature, gestational thrombocytopenia explains 70-80% of all cases of thrombocytopenia in pregnancy. It is said to be the second leading cause of blood disorders in pregnancy after anaemia. Hypertensive disorders (preeclampsia, Eclampsia, HELLP syndrome, acute fatty liver of pregnancy) causing thrombocytopenia ranks the second among the causes for low platelet count in pregnancy. In this study 04% cases were having hypertensive disorders associated with pregnancy in contrast to much higher rate of incidence reported in literatures [3]. A total of 43/1000 (04.30%) patients were reported as megaloblastic anaemia in the present study. There are several studies reporting megaloblastic anaemia as an aetiological factor for peripheral thrombocytopenia.

Peripheral thrombocytopenia develops as the severity of anaemia increases and is followed by neutropenia. Hypo production of platelet is considered to be the cause and bone marrow showed decreased megakaryocytes as discussed in other literatures [44,45]. 21 patients among the present study were having spurious thrombocytopenia (pseudo thrombocytopenia). All patients were found to have platelet aggregates when examined with peripheral smear.

Incidence of spurious thrombocytopenia was found to be 02.1% in this study, which was found to be definitely higher compared to other literatures which reported about 0.03% to 0.27% of incidence in general population [46, 47, and 48]. 09 out of 21

(42.8%) cases of spurious thrombocytopenia were reported to have COVID positive reports.

Low incidence of spurious thrombocytopenia cases in other studies could be explained, as most of them were conducted before 2019 when COVID cases were not included, and this finding signifies the importance of further research including more number of COVID patients to be included.

**Conclusion:** Prevalence of pseudo thrombocytopenia (02.10%) among 1000 patients with thrombocytopenia is significant. Among the true thrombocytopenia patients viral infections were the commonest cause.

The other causes were Alcoholic liver disease, malarial parasitic infection and Leukaemias. These observations findings were of great significance as prior studies did not show viral infections as the major concern especially COVID-19 infections. Further studies are to be done to check prevalence of pseudo thrombocytopenia in post COVID years.

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