Republic of Yemen
Ministry of Higher Education and Scientific Research
21September University of Medical & Applied Sciences
Faculty of Medicine

الجمهورية اليمنية
وزارة التعليم العالي والبحث العلمي
جامعة ٢١ سبتمبر للعلوم الطبية والتطبيقية
كلية الطب البشري

Incidence and Etiological Spectrum of Thrombocytopenia among Admitted Pediatric Patients in Major Hospitals, Sana'a City, Yemen 2022.

A Research Submitted for Obtaining a Bachelor Degree in Medicine from Faculty of Medicine at 21September UMAS.

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معدل حدوث قلة الصفيحات الدموية والأسباب المحتمله للمرض بين مرضى الأطفال المقبولين في المستشفيات الكبرى في مدينة صنعاء اليمن ٢٠٢٢

للعلوم سبتمبر جامعة من كلية الطب في 21 البشري حث مقدم للحصول على درجة البكالوريوس في الطبب الطبية والتطبيقية

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بسم الله الرحمن الرحيم

وَإِذْ قَالَ رَبُّكَ لِلْمَلَٰٓئِكَةِ إِنِّي جَاعِلٌ فِي ٱلْأَرْضِ خَلِيفَةً ۖ
قَالُوٓا۟ أَتَجْعَلُ فِيهَا مَن يُفْسِدُ فِيهَا وَيَسْفِكُ ٱلدِّمَآءَ وَنَحْنُ
نُسَبِّحُ بِحَمْدِكَ وَنُقَدِّسُ لَكَ ۖ قَالَ إِنِّيٓ أَعْلَمُ مَا لَا تَعْلَمُونَ
﴿٣٠﴾ وَعَلَّمَ ءَادَمَ ٱلْأَسْمَآءَ كُلَّهَا ثُمَّ عَرَضَهُمْ عَلَى ٱلْمَلَٰٓئِكَةِ
فَقَالَ أَنۢبِـُٔونِي بِأَسْمَآءِ هَٰٓؤُلَآءِ إِن كُنتُمْ صَٰدِقِينَ ﴿٣١﴾ قَالُوا۟
سُبْحَٰنَكَ لَا عِلْمَ لَنَآ إِلَّا مَا عَلَّمْتَنَآ ۖ إِنَّكَ أَنتَ ٱلْعَلِيمُ ٱلْحَكِيمُ

Dedication:

To our parents and families who have been our source of inspiration , and give us strength when we thought of giving up , who continually provide us their moral , spiritual , emotional , and financial support .

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We thank Allah, First and foremost for the great grace that has bestowed upon us, then we beloved parents do not cease to us for all their effort from the moment of our birth to these blessed moments. For everyone who advised us, guided us, contributed, or directed us with us in preparing this research and connecting us to the required references and sources at any of the stages it went through, and we especially thank the distinguished Dr. Mohammed Aqlan, and Dr. Khaled AL-jamrah for helping us, supporting us, and guided us with advice, education, correction and all that they did with us.

We are also pleased to thank the esteemed faculty of medicine at 21 September UMAS & the governmental hospitals in Sana'a City for facilitating the obstacles for completing this study.

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Abstract

Background: Thrombocytopenia is characterized by decrease in platelet counts below 150,000 cells / micro L. It is a significant finding which is often missed in hospitalized patients if platelet parameters are not evaluated routinely. Therefore, this study aimed to determine the incidence and etiology of thrombocytopenia in pediatrics in major hospitals, Sana'a City, Yemen 2022.

Methodology: A retrospective cross-sectional descriptive study was conducted by collecting the data from the hospital's records of thrombocytopenic children aged (1-15 years), who admitted to the major public hospitals in Sana'a City, from January 1st, 2022 to December 31st, 2022. Data were collected and analyzed by using the (SPSS) version 26. Descriptive measures, including frequency, incidence, percentage, and standard deviation will be presented. Chi square was used to find association between age, gender and etiology and outcome. The test was considered to be significant when p value < 0.05. Approval from 21 September University was obtain.

Results: Two hundred and twenty-sixthrombocytopenic paediatric patients were identified out of 3236 admitted patients recorded during the study period. The .incidence for thrombocytopenia in paediatric patients was 7%The majority of them were = males (n130; 57.5 (%and ;in the age group of <5 years (143 63.3%The .(majority of the thrombocytopenic patients accidentally identified by a primary care provider who performs a complete blood count (CBC) for other indications (n = whereas the patients presented with bleeding symptoms were (n= ,(٪٦٨,٦ ;١٥٥ patients, of whom (n = 64; 90.1%) were ecchymosis followed by (٪٢٦,٧ ;٧١ epistaxis then hematuria. The most common nonspecific symptoms were fever (n followed by fatigability and pallor. The laboratory tests revealed that (٪٨٨ ;١٩٩ = the majority of patients had severe thrombocytopenia (n = 66; 29.2%) followed by very severe thrombocytopenia (n = 59; 26%), that's platelets count equal 20,000-µl and <20,000/µl respectively. The findings revealed that the most /٥٠,٠٠٠ common identified cause for all cases was Infectious diseases (especially post viral) (n = 95; 42%) followed by leukemia (n = 56; 24.8%) then anemia (n = 45;

Among the 226 cases of moderate and sever thrombocytopenia, 94 patients (٢٠٪). were required platelets transfusions. Only 17 patients required IV (٤٢٪) immunoglobulin therapy from a hematologist. The outcomes of the patients were cured (n = 77; 27.8%) followed by referred (n = 73; 26.4%) and died (n = 29; (١٠,٥٪). There are significance association between age factor and some etiologies including autoimmune, ITP, and post medication . The bleeding tendency was significantly associated with the severity of thrombocytopenia (p value <0.05). There are relationship between the etiology of thrombocytopenia and the clinical characteristics, .and outcomes (p value < 0.021)

Conclusion and Recommendations: In conclusion, thrombocytopenia is an important in admitted paediatric patients although the most common causes are infectious diseases and leukemia in the majority of cases. Several patients factors showed significant associations with etiology of thrombocytopenia. A complete CBC and .platelet count were recommended before any medical intervention

الملخص

الخلفية: تتميز قلة الصفيحات بانخفاض عدد الصفائح الدموية أقل من ١٥٠,٠٠٠ خلية / ميكروليتر وهي نتيجة مهمة غالبًا ما يتم إغفالها في مرضى المستشفيات إذا لم يتم تقييم معلمات الصفائح الدموية بشكل روتيني. لذلك هدفت هذه الدراسة إلى تحديد مدى حدوث وأسباب قلة الصفيحات خلال مرضى

الأطفال في المستشفيات الكبرى ، في مدينة صنعاء ، باليمن خلال عام ٢٠٢٢

المنهجية: تم إجراء دراسة وصفية مقطعية بأثر رجعي من خلال جمع البيانات من سجلات المستشفى للأطفال المصابين بنقص الصفيحات الذين تتراوح أعمارهم بين (١-١٥ عامًا) ، والذين تم إدخالهم إلى المستشفيات العامة الرئيسية في مدينة صنعاء ، من ١ يناير ٢٠٢٢ إلى ٣١ ديسمبر ٢٠٢٢ . حيث تم جمع البيانات وتحليلها باستخدام برنامج الحزمة الإحصائيه للعلوم الإجتماعيه الإصدار ٢٦ . وسيتم تقديم المقاييس الوصفية ، بما في ذلك التكرار والوقوع والنسبة المئوية والانحراف المعياري. تم استخدام مقياس مربع تشي لإيجاد ارتباط بين العمر والجنس والمسببات والنتيجة. حيث يعتبر الاختبار مهمًا عندما تكون قيمة ص <٠,٠٥ وقد تم الحصول على موافقة جامعة ٢١ سبتمبر

النتائج: تم التعرف على مائتين وستة وعشرين طفلا مريضاً يعانون من نقص الصفيحات من بين ٣٢٣٦ مريضاً تم قبولهم خلال فترة الدراسة. حيث كانت نسبة الإصابة بنقص الصفيحات عند مرضى الأطفال (٧٪). وكان معظمهم من الذكور (العدد = ١٣٠ ؛ ٥٧,٥٪) وفي الفئة العمرية أقل من ٥ سنوات (١٤٣ ؛ ٦٣,٣٪). غالبية مرضى نقص الصفيحات الذين تم تشخيصهم عن طريق الصدفة من قبل مقدم الرعاية الأولية الذي يقوم بإجراء تعداد الدم الكامل كأجراء روتيني (ع = ١٥٥ ؛ ٦٨,٦ ٪) ، في حين أن المرضى الذين ظهرت عليهم أعراض النزيف كانوا (ع = ٧١ ؛ ٢٦,٧ ٪) ، من بينهم (ع = ٦٤ ؛ ٩٠,١٪) يعانون من كدمات تليها رعاف ثم بيلة دموية. كانت الأعراض غير النوعية الأكثر شيوعًا هي الحمى (ع = ١٩٩ ؛ ٨٨٪) تليها التعب والشحوب. وكشفت الاختبارات المعملية أن غالبية المرضى يعانون من حالة قلة الصفيحات الشديدة (ع = ٦٦ ؛ ٢٩,٢٪) تليها حالة قلة الصفيحات الشديدة جدًا (ع = ٥٩ ؛ ٢٦٪) ، وهذا يعني أن عدد الصفائح الدموية يساوي ٢٠,٠٠٠-٥٠,٠٠٠ / ميكرولتر و <٢٠,٠٠٠ / ميكرولتر على التوالي. أظهرت النتائج أن السبب الأكثر شيوعًا لجميع الحالات هو الأمراض المعدية (خاصة ما بعد الفيروسيه) (ع = ٩٥ ؛ ٤٢٪) تليها سرطان الدم (ع = ٥٦ ؛ ٢٤,٨٪) ثم فقر الدم (ع = ٤٥ ؛ ٢٠٪). من بين ٢٢٦ حالة مصابة بقلة الصفيحات المتوسطة والشديدة ، كان هناك ٩٤ مريضًا (٤٢ ٪) بحاجة إلى نقل الصفائح الدموية. ١٧ مريضًا فقط احتاجوا إلى علاج الغلوبولين المناعي الوريدي من أخصائي أمراض الدم. من بين نتائج المرضى تم علاج (ع = ٧٧ ؛ ٢٧,٨٪) تليها إحالة (ع = ٧٣ ؛ ٢٦,٤٪) والمتوفين (ع = ٢٩ ؛ ١٠,٥٪). هناك ارتباط مهم بين عامل العمر وبعض المسببات بما في ذلك امراض المناعة الذاتية، نقص الصفائح الذاتي، ومابعد استخدام الأدوية . وكما وجِد ارتبط ميل النزيف بشكل كبير مع شدة قلة الصفيحات (قيمة ص <٠,٠٥). هناك علاقة بين مسببات قلة الصفيحات والخصائص السريرية والنتائج قيمة ص <٠,٠٢١

الخلاصة والتوصيات: في الختام ، قلة الصفيحات مهمة في مرضى الأطفال المقبولين على الرغم من أن الأسباب الأكثر شيوعًا هي الأمراض المعدية وسرطان الدم في معظم الحالات. حيث أظهرت العديد من عوامل المرضى ارتباطات كبيرة مع مسببات قلة الصفيحات. يوصى بإجراء تعداد كامل للدم وللصفائح الدموية قبل أي تدخل طبي

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ABBREVIATIONS

AA **Aplastic Anemia**

ADP	**:**	**Adenosine Diphosphate**
AMP	**:**	**Adenosine Monophosphate**
AML	**:**	**Acute myeloid leukemia**
APS	**:**	**Anti-Phospholipid Syndrome**
ATP	**:**	**Adenosine Tri-Phosphate**
BMA	**:**	**Bone marrow aspiration**
CBC	**:**	**Complete cell counts**
CMV	**:**	**Cytomegalovirus**
CVID	**:**	**Common Variable Immunodeficiency Disease**
DIC	**:**	**. Disseminated Intravascular Coagulopathy**
DMS	**:**	**Demarcation Membrane System**
DNA	**:**	**DeoxyriboNucleic Acid**
DTS	**:**	**Dense tubular system**
EDTA	**:**	**Ethylene-Diamine-Tetra-Acetic acid**
Fc	**:**	**Fragment complement**
GPCR	**:**	**G Protein Coupled Receptor**
GPs	**:**	**Glycoprotein**
GTP	**:**	**Guanosine Tri-Phosphate**
Hb	**:**	**Hemoglobin**
HIT	**:**	**Heparin Induced Thrombocytopenia**
HIV	**:**	**Human immunodeficiency virus**
HUS	**:**	**Hemolytic uremic syndrome**
ICU	**:**	**Intensive care unit**
IgA	**:**	**Immunoglobulin A**
IgG	**:**	**Immunoglobulin G**
IgM	**:**	**Immunoglobulin M**
IPF	**:**	**Immature Platelet Fraction.**
ITP	**:**	**Immune thrombocytopenic purpura**
KD	**:**	**Kilo Dalton**
MDS	**:**	**Myelodysplastic Syndrome**
KMS	**:**	**Kasabach-Merritt Syndrome**
MCV	**:**	**Mean Corpuscular Volume**
MKs	**:**	**Megakaryocytes**
MPV	**:**	**Mean Platelet Volume.**
MYH9	**:**	**Myosin Heavy Chain 9**
NEC	**:**	**Necrotizing enterocolitis**
NSI	**:**	**Non Structural Protein**
OCS	**:**	**Open canalicular system**
PAR	**:**	**Protease Activated Receptors**
PBS	**:**	**Peripheral Blood Smear**

PCT	**:**	**Plateletcrit.**
PDW	**:**	**Platelet Distribution Width.**
PH	**:**	**Power of Hydrogen (hydrogen-ion concentration)**
PICO	**:**	**Pediatric intensive care unit**
P-LCR	**:**	**Platelet Large Cell Ratio.**
PSGL-1	**:**	**P-Selectin Glycoprotein Ligand1**
PT	**:**	**Prothrombin Time**
PTT	**:**	**Partial Thromboplastin Time**
RNA	**:**	**Ribonucleic Acid**
SLE	**:**	**Systemic lupus erythematosus**
SPSS	**:**	**Statistical Package for Social Sciences**
TLC	**:**	**Total Leucocyte Count**
TP	**:**	**Thrombocytopenia**
TPE	**:**	**Therapeutic Plasma Exchange**
TPO	**:**	**Thrombopoietin**
TTP	**:**	**Thrombotic Thrombocytopenic Purpura.**
Tx A2	**:**	**Thromboxane A2**
vWF	**:**	**von Willebrand Factor**
WASP	**:**	**Wiskott Aldrich Syndrome Polymerase**
WBC	**:**	**White Blood cells**

1-Chapter One: Introduction

1.1-Background

Thrombocytopenia is defined as platelet counts under 150,000/mL, results from either decreased production or increased destruction. Manifestations of thrombocytopenia include spontaneous bleeding, prolonged bleeding time and normal prothrombin time (PT) and partial thromboplastin time (PTT). The lower the platelet count, the greater the risk of bleeding. Patients with less than 10,000 platelets/μL are at greatest risk of spontaneous hemorrhage.[1]

Many researches and theories have been proposed to explain causes of thrombocytopenia, although the literature covers a wide variety of such theories, this review will focus on four major categories which emerge repeatedly throughout the literature review. These categories are: Increased destruction, decreased production, drugs Induced, and other causes. Most early researches of increased destruction of platelets were concerned with inherited disorders such as idiopathic thrombocytopenic purpura (ITP) which is autoimmune disorder in which platelets coated with mainly antibodies against platelets GPIIb/IIIa and GPIb/IX are destroyed in the spleen.[115]

Decrease platelet production can result from multiple congenital or acquired defects in megakaryocytopoiesis, including diseases that affect the marrow generally, abnormalities that selectively impair platelet production and defects that lead to ineffective megakaryocytopoiesis.[19] Marrow infiltration with malignant cells or bone marrow failure (e.g., in patients with aplastic anemia or who received radiotherapy or chemotherapy) may Cause pancytopenia including thrombocytopenia.[2] Certain viral infections, such as cytomegalovirus (CMV) and HIV, and certain drugs impair platelet production.[23] (HIV may also increase platelet destruction; see below.) Megaloblastic anemia and myelodysplasia may cause thrombocytopenia due to ineffective megakaryopoiesis.[19] May-Hegglin anomaly is a congenital form of thrombocytopenia that entails decreased platelet production.[20]

The most common family inherited thrombocytopenia is called myosin heavy chain 9 (MYH9)-related platelet disorders. There are 3 other overlapping disorders: Epstein syndrome, Fechtner syndrome and Sebastian platelet syndrome. These all lead to megakaryocyte maturation and abnormally large platelets (macrothrombocytopenia). Increased platelet destruction can result from immune mediated damage with consequent removal of circulating platelets, as in idiopathic thrombocytopenic purpura and drug induced thrombocytopenia. Or, excessive platelet destruction occurs by nonimmunologic conditions such as intravascular platelet aggregation (e.g., in TTP). Abnormal platelet distribution, or pooling, is seen in disorders of the spleen and hypothermia.[12]

In addition the thrombotic thrombocytopenic purpura which is formation of platelet thrombi in the microvascular leads to consumes platelet. [124]

In Yemen, there are some infections couse thrombocytopenia,[86] such as dengue fever,[99] sever complicated malaria,[103] and acute tropical infectious disease.[104]

The researches which were concerned about the drug induced thrombocytopenia are : heparin,[105] meropenem,[106], and most chemotherapy drugs such as methotraxate [108] and antiepileptic valoperic acide.[114]

1.2-Study Problem

The high prevalance of thrombocytopenia among admitted pediatric patients all over the world with many different couses make it a major global health problem, that lack of essential data and studies on the incedince and etiological spectrum of thrombocytopenia and thier clincal presentation among hospitalized pediatric patients in Yemen would increase the complications among these patients, serious sequelae may occur due to the absence of the specific diagnosis and effective treatment of thrombocytopenia. Investigation of the etiology of thrombocytopenia requires careful consideration of clinical history and laboratory features. A complete blood count and peripheral smear review are essential components of the diagnostic work-up, and physicians should be knowledgeable about appropriate selection and interpretation of more specialized tests, including bone marrow examination, to assist with specific diagnosis. This review article aims to summarize and address appropriate work-up of the major and/or life-threatening causes of thrombocytopenia and some of the better-characterized congenital thrombocytopenias.

1.3- Study Objective

1.3.1- Aim of The Study:

To determine the incidence and Etiology of thrombocytopenia in children in .major hospitals, Sanaa city, Yemen, 2022

1.3.2- Specific objectives

- To describe the characteristics and clinical presentation of children with .thrombocytopenia in major hospitals, Sana'a city
- To determine the incidence of children with thrombocytopenia, laboratory association finding to the children with thrombocytopenia and categories of .thrombocytopenia in children
- .To find out specific causes of thrombocytopenia in children
- To determine the main treatments, outcomes and causes of death of children .with thrombocytopenia

1.3-Research Questions:

What are the incidence and Etiology of thrombocytopenia in children in major .?hospitals, Sana'a City, Yemen ,2022

1.3.1- Sub-questions of the Research:

- What are the incidence and Etiology of thrombocytopenia in children in ?major hospitals, Sana'a City, Yemen, 2022
- What are the characteristics and clinical presentation of children with ?thrombocytopenia in major hospitals, Sana'a city
- What are the laboratory association finding and categories of ?thrombocytopenia in children
- ?What are the specific causes of thrombocytopenia in children
- What are the main treatments, outcomes and causes of death of children ?with thrombocytopenia

1.4- Significance of the study:

The study data will reflect the major causes of thrombocytopenia, and send them to the ministry of public health to make physicians more approached to common causes of thrombocytopenia in Yemen and this may be the point for

further researches on the causes of thrombocytopenia in Yemen, based on the .results in this study

1.5- Limitations of study :

: The limitations of our study are the following

.Incomplete documentation or missing of archive files

.Cases without clear confirmed diagnosis

.Absence of some advanced investigation

Chapter Two: Literature Review:

2.1 - Platelet

2.1.1- HISTORY

Platelets were recognised as a distinct blood element in the late 19th century by Bizzozero, in 1882, who demonstrated that platelets were responsible for formation of clots at the sites of vascular injury in guinea pig microvessels in vivo.[9] Platelets are considerably smaller than the other previously recognised blood elements such as erythrocytes and leucocytes.

Platelets (also called thrombocytes) are minute discs 1 to 4 micrometers in diameter. They are formed in the bone marrow from megakaryocytes, which are extremely large cells of the hematopoietic series in the marrow; the megakaryocytes fragment into the minute platelets either in the bone marrow or soon after entering the blood, especially as they squeeze through capillaries. The normal concentration of platelets in the blood is between 150,000 and 300,000 per microliter. Platelets have many functional characteristics of whole cells, even though they do not have nuclei and cannot reproduce. The platelet-plugging mechanism is extremely important for closing minute ruptures in very small blood vessels that occur many thousands of times daily. A person who has few blood platelets develops each day literally thousands of small hemorrhagic areas under the skin and throughout the internal tissues, but this does not occur in the normal person.[10]

When a blood vessel wall is injured, platelets adhere to the exposed collagen and von Willebrand factor in the wall via receptors on the platelet membrane. Von Willebrand factor is a very large circulating molecule that is produced by endothelial cells.

Binding produces platelet activations which releases the contents of their granules. The released ADP acts on the ADP receptors in the platelet membranes to produce further accumulation of more platelets (platelet aggregation).[11]

Platelets are anucleate cells arising from cytoplasmic fragmentation of megakaryocytes in the bone marrow, and have a diameter of 2-3 μm. Platelets were once called as “cellular dusts”. Platelets circulate in a discoid form and their average lifespan in

humans is ~10 days.[9] Normal human platelet count is ~150,000- 450,000/µl.However, spontaneous bleeding does not occur until platelet count falls below 10,000/µl.[5]

Despite their lack of nucleus, platelets are actively involved in broad range of physiologic and pathologic process. Platelets contain a variety of mediators that regulate hemostasis and thrombosis as well as other functions including recruitment of other cells (chemotaxis) vasomotor function, cell growth and inflammation. The relevant constituents for thrombosis are present both on cell membrane and in the cytoplasm, mainly within platelet granules.[6]

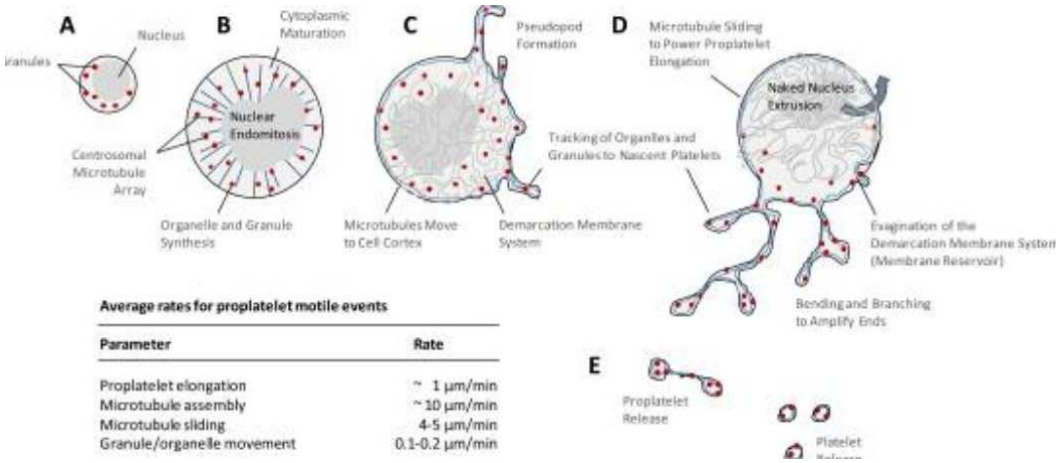
2.1.2- Platelet Formation :

Megakaryocytes (MKs)are highly specialized precursor cell in the bone marrow that function solely to produce and release platelets into circulation through a series of cellular events. MKs are the largest (50-100µm) and the rarest cell (constituting ~0.01% of nucleated bone marrow cells) in the bone marrow.

MKs are developed from pluripotent hematopoietic stem cells .Thrombopoietin (TPO) acts as a major factor that helps in the growth and development of MKs from stem cell precursors.)Figure 1)

MKs undergo a process called endomitosis which is DNA replication without cell division. Endomitosis is a TPO driven process during which MKs become polypoid and initiate a rapid cytoplasmic extension which is characterised by development of demarcation membrane system(DMS) and increased accumulation of cytoplasmic proteins and granules essential for platelet function.

Once on maturation, the bulk of cytoplasm is packed into multiple long processes called proplatelets and the nucleus is extruded. A MK may extend to form 10-20 proplatelets. Platelets are formed at the tips of proplatelets, as platelets develop they receive their granules and organelle content transported from MK cell body.[107] The time taken by the MKs to mature and produce platelets is ~5 days .



Average rates for proplatelet motile events

Parameter	Rate
Proplatelet elongation	~ 1 μm/min
Microtubule assembly	~ 10 μm/min
Microtubule sliding	4-5 μm/min
Granule/organelle movement	0.1-0.2 μm/min

2.1.3- Structure of Platelet

The platelet membrane consists of a typical bilayer phospholipid ,which contains membrane glycoproteins that interact with various ligands, either soluble ligands that activate the platelets ,or fixed ligands within vessel wall or on other cells through which the platelets adhere to these structures. Its plasma membrane contains a network of numerous invaginations into the platelet interior, connected to the exterior through small pores known as open canalicular system(OCS).[109]

Platelets contain a second channel system, derived from megakaryocyte smooth endoplasmic reticulum, known as dense tubular system (DTS). The DTS stores calcium and a variety of enzymes involved in platelet activation. The DTS does not associate with the plasma membrane in contrast to OCS.[110]

2.1.4- Platelet Granules

Platelet granules serve as seretory vesicles, releasing components to the extracellular fluid and also serve to direct molecules to the plasma membrane in a

process of exocytosis. Three main populations of granules are evident in inactivated, normal platelets which differ in their ultrastructure, granule contents, kinetics of exocytosis and function.

1 - Alpha Granules

Alpha granules are the largest (~200-400nm) and most prevalent and heterogenous platelet granules.[111]

There are about 50-60 granules per platelet and are responsible for the granular appearance of the cytoplasm in peripheral blood smears. These granules contain the majority of platelet factors involved in hemostasis and thrombosis. They also contain proteins involved in inflammation and wound healing .

These include large polypeptides such as thrombospondin, p-selectin, platelet factor 4 and beta thromboglobulins as well as several factors involved in coagulation(factors V,XI,XIII, fibrinogen, von Willebrand factor and high molecular weight kininogens).

α- granules contain a variety of adhesion molecules involved in platelet-vessel wall interaction such as fibronectin. The membrane of α granules contain several proteins that are also expressed on platelet cell membrane such as GPIb complex ,GP VI ,GP IIb/IIIa and P-selectin.

2- Dense Granules

Platelet dense granules are the smallest granules (~150nm) and appear as dense bodies on electron microscopy, due to their high calcium and phosphate content.[112]

There are about 3-8 dense g ranules per platelet. They contain high concentrations of adenine nucleotides (ADP, ATP) and serotonin. Dense granues also contain small GTP-binding proteins and have been reported to contain relevant adhesion molecules present on platelet compartments including GPIb complex, GP IIb/IIIa and P-selectin.

Dense granule membrane proteins incorporate with the platelet plasma membrane and granule contents are released into extracellular environment. The released constituents

contribute to recruit other platelets (aggregation) and also contribute to local vasoconstriction (serotonin).

3- Platelet Lysosome

Lysosomes represent the third category of platelet granules with a size intermediate between α- and dense granules (~200-250nm). They contain an intraluminal acidic pH with hydrolytic enzymes active towards constituents of the extracellular matrix.[113,111]

2.1.5- Platelet adhesion molecules

Platelets contain numerous adhesion molecules both on the plasma membrane and within granules that are releant for hemostasis and thrombosis. The main molecules involved are :

1- P-Selectin:

P-Selectin(~140 kD) is the largest of the selectin family of adhesion molecules. It is contained primarily on platelet α-granules, dense granules and also on the Wiebel-Palade bodies of endothelial cells.

Following platelet activation, the fusion of granule membranes with the cell membrane results in rapid expression of P-Selectin on the cell surface.[115] P-Selectin surface expression is commonly used as a marker of platelet activation.[116]

The ligands for P-Selectin include P-Selectin glycoprotein ligand1 (PSGL-1), which is expressed primarily on leucocytes,[117] von Willebrand factor,[118] glycoprotein Ibα[119] and sulfatides.[120]

2- Glycoprotein Ib/IX/V(GPIb/IX/V)

This receptor complex is the main platelet receptor for von Willebrand factor (vWF). Binding of vWF to GPIb initiates signal transduction events leading to th activation of the platelet integrin GPIIb/IIIa, which becomes competent to bind vWF or fibrinogen to mediate platelet aggregation.

3- Glycoprotein IIb/IIIa(GP IIb/IIIa)

This is essential for platelet aggregation. It is a heterodimer with an alpha (α~136 kD) and beta (β~92kD) subunit. These molecules are in surface of unstimulated human platelets and in the membranes of platelet granules are translocated to the platelet surface during platelet secretion. Platelet GPIIb/IIIa can bind to fibrinogen and other ligands such as vWF and fibronectin.

4- Collagen receptors

The α2β1 integrin and glycoprotein VI are the primary collagen receptors. They bind to specific sequences on collagen with different affinities. GP VI mainly binds to collagen types that can form large collagen fibrils such as collagen typeIII.GP VI is a key adhesion molecule involved in hemostasis and thrombosis. Absence of this receptor leads to predisposition of bleeding.

5- G-protein coupled receptor.

a.Thrombin

Thrombin is a key component of the coagulation pathway and potent stimulator of platelets. Platelet responses to thrombin are mediated by protease activated receptors (PAR). Thrombin signalling via either PAR 1 or PAR 4 induces platelet activation, shape change and granule release.[121]

b.Adenosine di phosphate (ADP)

The response of platelet function to ADP varies on concentration of ADP. Exposure of human platelets to low concentrations of ADP results in an initial reversible aggregation without granule release. Higher concentrations of ADP induce release of granules and synthesis of prostaglandins giving rise to characteristic biphasic response with irreversible aggregation.[122]

c.Prostanoids

Thromboxane A2 (TXA2) is a product of arachidonic acid metabolism; two isoforms of thromboxane receptors have been described : TP α and TP β.[21] TP is also a member of G protein coupled receptor (GPCR) family and it results in phospholipase C activity. [123]

TXA2 results in platelet shape change, aggregation, degranulation and enhancement of response to other agonists, thus amplifying platelet activation. Platelets express receptors for other prostanoids, including prostacyclin (which mediates inhibition of platelet aggregation) and prostaglandin E (which has biphasic effect on platelets).

2.1.6 - Automated Hematology Analysers:

Hematology analysers are the workhorses of the laboratory. High end, high volume analysers are computerised, highly specialised and automated machines that delivers reliable red blood counts, platelet counts and 5 part differentials of white blood cells identifying lymphocytes, monocytes, neutrophils, eosinophils and basophils. Nucleated red blood cells and immature granulocytes are emerging as sixth and seventh parameters. (figure 3)

2.1.6.1 - Evalution of the Analysers:

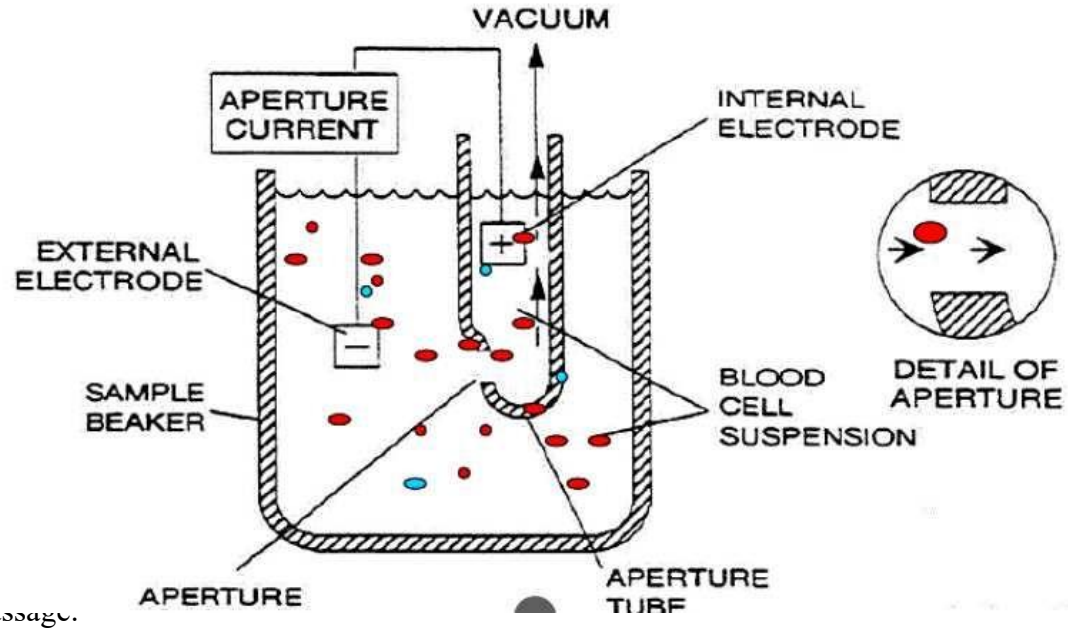
The first automated cell counters came out in the 1950s based on Coulter's electrical impedance principle in which cells pulled through an aperture break an electric circuit, indicating both the presence of a cell and the size of the cell. But the truly functional and automated versions of these machines did not become available for two more decades. Before this time, cell counts were performed manually.

There are many disadvantages of manual cell counting such as most labor intensive, overestimation of lymphocytes, underestimation of monocytes, association with distinguishing lymphocytes from monocytes, band forms from segmented forms and increased cell concentrations along edges.[125]

2.1.6.2 - Principle :

The automated hematology analysers functions using large number of principles such as electrical impedance, light scatter and fluorescence.

1- Electrical Impedance :



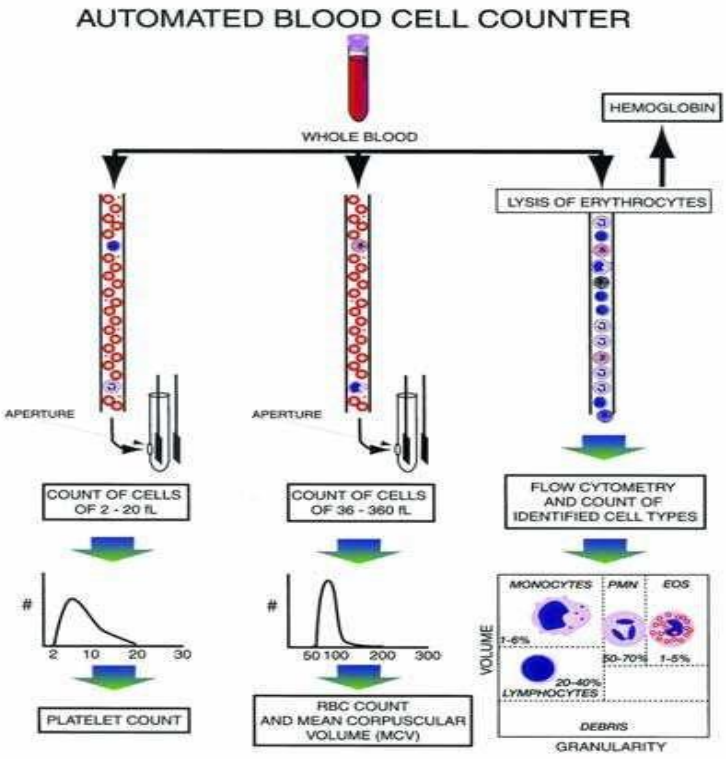
passage.

Whenever the cell passes through it, flow of current is impeded and a pulse is generated. The height of the pulse determines the cell volume and the width of the pulse shows time taken by the cell to traverse. The number of pulses generated during a specific period is proportional to the number of cells. The output histogram is a display of the distribution of cell volume and frequency. Each pulse on the *x*-axis represents size in femtoliters (fL); the *y*-axis represents the relative number of cells.

Figure 2: Coulter Principle.

2- Light Scatter :

In some hemato directed through which a beam is measures as ligh of scatter are measured at Forward scatter measures exities of the cell. This is r



3- Fluorescenc

This is used for ed RBCs and cell surface a

The EDTA antic chamber, RBC and platele count of the leucocytes moglobin method. Any pa -20 fl is measured as platelets and 35-450 fl is measured as WBCs.

Sysmex measures parameters with cells in fluid suspension. in addition to hydrodynamic focussing to ensure that the cells travel in a straight line through the aperture. This prevents cells flowing through the edge of the aperture and causes spurious changes in the electrical field.[126,]

Figure 3: Automated Blood Cell Counter

In platelets, there can be factitious increase in platelet count due to markedly microcytic or fragmented RBCs and white cell fragments in case of leukemia. There can be falsely low counts when giant platelets are being identified as red cells or due to EDTA induced platelet clumping or satellitism.[17]

2.1.7- Platelet Indices:-

Platelet indices are potentially useful markers for the early diagnosis of the causes for thrombocytopenia. The platelet indices include platelet count, mean platelet volume, platelet distribution width, platelet large cell ratio and immature platelet fraction.

2.1.7.1 - Mean Platelet Volume (MPV):

MPV is a platelet marker which can be obtained as a part of complete blood count (CBC) using automated hematology analyser which measures the average size of the platelets present in the blood.[128]

MPV is an indicator of activity of the platelets .Larger platelets are more active enzymatically and metabolically when compared to small sized platelets which are depicted by increased MPV.

MPV correlates with platelet aggregation, whether measured in platelet rich plasma or whole blood.Large platelets also express increased levels of adhesion molecules like P-Selectin, GP IIb/IIIa, although the surface density of these glycoproteins is usually constant, independent of the platelet volume.[129]

Platelet count is derived through the electrical impedance and the distribution curve obtained is thus the actual data and not the fitted curve. MPV is calculated from the curve using the formula- MPV(fl)=Pct(%)x100/ Plt($x10^3/\mu L$).[130]

EDTA causes the platelet to swell in a time dependent manner. Most of the increase in MPV occurs during the first hour and the process continues over the next 24 hours. EDTA is thought to increase cyclic AMP and change plasma membrane permeability. This situation is further complicated since most of the analysers use light diffraction to measure particle size by assessing optical density.[131]

The analysers used to record reduced MPV with time since platelet swelling results in a lower optical density as a result, studies reported that MPV measurements made in EDTA sample are questionable in research unless MPV is assessed at a consistent time following phlebotomy or once the swelling has ceased at 24 hours. In contrast to all these facts, MPV measured in high concentration sodium citrate does not change with time and hence considered as gold standard.[131]

The normal range of MPV has yet to be adequately determined, but studies have shown that MPV in normal subjects suggest an approximate range of 7.5-11.5 fl with a mean of 9.5 fl.

MPV is increased in conditions like immune thrombocytopenic purpura, disseminated intravascular coagulation, myeloproliferative disorders, pre-leclampsia and HELLP syndrome, non–alcoholic liver disease, sepsis, hyperthyroidism, bone marrow

stimulating drugs like erythropoietin or thrombopoietin and recovery from transient hypoplasia (cytotoxic chemotherapy).[132]

MPV is decreased in conditions with under production of platelets like bone marrow aplasia such as aplastic anemia, bone marrow failure, splenomegaly, hypothyroidism, iron deficiency anemia and HIV/AIDS.[132]

2.1.7.2-Platelet Distribution Width (PDW):

PDW is an important index in platelet parameters. It reflects how uniform the platelet are in size. PDW reflects the variability in platelet size and increased in presence of platelet anisocytosis. Activated platelets with increased number and size of the pseudopodia differ in size, leading to the alteration in the PDW. It is the relative width of the distribution of platelets in volume index of the heterogeneity of platelets.

A normal PDW indicates that the platelets are mostly of same size, while a high PDW indicates platelet size varies greatly giving a clue that there may be a disorder affecting platelets. Increased variation in PDW indicates platelet heterogenicity along with the destruction and splenic pooling. PDW also varies inversely with platelet count.[133]

2.1.7.3- Platelet Large Cell Ratio (P-LCR):

P-LCR is the increased percentage of large platelets. It is the ratio of large platelets from the 12fL discriminator or larger.[135] Larger platelets are more reactive and contribute to thromboembolic events because of the higher production of Thromboxane A2. P-LCR was inversely related to platelet count and directly related to PDW and MPV.

The optimal method for measuring P-LCR is by utilising the changes in electrical impedance. It is calculated as a ratio comparing the number of particles between the fixed discriminator and upper discriminator, to the number of particles between upper and lower discriminator.[136] Normal range of P-LCR is 15-35%.

2.1.7.4- Plateletcrit (PCT):

PCT is a measure of total platelet mass. PCT is the volume occupied by platelets in blood. Under physiological conditions, the amount of platelets in the blood is maintained in an equilibrium state by regeneration and elimination. In healthy subjects, platelet mass is closely regulated to keep it constant, while MPV is inversely related to platelet counts.

Plateletcrit is an effective screening tool for detecting platelet quantitative abnormalities. PCT is directly related to the platelet count and the size of the platelets.

The optimal method for calculating PCT is through electrical impedance and is calculated using a formula PCT=(platelet count x MPV)/10000 and given in percentage. The normal range for PCT is 0.22-0.24%.[137]

2.1.7.5- Immature Platelet Fraction (IPF):

IPF is an index of thrombopoiesis and can help determine the mechanism of thrombocytopenia. IPF levels rise as bone marrow produces more platelets. IPF reflects marrow platelet production from the peripheral blood sample. IPF is a modern parameter that measures young and more reactive platelets in peripheral blood.

Platelets that are newly formed are more reactive than mature platelets and contain RNA, hence the other name for IPF is reticulated platelets.

IPF is an indirect means to evaluate the necessity and timing of platelet transfusion. IPF may also be used as an indicator of imminent platelet recovery after cytotoxic therapy or post transplant.IPF increases before the platelet count, hence used as a tool for monitoring patient response.

The optimal method for calculating IPF is by flow cytometry techniques and the use of nucleic acid specific dye in the reticulocyte / optical platelet channel. The clinical utility is made in the laboratory diagnosis of thrombocytopenia due to increased platelet destruction such as ITP. Reproducibility and stability results over 48 hours were good. An IPF reference range in healthy individuals was 6.1% with a mean of ٤,٣٪.[138]

2.1.8- Advantages of Platelet Indices :

The introduction of automation in laboratory analysis has brought about accurate and rapid results. Automation also had made it possible to measure certain parameters that had not previously been determined. The platelet indices offer valuable information about the morphology and maturity of platelets.

The platelet indices plays an important role in the rapid evaluation of bone marrow activity of patients with platelet associated disorder. MPV and IPF are indicators of bone marrow activity, as new platelets are larger and contain more RNA. The MPV and IPF offer a method of assessing bone marrow activity without performing a bone marrow aspirate, which is an invasive procedure. PCT and PDW can be used to differentiate reactive thrombocytosis from myeloproliferative disorders.[139]

2.2-Thrombocytopenia

2.2.1- Definition Thrombocytopenia:

Thrombocytopenia is characterized by decrease in platelet counts. Thrombocytopenia is a significant finding which is often missed in hospitalized patients if platelet parameters are not evaluated routinely.[1] Normal platelet value ranges from 1,50,000 to 4,50,000 cells/ microL. Platelet counts below 1,50,000 cells / microL define thrombocytopenia, but they do not reveal the underlying pathology.[2]

The three main reasons for thrombocytopenia are: a) decreased platelet production, b) increased platelet destruction and c) disorders of platelets distribution.[3] While evaluating the thrombocytopenic patients, it is important to identify the cause for thrombocytopenia whether it is due to decreased production or increased destruction, which will have the impact on correct management of the patients.[4]

Thrombocytopenia can be divided into three grades, based on their platelet values such as Mild: 100,000 - 150,000/ micro L, Moderate: 50,000 - 100,000/ micro L and Severe:< 50,000/ micro L.

This grading is essential for assessing the severity of the thrombocytopenia.[5] Usually thrombocytopenia is not detected clinically until the platelet value has fallen below 100,000 cells/ micro L. Not all thrombocytopenic patients present with bleeding, only those with severe thrombocytopenia has increased risk for intra-cerebral and intraabdominal bleeding.[6] The diagnosis of these patients on time is essential and timely management would be life saving.[7]

2.2.2 - Epidemiology of Thrombocytopenia:

Epidemiology of thrombocytopenia have been obtained through a lot of researches around the world, but in different target group such as neonates or ICU pediatric patients. In central Saudi Arabia, the period incidence of neonatal thrombocytopenia was 84/4379 (1.9%). The mortality rate associated with the condition was 68/100,000 births. The male-

female ratio of neonates with thrombocytopenia was 2.4:1. The mean (standard deviation) time to disease onset was 1.83 (1.29) days, whereas that of recovery duration was 15.35 (18.46) days.[23]

In China among 6,725 children admitted to PICU in one hospital from January 2008 to December 2017, there were 683 children with TP, with the incidence of 10.2%. Among 683 children with TP, there were 387 males and 296 females, with the median age of 2.72 (0.61, 3.08) years, and 92 children died, with a total mortality of 13.5%.[25]

The database in Italian institutions from year 2004 to 2008 was evaluated and all cases of thrombocytopenia were identified and analyzed with regard to age, sex, associated diseases, therapeutics procedures and bleeding complications, found 368 patients discharged from 2004 to 2008 with thrombocytopenia, correspondent to 0.1% of discharge rate and to a rate of 73.6 patients/year. The incidence of thrombocytopenia for this period was 14.8 cases per 100 000 per year, when considering patients with diagnosis of immune thrombocytopenia, the incidence was of 6.8 cases per 100 000 per year.[29]

In Tunis thrombocytopenia is a common clinical problem in neonatal intensive care units, affecting about 20 to 35% of all admitted neonates. Thrombocytopenia occurred in the first 3 days of life in 74.1% of cases. Thrombocytopenia was mild in 22.3%, moderate in 36.7% and severe in 41%. Intrauterine growth restriction was the most common cause of early thrombocytopenia. [26]

In United States immune thrombocytopenia (ITP) occurs with an incidence rate of 1.6 to 3.9 per 100,000 patient-years, which increases with age and has a slight female preponderance. [28]

2.2.3 -Diagnosis of Thrombocytopenia:

Thrombocytopenia is a diagnosis sign, not a disease. The detailed history such a family history of bleeding or thrombocytopenia, recent intake of drugs, live virus vaccination, recent diagnosis of hematological diseases or non hematological diseases which tend to decrease platelet values (such as eclampsia, sepsis, DIC, anaphylactic shock, hypothermia and massive transfusions), nutritional status, menstrual status, alcohol consumption and pregnancy should be obtained.[8] Following detailed history, physical examination such as petechia, purpura, gum bleeding, ecchymosis, bleeding into muscle and joints were evaluated as they can help in differentiating the causes of thrombocytopenia. Then laboratory investigations are done such as complete blood count and peripheral smear. It is essential to look into peripheral smear to rule out artifact or pseudothrombocytopenia, that happened falsely during testing of platelet clumping and Satellitism.

In severe thrombocytopenia, a bone marrow study can determine the number, size, and maturity of the megakaryocytes. This information may identify ineffective platelet production as the cause of thrombocytopenia and rule out a malignant disease process at the same time.[30]

2.2.3.1-Platelet Clumping

Platelet clumping is mainly due to EDTA induced alteration of surface glycoprotein and anionic phospholipids which in turn causes binding of the antiplatelet antibodies which further causes agglutination .Most of the antibodies are of IgG followed by IgM and IgA.[13] Most of the agglutinins react at room temperature (37 ˚C) or at low temperature(22˚C) .[14] The count will be flagged as low platelet count by automated analysers considereing platelet clumps as leucocyte. (figure 4)

2.2.3.2-Platelet Satellitism

Platelet satellitism which is an in-vitro phenomenon, associated with EDTA treated blood at room temperature. One of the mechanism is that immunoglobulin autoantibodies directed against the glycoprotein IIb/IIIa complex of the platelet membrane and the neutrophil Fc gamma receptor. This is seen as platelets adhering to the polymorphonuclear leucocytes producing a rosette like appearance.[15] It is seen in patients with vasculitis, lupus, chronic liver disease [16], mantle cell lymphoma and marginal zone B cell lymphoma.[17],[18] (figure 5)

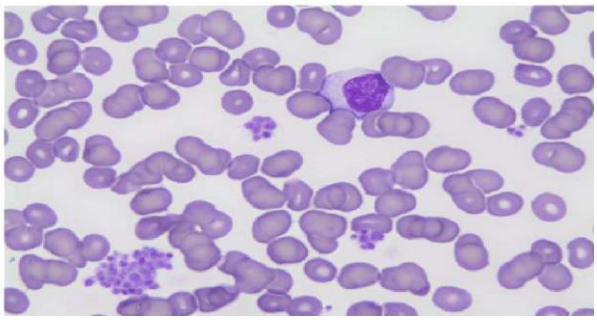


Figure 4: Platelet Clumping

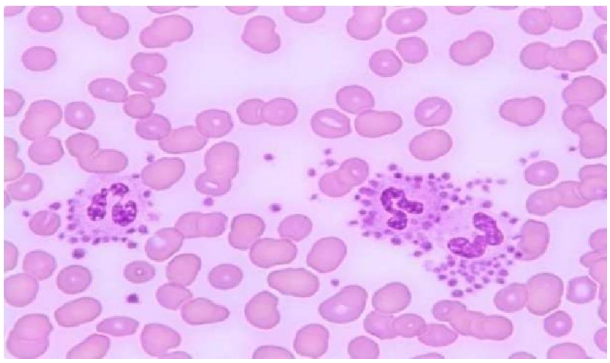


Figure 5: Platelet Satellitism

2.2.4 - Signs and Symptoms of Thrombocytopenia :

Thrombocytopenia usually has no symptoms and is picked up on a routine complete blood count. Some individuals with thrombocytopenia may experience external bleeding, such as nose bleeds or bleeding gums. Some women may have heavier or longer periods or break through bleeding. Bruising, particularly purpura in the forearms and petechiae in the feet, legs, and mucous membranes, may be caused by spontaneous bleeding under the skin.[32]

Eliciting a full medical history is vital to ensure the low platelet count is not secondary to another disorder. Ensuring that the other blood cell types, such as red blood cells and white blood cells, are not also suppressed, is also important. Painless, round, and pinpoint (1 to 3 mm in diameter) petechiae usually appear and fade, and sometimes group to form ecchymoses. Larger than petechiae, ecchymoses are purple, blue, or yellow-green areas of skin that vary in size and shape. They can occur anywhere on the body.[31]

A person with this disease may also complain of malaise, fatigue, and general weakness (with or without accompanying blood loss). Acquired thrombocytopenia may be associated with the use of certain drugs. Inspection typically reveals evidence of bleeding (petechiae or ecchymoses), along with slow, continuous bleeding from any injuries or wounds. Adults may have large, blood-filled bullae in the mouth.[33] If the person's platelet count is between 30,000 and 50,000/μL, bruising with minor trauma may be expected; if it is 15,000- 30,000/μL, spontaneous bruising will be seen (mostly on the arms and legs).[34]

2.3- Etiology of Thrombocytopenia :

The system used most often to categorize the different causes of thrombocytopenia is based on the underlying pathologic mechanism leading to the thrombocytopenia, that is, either increased destruction or decreased production of platelets as following (table 2.1)[76]

Table 2.1 : Causes of thrombocytopenia

Table 1. **Causes of Thrombocytopenia**

Increased Platelet Destruction

- Immune-mediated
  - –Immune thrombocytopenic purpura
  - –Neonatal alloimmune thrombocytopenia
  - –Neonatal autoimmune thrombocytopenia
  - –Autoimmune diseases
  - –Drug-induced
- Platelet activation/consumption
  - –Disseminated intravascular coagulation
  - –Hemolytic-uremic syndrome
  - –Thrombotic thrombocytopenic purpura
  - –Kasabach-Merritt syndrome
  - –Necrotizing enterocolitis
  - –Thrombosis
- Mechanical platelet destruction
- Platelet sequestration
  - –Chronic liver disease
  - –Type 2B and platelet-type von Willebrand disease
  - –Malaria

Decreased Platelet Production

- Infection
- Cyanotic congenital heart disease
- Bone marrow failure or infiltrate
  - –Acute lymphoblastic leukemia and other malignancies
  - –Acquired aplastic anemia
  - –Fanconi pancytopenia
- Nutritional deficiencies
- Genetically impaired thrombopoiesis
  - –Thrombocytopenia with absent radii syndrome
  - –Congenital amegakaryocytic thrombocytopenia
  - –Wiskott-Aldrich syndrome
  - –X-linked thrombocytopenia with thalassemia
  - –Giant platelet disorders
  - –Bernard-Soulier syndrome
  - –May-Hegglin/Fechtner/Epstein and Sebastian syndromes

2.3.1- Decreased Platelet Production

Megakaryocytes are the only one which are responsible for the production of platelets. The suppression of megakaryocytes or bone marrow suppression will decrease the production of platelets leading to thrombocytopenia. It can result from any number of causes. It could be due to ineffective thrombopoiesis or due to decreased production of thrombopoietin. Hypoproductive thrombocytopenia could be due to hereditary and acquired causes. There are two types, one is associated with the megakaryocyte hypoplasia in the bone marrow, and the other is associated with ineffective thrombopoiesis. The most common causes are marrow injury by myelosuppressive drugs or irradiation and aplastic anemia.

Impaired platelet production may be due to loss of bone marrow space from infiltration, suppression or failure of cellular elements, or a defect in megakaryocyte development and differentiation. In this setting, examination of the bone marrow generally shows decreases in the number of megakaryocytes.

2.3.1.1-Inherited Thrombocytopenia/Congenital Hypoplasia

Most inherited thrombocytopenia are due to specific chromosomal abnormalities or genetic defects. The lack of adequate bone marrow megakaryocytes (megakaryocytic hypoplasia) is seen in a wide variety of congenital disorders. [76]

1-May- Hegglin Anomaly:

It is a rare congenital syndrome, which has autosomal dominant inheritance and was first described by May in 1909 and in 1945 by Hegglin. The incidence of this anomaly is unknown. It is characterized by variable thrombocytopenia and inclusions resembling dohle bodies within the granulocytes (the inclusions are large, spindle shaped, pale blue staining bodies) and giant platelets (20µm in diameter).[19] Thrombocytopenia is seen in nearly half of the patients. Most of the patients are asymptomatic and symptoms such as epistaxis, gingival bleeding, easy bruising, menorrhagia and excessive bleeding associated with surgical procedures which are seen when the platelet values are less than 50,000 cells/cu.mm.[20]

Patients have a mutation of MYH9 gene present in chromosome 22q12–13. *MYH9* gene encodes for nonmuscle myosin heavy chain (a cytoskeletal protein in platelets).[21] The mutation results in disordered production of nonmuscle myosin heavy chain type IIA.This leads to thrombocytopenia secondary to defective megakaryocytic maturation and fragmentation. Leukocyte inclusions are precipitates of myosin heavy chains. Neutrophil and platelet function is considered to be normal. Bleeding time is prolonged in proportion to the degree of thrombocytopenia.[22]

Despite variable thrombocytopenia, there is only giant platelets but the platelet function remains normal. Bone marrow shows adequate megakaryocytes with normal lobulation and granularity. (figure 6)

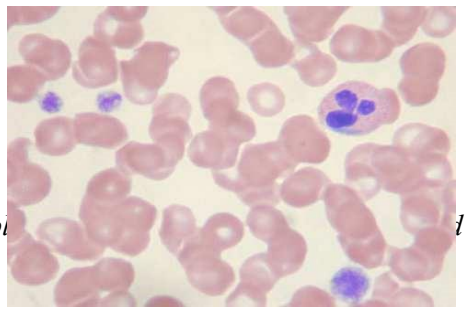


***Figure 6**: Peripheral bl l Dohle body like*

2-Myh9 Gene Related Disorders

There are three other disorders involving mutations of the MYH9 gene have been reported such as Sebastian syndrome, Fechtner syndrome, and Epstein syndrome. They represent variable expression of a single gene defect. They are all hereditary forms of thrombocytopenia. Each syndromes are associated with certain clinical features. e.g. Epstein syndrome is associated with interstitial nephritis and nerve deafness; Fechtner syndrome with nephritis, nerve deafness and congenital cataracts. Sebastian syndrome is inherited as an autosomal dominant disorder characterized by large platelets, thrombocytopenia, and granulocytic inclusions.[24]

3-Thrombocytopenia with Absent Radius (Tar) Syndrome:

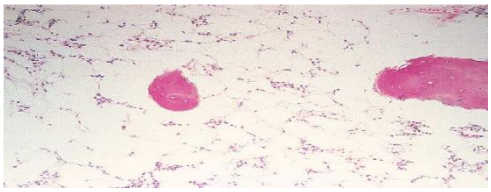
It is a rare autosomal dominant disorder with the combination of thrombocytopenia and absent radius which was first described by Greenwald and Sherman in 1929 and was delineated as a syndrome with a description of cardinal manifestations by Hall et al in 1969.[25,26] It occurs due to the mutation in the RBM8A gene located on the long arm of chromosome 1 (1q21.1). Patients have a high incidence of transient leukemoid reactions with elevated white blood cell counts above 100,000cells/cu.mm in 90% of patients.[27]

Thrombocytopenia (100%) is the most common clinical manifestation and 90% of the cases are symptomatic within the first four months of life. Platelet counts are in the range of 15 - 30x10^9/L in infancy and improve to near normal range by adulthood. The thrombocytopenia occurs secondary to impaired bone marrow production of platelets, despite normal thrombopoetin production and slightly elevated serum levels. The number of megakaryocytes in the bone marrow is very much reduced. Though Platelet aggregation and survival times are reduced, the overall platelet function tends to be normal and bleeding occurs secondary to low platelet numbers.

4-Wiskott- Aldrich Syndrome:

It is an X- linked hereditary disease which is characterised by thrombocytopenia with small platelet size which is a consistent finding in patients with mutations in the WASP gene.[68]WASP is a key regulator of actin polymerization in hematopoietic cells.[69] WASP gene is involved in the development of proplatelet and proplatelet release from megakaryocytes.[70-71] In addition , platelets are not released directly from within marrow , there is a transendothelial migration of the megakaryocytes which requires reorganization of actin filaments and formation of pseudopods.[72] A mutation occurs in any 1 of 8 exons which affect the function of WASP gene and thereby affecting the functions of the WASP gene.The platelet abnormalities are due to defect in proplatelet production as a consequence to abnormal interaction between WASP and cytoskeleton.[73]

Though the defect is not these elevated



exact mechanism of this platelet known, splenectomy done on patients are known to have platelet count towards normal with normal morphology .These data suggests the fact that the thrombocytopenia is due to peripheral destruction of platelets.[74][76] Despite increased peripheral destruction, marrow megakaryocytes are normal or increased in number suggesting ineffective thrombopoiesis.[77] Thrombopoietin (TPO) level in plasma was normal or slightly elevated.[78]

2.3.1.2.-Ineffective Thrombopoiesis (bone marrow failure or infiltrate):

1-Aplastic Anemia:

Aplastic anemia (AA) is a bone marrow failure syndrome characterised by pancytopenia in peripheral blood and aplasia/hypoplasia in bone marrow. It is a rare and life threatening haematological disorder caused by the destruction of the pluripotent stem cell.[38] It can be either congenital (15-20%) or acquired(75-80%). Congenital aplastic anemia is rare and usually associated with Fanconi anemia and dyskeratosis congenita.[39] Acquired type, in more than 50% cases, the etiology is unknown. Some of the causes may be autoimmune disease, iatrogenic agents, viral infection such as parvo virus and pregnancy. [40]

Peripheral blood pancytopenia is diagnosed by the following criteria such as haemoglobin <10g/dl, total leucocyte count <4000 cells/cu.mm, and platelet count < 1,00,000 cells/cumm, but the diagnosis of aplastic anemia was done by marrow cellularity that is decrease or loss of hematopoietic cell <30%.[41] (figure 7)

Figure 7: Bone marrow trephine biopsy – hypocellular(hematopoietic)

2-Elements Replaced by Fat

The deficiency of stem cell, abnormal microenvironments of bone marrow, the system of immune dysregulation and decreased growth factors, all these factors contribute for developing aplastic anemia. Bone marrow is hypocellular and the bone marrow has been filled fat and stromal cell. Decreased hematopoietic stem and progenitor cell numbers and function, resulting in impaired megakaryopoiesis and insufficient mature platelet production, which are the causes of thrombocytopenia.[42]

3-Inherited Aplastic Anemia:

Fanconi Anemia : It is an autosomal recessive condition first described by the Swiss paediatrician Guido Fanconi in the year 1927 , who described a familial form of aplastic anaemia in three brothers with short stature, hypogonadism and skin pigmentation.[43] the incidences of aplastic anaemia, myelodysplastic syndrome (MDS), and acute myeloid leukaemia (AML) are all greatly increased in homozygotes.It is the most common cause for inherited aplastic anemia.The most common clinical features are haematological manifestations.The blood and bone marrow appears normal at birth and then macrocytosis with anisopoikilocytosis is the first developed abnormality followed by thrombocytopenia and neutropenia. Pancytopenia usually develops by 5-10 years of age.[44, 45]

4- Acquired Aplastic Anemia(AA): Most cases(70%) are due to idiopathic reasons. 10-15% case occurs secondary to the drugs, virus and other causes. It is diagnosed after excluding the causes for inherited aplastic anemia usually in patients between 6 and 9 years of age.[46] One of the infectious agents causing acquired AA is Parvo virus B 19. The human erythroid precursor is the only known host cell of Parvo virus B19.[47] Erythrocyte P antigen(globoside) acts as receptor for the virus.The non structural protein (NS1) is responsible for the G1 arrest and apoptosis of the erythroid precursors' whereas megakaryocytes are lysed by restricted expression of viral proteins in the

absence of viral propagation. This explains reticulocytopenia without thrombocytopenia in patients with haemolytic anemia, who have shortened erythrocyte survival.[48] Direct cytotoxicity by these viral proteins also causes destruction of the marrow elements. Also immune mediated destruction of the marrow elements expressing viral proteins plays a role in aplasia.[49,50]

5-Megaloblastic Anemia: Megaloblastic anemia is a group of hematologic disorder which is characterised by abnormal DNA synthesis and results in blood and bone marrow disorders. [51]The presence of macroovalocytes with an MCV >115 fl, anisocytosis, poikilocytosis and hypersegmented neutrophils in peripheral blood are suggestive of megaloblastic disorder associated with a nutritional deficiency, i.e., vitamin B12 or folate deficiency. Bone marrow also shows megaloblastic hyperplasia with megaloblasts, which are due to the asynchrony between nuclear and cytoplasmic maturation, cytoplasm which has no DNA, does not mature fully, whereas nucleus has RNA, mature fully with hemoglobinisation .[52,53] (figure 8)

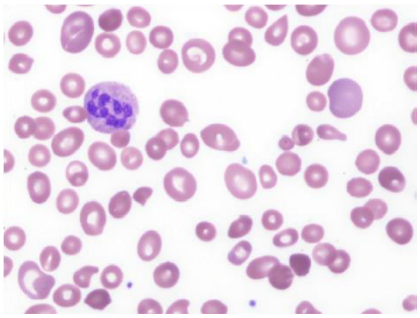


Figure 8*: peripheral smear showed macro-ovalocyte and hypersegmented*

Thrombocytopenia was seen in 20% of patients with megaloblastic anemia due to vitamin B12 and folic acid deficiency because of ineffective thrombocytopoiesis. Rarely, severe thrombocytopenia may occur.[54] Diminished platelet aggregation and reduced release of ADP and ATP from granule stores in response to different agonists have been reported.[55]

6-Leukemia:

Leukemia is a clonal disorder which is characterised by rise of immature cells in lymphoid and myeloid series. Leukemia are of two groups:

a) Acute leukemia and b) Chronic leukemia. In acute leukemia, 1/3 of patients have petechia, ecchymosis and nose bleeding relation with thrombocytopenia.[56]

Incidence and severity of thrombocytopenia in patients with leukemia vary according to the type and stage of leukemia. Thrombocytopenia is very common at presentation in cases of acute leukemia.The reasons for thrombocytopenia are diffuse bone marrow infiltration by leukemic cells leading to decreased production of platelets, increased platelet destruction from hypersplenism, immune mediated destruction of platelets as in case of chronic lymphocytic leukemia and following chemotherapy .[57]

2.3.1.3-Chronic Liver disease:

Thrombocytopenia is the most common haematological abnormality encountered in patients with chronic liver disease. Multiple factors resul in thrombocytopenia such as decreased production, splenic sequestration and increased destruction.[58]

Thrombocytopenia occur as the result of the liver cirrhosis with congestive splenomegaly or deficiency of folic acid. Diminished thrombopoietin levels along with marrow suppression results in decreased platelet production.[59]

2.3.1.4-Infectious Diseases:

Thrombocytopenia can be seen in patients with viral, bacterial, fungal and parasitic infections. Cytomegalovirus, Epstein-Barr virus and Hepatitis C virus and human immunodeficiency cirus(HIV) can produce thrombocytopenia during viral infections. Thrombocytopenia in many infectious appears due to hypoproduction rather than due to immune mediated destruction. Sometimes immune mediated destruction also happens in certain infections.

2.3.1.5-Acquired Drug Induced Hypoplasia:

Chemotherapy Or Radiotherapy:

Chemotherapeutic agents that are used for the treatment of hematologic and non hematologic malignancies will suppress the production of bone marrow megakaryocyte and other hematopoietic cells. The main dose-limiting factor for many chemotherapeutic agents is drug-induced thrombocytopenia.[62]

Chemotherapy or radiation therapy is an important cause of the thrombocytopenia. Bone marrow suppression (myelosuppression) is a common side effect of chemotherapy which increase the chances of anemia, thrombocytopenia and neutropenia.

Drugs like nitrosoureas, mitomycin and 5- florouracil can produce bone marrow toxicity. Zidovudine (used for the treatment of HIV infection) is also known to cause myelotoxicity and severe thrombocytopenia.[63]Interferon therapy commonly causes mild to moderate thrombocytopenia. Interferon-α and interferon-γ inhibit stem cell differentiation and proliferation in the bone marrow.[64]This thrombocytopenia leads to hemorrhage, and so the platelet count should be monitored closely. The lowest blood count occurs within 7-10 days after chemotherapy and recover after 2 to 3 weeks and for its treatment platelet transfusion is necessary.[65]

2.3.2- Increased Destruction of Platelets:

Accelerated platelet destruction is the most common cause of thrombocytopenia. Increased platelet destruction may lead to stimulation of thrombopoiesis and results in the increase in the number, size, and rate of maturation of the precursor megakaryocytes. When the platelet destruction exceeds that of the platelet production rate, it results in thrombocytopenia.[66]

Platelet destruction occurs due to both intracorpuscular defects and extracorpuscular abnormalities. Platelet destruction is seen most often in extracorpuscular defects with intracorpuscular defects are very rare as seen in hereditary thrombocytopenia such as Wiskott-Aldrich Syndrome.[67]

Disorders involving increased destruction or removal of platelets from the circulation typically result in the appearance of enlarged platelets on the peripheral blood smear (PBS), indicating that the bone marrow is producing new platelets to compensate for the increased destruction. In this setting, examination of the bone marrow generally shows normal or increased numbers of megakaryocytes. The destructive mechanisms resulting in thrombocytopenia included: Immune-mediated destruction, platelet activation and consumption, mechanical platelet destruction and platelet sequestration and trapping.[76]

2.3.2.1- Immune Mediated Thrombocytopenia:

The most common cause of thrombocytopenia due to increased destruction of platelets in infants and children is an immune-mediated process. Autoantibodies, drug-dependent antibodies, or alloantibodies may mediate platelet destruction through interaction with platelet membrane antigens, leading to increased platelet clearance from the circulation.

It is characterised by immune mediated destruction of platelets and impaired production of platelets. It could be auto-antibody mediated or alloantibody mediated. The alloantibody mediated thrombocytopenia is seen in neonatal alloimmune thrombocytopenia, post transfusion purpura and platelet alloimmunization after platelet transfusions

1-Immune Thrombocytopenia(ITP):

It is the most common cause for isolated thrombocytopenia.It occurs in all age groups. Childhood ITP is acute in onset and occurs following viral infection or after

vaccination, though the thrombocytopenia is severe yet it resolves spontaneously within few weeks to 6 months. Whereas adult ITP is chronic in onset and does not resolve spontaneously.[79]

In ITP, the platelet counts are often less than 1,00,000 cells/cu.mm. It is classified as primary ITP and secondary ITP.[80]

Primary ITP is denoted by the absence of any other underlying pathology. It is due to the antiplatelet antibodies, impaired megakaryocytopoiesis and T-cell mediated destruction of platelet.[81]Secondary ITP is due to underlying disorders such as: autoimmune disease (systemic lupus erythematosis (SLE) or rheumatoid arthritis), HIV, *helicobacter pylori*, or underlying immune dysregulation syndromes such as Common Variable Immunodeficiency (CVID).[82]

The typical case of symptomatic childhood ITP is characterized by the sudden appearance of bruising or mucocutaneous bleeding in an otherwise healthy child, often after a preceding viral illness. An increased risk of ITP is also associated with measles, mumps, rubella immunization, which accounts for perhaps 50% of all ITP cases during the second year after birth. This form of ITP tends to be transient and rarely is the bleeding severe. The history should reveal no systemic symptoms such as fever, weight loss, or bone pain. Other than mucocutaneous bleeding, patients should appear well. No lymphadenopathy or hepatosplenomegaly should be present. If one or more of these findings are present, another diagnosis should be strongly considered. Otherwise, the diagnosis of ITP can be made based on two criteria: 1) isolated thrombocytopenia with otherwise normal blood counts and PBS and 2) no clinically apparent associated conditions that may cause thrombocytopenia.

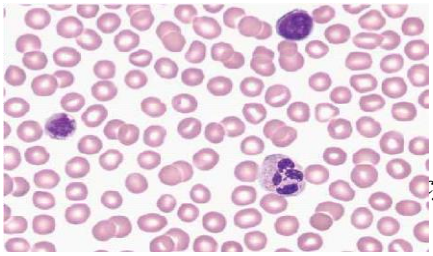
Primary ITP:

About 80% of cases are primary ITP.[83] About 60-70% of these patients have platelet specific IgG antibodies which was directed against platelet surface glycoproteins, GPIIb/IIIa and GP1b/IX/V.[84] These antibodies act differently based on the epitope they attack, resulting in defective clearance, inhibit megakaryopoiesis or induce platelet apoptosis .[85-87]

There are some patients who have abnormal T cells that results in platelet destruction and few patients have T cell dysregulation that results in autoantibody production .[88]

Diagnosis of ITP is generally made by review of peripheral smear and evaluation of history and examination of the patient. Peripheral smear show reduced platelets, but the platelets are greater in diameter. Bone marrow shows megakaryocytic hyperplasia.[89] (figure 9,10)

***Figure 9**: Peripheral blood showing scarce platelets with one giant*

***Figure 10** : Bone*  *ytic hyperplasia[124]*

SECONDARY ITP:

Secondary ITP occurs due

The thrombocytopenia sponse modifiers such as interferons is immune m of platelet associated Ig G have been measured anc after the removal of the agents.[90]

In systemic lupus erythematosus(SLE), which is an autoimmune disorder with broad spectrum of clinical manifestations. The common haematological abnormalities in SLE is thrombocytopenia and leucopenia.[91]The most common mechanism for thrombocytopenia is believed to be increased platelet clearance mediated by anti-platelet autoantibodies. The severity of thrombocytopenia and response to treatment should be closely monitored to predict the prognosis in SLE patients.[92]

Antiphospholipid antibody syndrome (APS) which is characterised by recurrent arterial and venous thrombosis and recurrent abortions. Thrombocytopenia is rarely severe and is the most common non–criteria hematologic manifestation of APS. Thrombocytopenia is seen in 20-40% of patients with APS. The possible mechanism of thrombocytopenia in APS is APLA-related direct platelet destruction, immune platelet destruction by antibodies against platelet GPs, complement-mediated platelet destruction, and platelet aggregation and consumption.[93]

Certain drugs causes severe thrombocytopenia and bleeding. The mechanism is different for different drugs. Some drugs causes the bone marrow suppression or immune mediated destruction resulting in thrombocytopenia. Drug induced immune mediated destruction occurs through these mechanisms such as one is typed as quinidine- and quinine-induced thrombocytopenia, in which the antibody induced by drugs interacts with platelets only in the presence of the drug. The Fab portion of the IgG antibody binds to a platelet membrane proteins such as GP Ib/IX complex or the GP IIb/IIIa complex.[94]

Second mechanism is induction of hapten-dependent antibodies. That is some drugs are too small to induce an immune reaction, hence they act as a hapten and binds with carrier molecule like plasma protein and acts as an antigen.[95]

The third mechanism is that the drugs stimulate the formation of an autoantibody that binds to a specific platelet membrane glycoprotein with no requirement for the presence of free drug.

In heparin induced thrombocytopenia (HIT), which is a common side effect of unfractionated heparin administration in about 1% to 5% of patients. Despite the thrombocytopenia, patients with HIT usually are not at significant risk of bleeding, because the platelet count typically does not fall below 40,000 cells/cu.mm. 10 - 30% of patients with HIT develop thrombotic complications. It is caused by formation of autoantibodies to complex of platelet factor 4 and heparin.[96]

2 - Platelet Activation and Consumption

. In patients who experience disseminated intravascular coagulation (DIC) and the microangiopathic disorders hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), thrombocytopenia occurs because of systemic platelet activation, aggregation, and consumption (Table 2). More localized platelet activation and consumption contributes to the thrombocytopenia seen in Kasabach-Merritt syndrome (KMS), necrotizing enterocolitis (NEC), and thrombosis in infants and neonates. In infants who have KMS, thrombocytopenia results from shortened platelet survival caused by sequestration of platelets and coagulation activation in large vascular malformations ofthe trunk, extremities, or abdominal viscera. Cutaneous vascular lesions are noted at birth in approximately 50% of patients. Detection of visceral lesions requires imaging studies. All patients have severe thrombocytopenia, hypofibrinogenemia, elevated fibrin degradation products, and fragmentation of red blood cells on PBS.[76]

3 - Mechanical Platelet Destruction

The use of extracorporeal therapies, such as extracorporeal membrane oxygenation, cardiopulmonary bypass, hemodialysis, and apheresis, is associated with mechanical destruction of platelets, which may result in thrombocytopenia. Exchange transfusion also may reduce platelet number by loss in the exchange effluent. Severe ongoing hemorrhage requiring rapid and repeated red blood cell transfusions may lead to thrombocytopenia due to a “wash out” phenomenon.[76]

4 - Platelet Sequestration and Trapping

About one third of the platelet mass is normally sequestered in the spleen at any given time. A greater proportion of platelets are sequestered in patients who experience hypersplenism, reducing the number of circulating platelets and leading to thrombocytopenia. The survival of platelets in persons who have hypersplenism is normal or near normal. It is the pooling and unavailability of platelets "trapped" in the spleen that is the problem. Leukopenia or anemia also may accompany a low platelet count caused by hypersplenism. Conditions in this category include:

● Chronic liver disease with portal hypertension and congestive splenomegaly. Occasionally, isolated thrombocytopenia may be the initial manifestation of this type of chronic liver disease. The platelet count is typically in the range of 50,000-100,000/ μland usually does not represent a clinically important problem.

● Type 2B and platelet-type von Willebrand disease. Thrombocytopenia in this disorder is caused by increased removal of platelets from the circulation. Increased binding between larger von Willebrand factor multimers and platelets leads to the formation ofsmall platelet aggregates that are cleared from the circulation, resulting in a lower platelet count.

● Malaria with hypersplenism. This diagnosis should be considered in any child who has fever, splenomegaly, thrombocytopenia, and a history of recent travel to an endemic area.[76]

2.3.2.2-Non Immune Mediated Increased Destruction Of Platelets (platelet consumption):

1-Thrombotic Thrombocytopenic Purpura :

Thrombotic thrombocytopenic purpura (TTP) is a rare and life threatening thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, severe thrombocytopenia, and organ ischemia linked to disseminated microvascular platelet rich-thrombi. [97]TTP is characterised by the presence of a severe deficiency of ADAMTS13 (activity < 10%), which is the only biologic marker specific for TTP. [98]

Peripheral blood showed marked decrease in platelets, RBC polychromasia, and RBC fragmentation (microspherocytes, schistocytes, keratocytes), a triad characteristic of microangiopathic hemolytic anemias.[100] (figure 11)

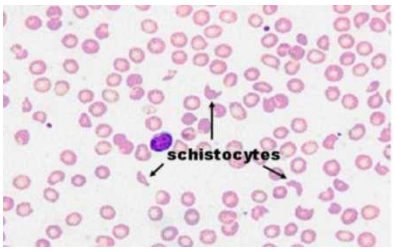


Figure 11: *Bone marrow trephine shows megakaryocytic hyperplasia*

2-Haemolytic Uremic Syndrome:

The main differential diagnosis for TTP is hemolytic uremic syndrome.

HUS results from food poisoning with enterohemorrhagic strains of Escherichia coli or other bacteria producing a shiga-like toxin (STEC-HUS). It is essential to distinguish TTP from other causes of thrombotic microangiopathy such as cancer, organ transplantation, sepsis, or pregnancy for preeclampsia and the hemolysis elevated liver enzymes low platelet count because patients with severe ADAMTS13 deficiency are likely to respond to therapeutic plasma exchange (TPE) , whereas those without ADAMTS13 severe deficiency often require treatments other than TPE.[101]

2.3.2.3-Abnormalities In Distribution Of Platelets:

The normal spleen sequesters approximately one third of the total platelet mass. Mild thrombocytopenia may be present in conditions causing splenomegaly. The total body platelet mass is normal in these disorders, since numerous platelets are sequestered in the enlarged spleen, there will be reduced platelet count. Hypersplenism can be seen in many conditions such as chronic liver disease with portal hypertension and congestive

splenomegaly sickle cell anemia, hemoglobin C disease, thalassemia major, chronic infections, gaucher disease, myelofibrosis and lymphoma. The administration of massive amounts of stored whole blood may produce a temporary thrombocytopenia because the stored blood contains platelets whose viability is severely impaired by the effects of storage and temperature. They do not require any treatment since once splenectomy done, the platelet count comes to normalcy.[102]

2.4- Platelet Indices and Thrombocytopenia :

Platelet indices are becoming increasingly important in evaluating the thrombopoietic function. Reference ranges should be defined clearly and be accurate and valuable in interpretation of results to prevent unnecessary and costly follow up laboratory investigations.

Thrombocytopenia may result either from hypoproliferation in marrow or peripheral destruction of platelets. Distinction between these two categories is usually made by the bone marrow examination.Some studies in literature say that platelet indices are differently altered in various causes of thrombocytopenia.[140]

2.4.1- Mean Platelet Volume

The high MPV in platelet destruction explains the fact the newly produced platelets are larger than circulating platelets. In patients with thrombocytopenia secondary to peripheral destruction, MPV is increased, reflecting active bone marrow compensation with release of young platelets.[141] In a study by Numbenjapon et al [142] had concluded that MPV is a reliable diagnostic test to differentiate hypoproductive and hyperdestructive thrombocytopenia with a cut off value of 7.9fL. Higher MPV was noted in hyperdestructive thrombocytopenia.

Similarly, studies by Kaito et al,[143] Ntaios et al,[144] Khaleel et al,[145] and Shah et al[146] also reported that MPV was higher in ITP patients than hypoproductive thrombocytopenic patients, reflecting increase in the production rate with an established cut off values ranging from 9fL to 11fL.

Elsewefy et al[147] and Borkataky et al[148] found no significant difference in the MPV between both thrombocytopenic groups.

2.4.2- Platelet Distribution Width)PDW):

PDW represents the heterogenicity of platelets. Increased PDW represents anisocytosis of platelets.

In a study by Kaito et al,[142] Ntaios et al,[143] Khaleel et al,[144] and Shah et al[145] , they had reported that PDW was higher in ITP patients when compared to hypoproductive thrombocytopenia.

In a study by Nelson et al [148], he mentioned that patients with hyperdestructive thrombocytopenia whether due to infection, hemorrhage or immune destruction have larger platelets and high PDW. Whereas hypoproductive thrombocytopenia, PDW was similar to that seen in patients with normal cell counts.

2.4.3- Platelet Large Cell Ratio(P-LCR):

P-LCR was found to be significantly higher in ITP patients compared with the normal control group and was significantly lower in hypoproductive thrombocytopenic patients when compared with the control group with a cut off value greater than 33.6% which yielded 100% diagnostic sensitivity in a study by Elsewefy et al.[146]

Similarly ,Ntaios et al and Kaito et al reported nearly similar cut off value of greater than 30% with diagnostic sensitivity of 90.4 and 91.4% respectively.

Also studies by Babu and Basu [135]and Borkataky et al[147] reported that PLCR was increased in hyperdestructive thrombocytopenic patients than hypoproductive thrombocytopenic patients and concluded that P-LCR can be a good aid in the differential diagnosis of conditions associated with abnormal platelet counts.

2.4.4- Plateletcrit (PCT):

There is a significant overlap of PCT between thrombocytopenic patients and patients with low normal platelets.This is due to the variation in the MPV which is one of the factors affecting MPV.

In a study with a cutoff value of 0.20-0.36% was helpful in distinguishing thrombocytopenia from normal patients with a sensitivity of 90% and indicates that plateletcrit can be used instead of platelet counts alone to determine if the patients need platelet transfusion.[149]

In a study , PCT was significantly lower in ITP patients rather than the hypoproductive thrombocytopenic patients.Also some study show that the value is not altered by severity of thrombocytopenia of either hyperdestructive or hypoproductive etiology.[151]

2.4.5- Immature Platelet Fraction(IPF):

Rapid assessment of platelet production is determined by IPF.High IPF usually seen in hyperdestructive thrombocytopenia.

In a study by Adly AA et al, IPF was increased in patients with ITP than other groups , and ITP patients on remission showed lowest IPF. IPF was positively correlated to MPV ,PDW and P-LCR and negatively correlated to platelet count and plateletcrit.[152]

In other study done in 2004, Patients with ITP had the highest IPF levels of all patients with 73% of ITP patients showing elevated levels with range 9.2-33.1%. [153]

Levels were not elevated in patients on chemotherapy or in ITP/TTP patients in remission. In other research, patients with IPF values >9.0% were 100% specific for peripheral platelet destruction, with 89% sensitivity for ITP.[154]

Studies have shown that IPF is an early indicator of marrow recovery in patients rebounding from chemotherapy or hematopoietic stem cell transplant. IPF recovery defined as levels >7.0% occur on average 3.1 days earlier than platelet count recovery, and 3.8 days earlier than absolute neutrophil count recovery. Thus IPF may be useful to

guide and possibly limit prophylactic platelet transfusions in patients undergoing marrow suppressive therapy, in view of imminent recovery of the platelet count.[155]

In dengue fever patients, IPF is measured as an indicator to predict the recovery of platelets in patients, it is found that the IPF has a strong correlation with the recovery of platelet counts in dengue. Nearly 85% patients showed recovery within 24 hours after attaining peak IPF. A single value of IPF more than 10% was indicative of platelet recovery within 24-48 hours.[155]

2.5 - Treatment of Thrombocytopenia:

Treatment is guided by the severity and specific cause of the disease. Treatment focuses on eliminating the underlying problem, whether that means discontinuing drugs suspected to cause it or treating underlying sepsis. Diagnosis and treatment of serious thrombocytopenia is usually directed by a hematologist. Corticosteroids may be used to increase platelet production. Lithium carbonate or folate may also be used to stimulate .platelet production in the bone marrow[35]

Platelet transfusions may be suggested for people who have a low platelet count due to .thrombocytopenia[36]

Treatment of thrombotic thrombocytopenic purpura (TTP) is a medical emergency, since the associated hemolytic anemia and platelet activation can lead to kidney failure and changes in the level of consciousness. Treatment of TTP was revolutionized in the 1980s .with the application of plasmapheresis[60] Many cases of immune thrombocytopenic purpura (ITP), also known as idiopathic thrombocytopenic purpura, can be left untreated, and spontaneous remission (especially in children) is not uncommon. However, counts under 50,000/μL are usually monitored with regular blood tests, and those with counts under 10,000/μL are usually treated, as the risk of serious spontaneous bleeding is high with such low platelet counts. Any patient experiencing severe bleeding symptoms is also usually treated. The threshold for treating ITP has decreased since the 1990s; hematologists recognize that patients rarely spontaneously bleed with platelet counts .greater than 10,000/μL, although exceptions to this observation have been documented[61]

Thrombopoetin analogues have been tested extensively for the treatment of ITP. These agents had previously shown promise, but had been found to stimulateantibodies against endogenous thrombopoietin lead to thrombosis. Romiplostim (trade name Nplate, formerly AMG 531) was found to be safe and effective for the treatment of ITP in refractory patients, especially those who relapsed following splenectomy[75].

Chapter Three: Methodology

3.1- Study Design:

A retrospective cross-sectional descriptive study was conducted by collecting the data from the hospital's records of thrombocytopenic children within the age group (1-15 years), who admitted to the four major public hospitals in Sana'a City -Yemen.

3.2-Study Setting:

The present study was carried out in the four major public hospitals at Sana'a City, Yemen.

1- Al-Kuwait Hospital
2- Al-Thawra Modern General Hospital
3- Al Sabeen Hospital
4- Al-Gomhori Hospital

These hospitals were chosen because they are considered as referral hospitals to all health facilities in Yemen

3.3- Duration of Study:

This study conducted from May 2022, to December 2022.

3.4-Study Population:

All children, aged between one year and 15 years with thrombocytopenia in hospitals at Sana'a City, Yemen (Al-Kuwait Hospital, Al-Thawra Modern General Hospital, Al Sabeen Hospital, and Al-Gomhori Hospital) , who are eligible to participate in the study.

3.5- Sample Size Determination

Two hundred and twenty-sixthrombocytopenic paediatric patients were ,identified out of 3236 admitted patients recorded during the study periodwho were included in this study.

3.6- Inclusion and Exclusion Criteria

3.6.1-Inclusion criteria

All Children in the specific age from one year to 15 years old who have documented platelet counts less than 150,000 cell/µl , both male and female.

3.6.2-Exclusion criteria:

Children less than 1 year old , cases who haven't clear confirmed diagnosis and patient's files without CBC .

3.7-Study Variable.

3.7.1-Dependent variables

Quantitative variables: Age and hematological laboratory results

Qualitative variables: Gender, causes, clinical signs, final diagnosis and outcome.

3.7.2-Independent variables

No independent variables

3.8- Data Collection and Instruments;

3.8.1-Data Collection

The data Collection were obtained from hard copy of the patients' files in 2022 at the targeted hospitals, and the answers were filled in the questionnaire checklist by the researchers.

3.9-Pilot Study:

The pilot study was conducted on 30 thrombocytopenic children files to identify the practical or local problems that might be potentially affect the research process. Some questions were omitted, some added and others rephrased.

3.10-Data Analysis:

After the data had been collected, data were coded and processed by using the Statistical Package for Social Sciences (SPSS) version 23. The data were displayed in tables and graphs. Chi square was used to find association among age, gender and etiology.Descriptive statics, included frequency, incidence, percentage, and standard deviation will be presented. Chi square was used to find association among age, gender and etiology and outcome. The test will be considered significant when p value less than 0.05.

3.11- Ethical Considerations:

The study protocol was passed by Ethical committee of 21 September University for Medical and Applied Sciences. Consent was earned from the targeted hospitals where data will be collected.

Our team was honest and meticulous in collecting data

There is no names of the patients who was included in the research

Paying attention to files privacy and security in data collection

Chapter four: Results

A total of 3236 patients were admitted and discharged from the four major hospitals from 01/01/2022–12/31/2022. Of admitted patients, 226 patients have thrombocytopenia during their hospitalization. So the estimated incidence of thrombocytopenia is 7% (n = 226/3236).

4.1- Distribution of the Sample according to Socio-demographic characteristics:

The distribution of the study sample according to Socio-demographic characteristics, we found that among the 226 thrombocytopenic patients, 130 (57.5%) were males and 96(42.5%) were females.(figure 12)

The majorty of patients was in the age group of less than 5 years)143 ; 63.3%,(followed by 44(19.5%) in the age group of 6 to 10 years and the least number was 39(17.3%) in the age group of above 10years.The average age was (4.97) years, and Standard Deviation was (3.89) years.

The majority of the admitted pediatric patients from Sana'a City (n = 80; 35.4%) followed by Dhamar Governorate (n = 23; 10.2%) and Ibb Governorate (n = 18; 8.0%). (Table 4.1)

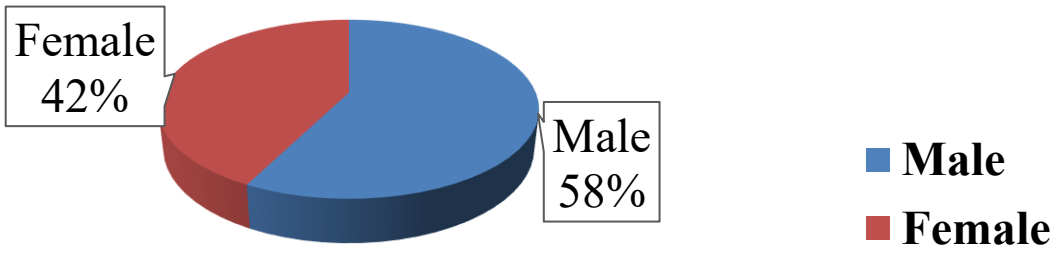


Figure12 : Distribution of the thrombocytopenic children according to gender in Sana'a City, 2022 (n=226)

Table 4.1 Distribution of the thrombocytopenic children according to :Socio-demographic characteristics in Sana'a City, 2022 (n=226)

Sex

Sex	N	%
Male	130	57.5%
Famale	96	42.5%

Age

Age group	N	%	Mean	Std. Deviation
<= 5 y	143	63.3%	4.97	3.89
6–10 y	44	19.5%		
> 10 y	39	17.3%		

Place of birth

Place of Birth	N	%
Sana'a Governorate	80	35.4%
Dhamar Governorate	23	10.2%
Ibb Governorate	18	8.0%
Al Hudaydah Governorate	14	6.2%
Taiz Governorate	14	6.2%
Hajjah Governorate	13	5.8%
Amran Governorate	12	5.3%
Al-Bayda Governorate	10	4.4%
Al-Jawf Governorate	9	4.0%
Others	33	14.5%

4.2 -Distribution of the Sample according to Laboratory Findings:

In our study we found that, the laboratory findings of HB, total leucocyte,

and platelet were as follows: The mean of Hb was 9.50, and standard deviation was (2.595), whereas the mean of TLC was 11.61, and a standard deviation of (14.542), lastly we found that, the mean PLTS was 57,850, and the standard deviation of (43,651).(table 4.2)

Table4.2 Distribution of the thrombocytopenic children according to Laboratory : findings in Sana'a City, 2022 (n=226)

laboratory test results	N	Minimum	Maximum	Mean	Std. Deviation
HB	226	1	16	9.21	2.595
TLC	226	1	123	11.61	14.542
LYMPHOCYTES	226	22	95	36.67	27.245
PLTS	226	1	149	57.85	43.651

The laboratory tests results of CBC revealed that, the majority of the sample patients had low hemoglobin level (<11 g/dL) (n =154 ; 68.2%), followed by normal Hb level (11-15 g/dL) and only one child had high Hb level (> 15 g/dL)

The CBC results of platelet counts revealed that, the majority of patients have severe thrombocytopenia (n = 66; 29.2%) followed by very severe thrombocytopenia (n = 59; 26%), that's platelets count equal 20,000-,µl and <20,000/µl respectively/ه٠,٠٠٠and the least number of patients have mild thrombocytopenia(n = 48; 21.2%).)Table 4.3)

The CBC results of leucocyte counts revealed that, the majority of patients have normal Leucocyte Count range (n = 86; 38.0%) followed by leucocytosis ,(n = 75; 33.2%)only 25.7% of patients have leukopenia and 3.1% of them have very high Leucocyte count more than 40,000 cell/ µl.

Bone marrow aspiration (BMA) is often performed in children with abnormal CBC results to rule out leukemia and some diseases. About tow thirds of patients didn't take BMA test (n= 136; 60%) , only 40% of patients took BMA.(figure13)

Table 4.3 :Dstribution of the thrombocytopenic children according to the laboratory findings grades in Sana'a City, 2022 (n=226)

Variables	Laboratory Findings			
Hemoglobin level	**Hemoglobin level**		N	%
	<11 g/dL		154	68.2%
	11-15 g/dL		71	31.4%
	> 15 g/dL		1	0.4%
Platelet count	Grading of thrombocytopenia	Platelet count	N	%
	Very sever	<= 20000µl	٥٩	.٢٦1%
	Sever	20000-50000µl	٦٦	٪٢٩,٢
	Moderate	50000-100000µl	53	23.5%
	Mild	100000-<150000µl	48	21.2%
Leucocyte count	Leucocyte ount		N	%
	<4 ×10³ cell/ µl		58	25.7%
	4 -10 ×10³ cell/ µl		86	38.0%
	11-40 ×10³ cell/ µl		75	33.2%
	>40 ×10³ cell/ µl		٧	3.1%
Bone marrow	Yes		90	39.8%
	No		136	60.2%

Figure13 : Distribution of the thrombocytopenic children according to bone marrow aspiration test in Sana'a City, 2022 (n=226)

4.3-Distribution of the Sample according to the Clinical Features:

The majority of thrombocytopenic pediatric patients presented without history of bleeding (n = 155; 68.8%), that's mean they were discovered accidentally by a primary care provider who performs a complete blood count (CBC) for other indications (n = 155; 68.6%), whereas the patients ,presented with bleeding symptoms were (n= 71; 26.7%) patients who were presented either with spontaneous hemorrhage (n= 58; 25.7%)or post surgery or trauma bleeding (n= 12; 5.3%) ,of whom (n = 64; 90.1%) were ecchymosis followed by epistaxis then hematuria. The most common

nonspecific symptoms were fever (n = 199; 88%) followed by fatigability).and pallortable 4.4)

Table 4.4:D stribution of the thrombocytopenic children according toclincal features in Sana'a City, 2022 (n=226)

Variables	Clincal features			
Bleeding Tendency			N	Percent
	Yes	Spontaneous hemorrhagic	58	25.7%
	Yes	Post-Surgery/ Trauma	13	5.8%
	No	Accidentally Discovered. (No history of bleeding)	155	68.6%
Bleeding symptoms	Ecchymosis/ petechiae / purpura		64	28.3%
	Epistaxis		49	21.7%
	Hematuria		14	6.2%
	Gingival bleeding		11	4.9%
	Hematochezia		11	4.9%
	Bleeding form puncture sites		8	3.5%
	Hematemesis		8	3.5%

	Hemoptysis	3	1.3%
Non specific symptoms	Fever	199	88.1%
	Fatigability	111	49.1%
	Pallor	107	47.3%
	Sweats	102	45.1%
	Hepatomegaly	84	37.2%
	Weight loss	78	34.5%
	Splenomegaly	77	34.1%
	Bleeding symptoms	71	31.4%
	Prodromal illness	66	29.2%

4.4-Description of Findings Related to the Diagnosis:

Infection was documented in 42% of all patients with thrombocytopenia, which is the most common identified cause for low platelet. Sources of the infection included: post viral and pneumonia (43.2%), which is the most common infectious disease associated with thrombocytopenia, Leshmaniasis(23.2%), malaria(10.5%), meningitis (4.2%), and gastroenteritis (3.2%).

The second most common cause was malignancy (n= 58; 25.7%), which included leukemia (96.6%) and lymphoma (3.4%).

The hematological couses was the third common couse of thrombocytopenia (n= 57; 25.3%), that included anemia (79%), and immune thrombocytopenic purpura (17.5%).

The other causes categorized into nutritional (n= 5; 2.2%), autoimmune (n= 3; 1.3%), post medication (n= 3; 0.9%) and lastly congenital disease (n=1 ; 0.4%).)Table 4.5)

Table4.5 Dstribution of the thrombocytopenic children according to the:etiological spectrum in Sana'a City, 2022 (n=226)

	Categories	N	Percent
Categories of etiology	Infection	95	42%
	Malignancy	58	25.7%
	Hematological	57	25.3%
	Nutritional	5	2.2%
	Autoimmune	3	1.3%
	Post Medication/Chemotherapy	2	0.9%
	Congenital / inherited	1	0.4%
	Others	5	2.2%
Specific etiology	Leukemia's	56	24.8%
	Anemia	45	19.9%
	Post-Viral / Pneumonia	41	18.1%
	Leishmaniasis	22	9.7%
	Malaria	10	4.4%
	Immune Thrombocytopenic purpura	9	4.0%
	Severe Acute Malnutrition	4	1.8%
	Meningitis	4	1.8%
	Others	35	15.5%
	Total	226	100.0%

4.5- Description of the Treatment Results:

The majority of thrombocytopenic pediatric patients were treated by combined supportive measures such as antibiotics)52%(, NSAID(69%), and platelet transfusion(42%). Among the 226 cases of moderate and sever thrombocytopenia, 94 patients (42%) were required platelets)transfusions. Only 17 patients6.1%required IV immunoglobulin therapy (.from a hematologist75 patients(27.1%) were treated by corticosteroids.Table 4.6

Table 4.6: Distribution of the thrombocytopenic children according to treatment, in Sana'a City, 2022 (n=226)

Treatment		N	Percent
Supportive	Antibiotics	118	52%
	platelet transfusions	94	42%
	NSAID	156	69%
Corticosteroid		75	27.1%
Iv Immunoglobulin		17	6.1%

4.6- Describing the Results of the Outcome:

Among 226 thrombocytopenic pediatric patients, 77 children (27.8%) were cured after they had been treated which was confirmed by serial platelet count tests evaluation. The outcomes of the other patients included refferal to other health facilities (26.4%), as leukemic patients were considered the most common reason for referring, dead (10.5%) with the most common causes of death were sepsis and heart failure, DAMA (9.0%) and lastly unknown outcome (4.7%).

Among 29 dead patients, 18 were males and 11 were females. The majority of them were young children of less than 5 years old (79.3%) and associated with anemia of less than < 11 g/dL (69.0%) . The most common identified cause of death was infections/ sepsis (41.4%), followed by heart failure and dehydration. There was correlation between mortality and severity of thrombocytopenia, 31.0% and 27.6% of dead cases had very severe and sever thrombocytopenia respectively, whereas only 10.3% of the dead cases had mild thrombocytopenia. (Table 4.7)

Table 4.7: Distribution of the thrombocytopenic children according to outcomes, in Sana'a City, 2022 (n=226)

Variables				
Outcomes	Categories		N	Percent
	Cure		77	27.8%
	Reffered		73	26.4%
	Dead		29	10.5%
	DAMA		25	9.0%
	Unknown		13	4.7%
Dead	SEX	Male	18	62.1%
		Female	11	37.9%
	AGE(YEARS)	< 5	23	79.3%
		5 - 10	5	17.2%
		>10	1	3.4%
	HB	< 11	20	69.0%
		11 - 15	8	27.6%
		> 15	1	3.4%
	PLTS	< 20000	9	31.0%
		20000 - 50000	8	27.6%
		50000 - 100000	9	31.0%
		> 100000	3	10.3%

INFECTION/ SEPSIS	12	41.4%
Heart failure / arrest	8	27.4%
Dehydration& Shock	4	13.8%
AKI	2	6.9%
Whooping cough	1	3.4%
Multi Organ Failure	1	3.4%
Liver failure	1	3.4%

4.7- Association between the Etiology of Thrombocytopenia and Sociodemographic Data :

There is no relationship between the sex factor and the aetiology of patients with thrombocytopenia. Because the level of significance for each of all etiology was greater than 0.05. So there is no significance in sex factor regarding the morbidity in these patient thrombocytopenia as shown in table (4.8)

Association between the etiology of thrombocytopenia and age factor was studied using chi-square and fisher's exact test were appropriate. Age group was significantly associated with morbidity of autoimmune (P value < 0.010), ITP (P value < 0.018),and post medication (P value < 0.008) as shown in Table 4.9

Table4.8 Association between :the ,etiology of thrombocytopenia and sex data among pediatric patients with thrombocytopenia, in Sana'a City, 2022 (n=226)

Causes of thrombocytopenia		Sex				Chi-Square	Sig.
		Male		Female			
		N	%	N	%		
Hematological	Yes	40	70.2%	17	29.8%	0.022	0.883
	No	90	63.4%	52	36.6%		
Infection	Yes	51	53.7%	44	46.3%	0.415	0.520

		No	71	54.1%	60	55.9%		
Nutritional		Yes	4	80.0%	1	20.0%	1.681	.195a
		No	126	57.0%	95	43.0%		
Congenital / Inherited		Yes	1	100.0%	0	0.0%	3.007	.083a
		No	129	57.3%	96	42.7%		
Malaria		Yes	7	70.0%	3	30.0%	0.667	.414a
		No	123	56.9%	93	43.1%		
Leshmaniasis		Yes	16	72.7%	6	27.3%	2.306	0.129
		No	114	55.9%	90	44.1%		
Post viral/Pneumonia		Yes	25	61.0%	16	39.0%	1.487	0.223
		No	105	56.8%	80	43.2%		
Anemia		Yes	25	55.6%	20	44.4%	0.089	0.766
		No	105	58.0%	76	42.0%		
Hypersplenism		Yes	1	100.0%	0	0.0%	0.742	.389a,b
		No	129	57.3%	96	42.7%		
DIC		Yes	0	0.0%	2	100.0%	0.013	.910a
		No	130	58.0%	94	42.0%		
ITP		Yes	5	55.6%	4	44.4%	0.351	0.554
		No	125	57.1%	92	42.9%		
Leukemias / malignancy		Yes	32	57.1%	24	42.9%	0.336	0.562
		No	98	57.6%	72	42.4%		

Table4.9 Association between etiology of thrombocytopenia and :age ,data among pediatric patients with thrombocytopenia, in Sana'a City, 2022 (n=226)

Causes of thrombocytopenia		Age						Chi-square	Sig.
		<= 5		6 - 9		>10			
		N	%	N	%	N	%		
Infection	Yes	65	68.4%	18	19.0%	12	12.6%	2.626	0.269
	No	78	59.6%	26	19.8%	27	20.6%		
Hematological	Yes	38	66.7%	10	17.5%	9	15.8%	0.724	0.696
	No	105	62.1%	34	20.1%	22	17.8%		
Autoimmune	Yes	1	33.3%	1	33.3%	1	33.3%	9.170	.010[a,*]
	No	142	63.7%	43	19.3%	38	17.0%		
Malaria	Yes	8	80.0%	1	10.0%	1	10.0%	1.264	.532[a]

	No	135	62.5%	43	19.9%	38	17.6%		
Leshmaniasis	Yes	18	81.8%	4	18.2%	0	0.0%	5.551	.062[a]
	No	125	61.3%	40	19.6%	39	19.1%		
Post viral / Pneumonia	Yes	26	63.4%	6	14.6%	9	22%	0.682	0.711
	No	117	63.2%	38	20.5%	30	16.2%		
Anemia	Yes	28	62.2%	9	20.5%	8	17.8%	0.027	0.987
	No	115	63.5%	35	19.3%	31	17.1%		
Hypersplenism	Yes	1	100.0%	0	0.0%	0	0.0%	0.583	.747
	No	142	63.1%	44	19.6%	39	17.3%		
ITP	Yes	6	66.7%	2	22.2%	1	11.1%	8.046	.018[a,*]
	No	137	63.1%	42	19.4%	38	17.5%		
SLE	Yes	1	25.0%	2	50.0%	1	25.0%	3.034	.219
	No	142	64.0%	42	18.9%	38	17.1%		
Leukemias	Yes	35	62.5%	8	14.3%	13	23.2%	2.566	0.277
	No	108	63.5%	36	21.2%	26	15.3%		
Post Medication	Yes	0	0.0%	0	0.0%	2	100.0%	9.675	.008[*]
/Chemotherapy	No	143	63.8%	44	19.6%	37	16.5%		

4.8-Association between the Bleeding Tendency and the Severity of Thrombocytopenia :

Association between the history of bleeding tendency and the severity of thrombocytopenia was studied using chi-square and fisher's exact test were appropriate. The bleeding symptoms were significantly associated with the lesser platelet count (P value < 0.000), as shown in Table 4.10

Table4.10 Association between :the bleeding tendency and the laboratory findings ,among pediatric patients with thrombocytopenia, in Sana'a City, 2022 (n=226)

	history of bleeding				Chi-square	Sig.
	history of bleeding		No history of bleeding			
	N	%	N	%		

PLTS	< 20000	36	64.3%	20	35.7%	55.794	0.000*
	20000 - 50000	26	41.9%	36	58.1%		
	50000 - 100000	7	11.7%	53	88.3%		
	> 100000	3	6.3%	45	93.8%		
HB	< 11	52	33.8%	102	66.2%	1.171	0.557
	11 - 15	20	28.2%	51	71.8%		
	> 15	0	0.0%	1	100.0%		
TRETMENT	PPT	34	36.6%	59	63.4%	1.609	0.205
	NO PPT	38	28.6%	95	71.4%		

4.9-Association between the Bleeding Tendency and the Etiology of Thrombocytopenia:

Association between bleeding symptoms and the couses of thrombocytopenia was studied using chi-square and fisher's exact test were appropriate. The bleeding tendency was significantly associated with infections (P value < 0.037), leukaemia (P value = 0.001), Post-Viral (P value = 0.011), ITP (P value = 0.022), and aplastic anaemia (P value = 0.022),as shown in Table 4.11.

And the total of significance for all etiology is 0.001 which indicate the presence of significant association between bleeding tendency and etiology of thrombocytopenia.

Table4.11 Association between the bleeding tendency and :Etiology ofThrombocytopenia , among pediatric patients with thrombocytopenia,in Sana'a City, 2022 (n=226)

	history of bleeding					
	No history of bleeding		history of bleeding		Chi-square	Sig.
	Yes	No	Yes	No		

	N	%	N	%	N	%	N	%		
Hematological	38	24.5%	117	%75.5	19	26.7%	52	73.3%	0.999	0.318
Infection	71	45.8%	84	54.2%	24	33.3%	48	66.7%	4.328	0.037
Nutritional	4	2.6%	151	97.4%	1	1.4%	71	98.6%	0.655	0.418
Congenital / Inherited	1	0.6%	154	99.4%	0	0.0%	71	100.0%	0.617	0.432
Autoimmune	2	1.3%	153	98.7%	1	1.4%	70	98.6%	0.219	0.64
Leukemia	29	18.7%	126	81.3%	27	38.0%	44	62%	12.109	0.001
Post-Viral / Pneumonia	40	25.8%	115	74.2%	1	1.4%	70	98.6%	6.449	0.011
Malaria	9	5.8%	145	94.2%	1	1.4%	71	98.6%	2.303	0.129
Leshmaniasis	17	11.0%	137	89.0%	5	6.9%	67	93.1%	0.936	0.333
Anemia	35	22.7%	119	77.3%	10	13.9%	62	86.1%	2.403	0.121
Hypersplenism	0	0.0%	154	100.0%	1	1.4%	71	98.6%	2.148	0.143
DIC	4	2.6%	150	97.4%	1	1.4%	71	98.6%	0.331	0.565
ITP	12	7.8%	142	92.2%	13	18.1%	59	81.9%	5.253	0.022
SLE	4	2.6%	150	97.4%	0	0.0%	72	100.0%	1.904	0.168
Aplastic Anemia	0	0.0%	154	100.0%	3	4.2%	69	95.8%	6.503	0.011
Lymphoma	1	0.6%	153	99.4%	1	1.4%	71	98.6%	0.306	0.58
Post Medication/Chemotherapy	3	1.9%	151	98.1%	1	1.4%	71	98.6%	0.088	0.766
Total									45.258	0.001

4.10-Association between the Etiology of Thrombocytopenia and the Clinical Characteristics:

There is relationship between the Causes Of Thrombocytopenia and the Clinical Characteristics, (Chi-square=1563.756, Sig=0.000). As shown in table 4.12

Table4.12 the relationship between the Clinical Characteristics and the aetiology of patients : ,with thrombocytopeniain Sana'a City,2022 (n=226)

Pearson Chi-Square Tests		Clinical Characteristics
Causes Of Thrombocytopenia	Chi-square	1563.756
	DF	580
	Sig.	0.000*,b,c
Results are based on nonempty rows and columns in each innermost subtable.		
*. The Chi-square statistic is significant at the .05 level.		
b. More than 20% of cells in this subtable have expected cell counts less than 5. Chi-square results may be invalid.		

c. The minimum expected cell count in this subtable is less than one. Chi-square results may be invalid.

4.11-Association between the Severity of Thrombocytopenia anTreatment :

There is no relationship between the severity of thrombocytopenia and the treatment , As shown in table 4.13

Table 4.13 : the relationship between the treatment and the laboratory findings, among pediatric patients with thrombocytopenia, in Sana'a City,2022 (n=226)

		TRETMENT					
		PPT		NO PPT			
		N	%	N	%		
PLTS	< 20000	25	44.6 %	31	55.4 %	1.114	0.774
	20000 - 50000	27	43.5 %	35	56.5 %		
	50000 - 100000	24	40.0 %	36	60.0 %		
	> 100000	17	35.4 %	31	64.6 %		

HB	< 11	67	43.5 %	87	56.5 %	2.817	0.244
	11 - 15	25	35.2 %	46	64.8 %		
	> 15	1	100 %	0	0.0 %		

4.12- The Correlation between the Etiology of Pediatric Thrombocytopenia and Their Outcomes :

The association between the etiology of pediatric thrombocytopenia and their outcomes was studied using chi-square and fisher's exact test were appropriate. The etiology of thrombocytopenia was significantly associated with outcomes (Chi-square=34.813, Sig=0.021). Table 4.14

The level of significance for each one of the couse (Infection, malignancies, leukaemia, post viral, Leshmaniasis, Anemia)was less than 0.05, which indicated the existence of a relationship between the pathogenesis of the these eyiologies and their outcomes . (Table 4.15)

Table 4.14 : correlation between causes of thrombocytopenia among pediatric patients and their outcome, in Sana'a City,2022 (n=226).

Causes Of Thrombocytopenia	DEAD				Chi-square	Sig.
	DEATH		ALIVE			
	Count	%	Count	%		
Infection	11	11.5%	84	88.5%	34.813	0.021
Hematological	5	8.8%	52	91.2%		
Nutritional	1	20%	4	80.0%		
Congenital / inherited	0	0.0%	1	100.0%		
Autoimmune	0	0.0%	3	100.0%		
Leukemia	10	17.9%	46	82.1%		

Post-Viral/ Pneumonia	9	22.0%	32	78.0%		
Malaria	0	0.0%	10	100.0%		
Leshmaniasis	3	13.6%	19	86.4%		
Anemia	9	20.0%	36	80.0%		
Hypersplenism	1	100.0%	0	0.0%		
DIC	2	40.0%	3	60.0%		
ITP	0	8.0%	23	92.0%		
SLE	0	0.0%	3	100.0%		
Aplastic Anemia	0	0.0%	3	100.0%		
Lymphoma	0	0.0%	2	100.0%		
Post Medication/ Chemotherapy	0	0.0%	4	100.0%		
Results are based on nonempty rows and columns in each innermost subtable.						
*. The Chi-square statistic is significant at the .05 level.						

Table4.15 : correlation between specific couses of thrombocytopenia among pediatric patients and their outcome, in Sana'a City,2022 (n=226).

Causes of thrombocytopenia	Outcome												Chi-square	Sig.
	Cure		Dama		Reffered		Unkown		Dead		Total			
	N	%	N	%	N	%	N	%	N	%	N	%		

Hematological	23	40%	15	26.3%	10	17.0%	4	6.9%	5	8.8%	57	25.2%	3.236a	0.519
Infection	39	41%	14	%14.7	29	30.5%	2	2.0%	11	11.5%	95	%42%	9.854a	0.043
Malignancy	10	17.0%	4	6.9%	32	55.2%	9	15.5%	5	8.6%	58	25.7%	26.372a	0.000
Leukemias	7	12.5%	5	8.9%	26	46.4%	8	14.3%	10	17.9%	56	24.8%	26.706	0.000
Post viral/ Pneumonia	15	36.5%	11	14.6%	6	22.0%	1	2.4%	8	19.5%	41	18.1%	21.496a	0.000
Anemia	20	44.4%	6	13.3%	9	20.0%	1	2.2%	9	20.0%	45	19.9%	9.610a	0.048
Autoimmune	0	0.0%	3	100.0%	0	0.0%	0	0.0%	0	0.0%	3	1.3%	3.988a	0.408
ITP	9	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	9	4.0%	.923a	0.921
Leshmaniasis	15	68.2%	2	9.1%	2	9.1%	0	0.0%	3	13.6%	22	9.7%	14.790a	0.005
Malaria	7	70.0%	0	0.0%	3	30.0%	0	0.0%	0	0.0%	10	4.4%	7.180a	0.127
Nutritional	0	0.0%	0	0.0%	3	60.0%	0	0.0%	2	40.0%	5	2.2%	6.723a	0.151
Congenital / Inherited	0	0.0%	1	100.0%	0	0.0%	0	0.0%	0	0.0%	1	0.4%	3.018a	0.555
SLE	1	33.3%	0	0.0%	2	66.6%	0	0.0%	0	0.0%	3	1.3%	1.722a	0.787
Post Medication/Chemotherapy	2	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	0.9%	4.042a	0.400
Aplastic Anemia	0	0.0%	2	66.7%	1	33.3%	0	0.0%	0	0.0%	3	1.3%	10.106a	0.039
Lymphoma	1	50.0%	0	0.0%	1	50.0%	0	0.0%	0	0.0%	2	0.9%	.853a	0.931
Hypersplenism	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	100.0%	1	0.4%	6.823a	0.146

Chapter Five: Discussion

Thrombocytopenia is defined as platelet counts under 150,000/mL, results from either decreased production or increased destruction This chapter presents a summary of the findings of the our study, and comperes with others studies and discuss causes and clinical picture and treatment .

the conclusions that have been revealed at, the recommendations that have been made by the researchers based on the findings and the suggestions on the areas of the researchers felt, that may require further investigation through research activity.

5.1-The results of Socio-demographic characteristics

Two hundred and twenty-six paediatric thrombocytopenia patients were identified out of 3236 admitted patients recorded during the study period. The incidence for thrombocytopenia in paediatric patients was 7%.

This incidence was close to a study done by (Xu Y, Jin D, Tong W, 2018)[156] revealed that among 6 725 children admitted to PICU in their hospital from January 2008 to December 2017, there were 683 children had TP with incidence of 10.2%.

The present study is considered as the first nationally study regarding incidence and etiology of thrombocytopenia in pediatric group, internationally, there are many studies mentioned different types of thrombocytopenia but specifically there were no studies reported incidence among admitted pediatric patients in whole departments as well.

Among 226 of thrombocytopenic patients were included in our study, (57.5%) were males whereas female were around (42.5%) and the predominant age group was between one to five years , when compare it to a study published by (Suresh P, Devi CY, Kumar CR, Jalaja Y. Evaluation, 2015)[157] showed that more than half of their population (54%) were male gender and another study also published by (Carlo L. Balduini et al, 2011)[158] showed that prevalence of TP was higher in age group of first 5 years .

5.2-The results of laboratory diagnosis

Regarding laboratory results in which severity was determent we found that 29 % of patient had sever thrombocytopenia , 26 % had very sever thrombocytopenia, 23% moderate and 21% mild thrombocytopenia , these results were less than pervious published studies in which a study done by (Imene Dahmane Ayadi, et al, 2016)[159], suggested that around 41% of their population had sever thrombocytopenia and another study done by (Keerthi Tirupathi, Keerti Swarnkar, Jayant Vagha, 2017)[160] suggested that the vast majority of the population around 81% had moderate to severe thrombocytopenia.

Out of 226 patients of our study , about almost of patients (55.3%) had platelet counts less than 50,000/ul, with mean of 57.85 (±43.651) , this result was similar to other studies whereas in a study done by (Sony Moluguri, 2021)[170], they found that among 100 patient of thrombocytopenia had 50% of patients had platelet levels <50,000 , another study done by(Nair PS, Jain A, Khanduri U, Kumar V, 2003)[161] showed that out of 109 patients 62 patients (56.8 %) had platelet count between 50000- 100000.

Regarding hemoglobin level, in our study the mean (SD) hemoglobin level was 9.21(±2.595) in which more than tow third of thrombocytopenic children around 68% had hemoglobin level of less than 11 g/dl , and 31% of them had hemoglobin level of between 11 – 15 g/dl and only 0.4% had hemoglobin level of more than 11 g/dl , when compare these results with other studies as a study done by (Mohamed Eltawel, 2013)[171] suggested that most of patients with hemoglobin levels of 15 to 20 g/dL, numbered 49 (60.5%), with a mean (SD) hemoglobin level of 16.9 (3.7) g/dL, also, another study done by (Sadia Sultan and others, 2019)[162] suggesting that mean hemoglobin at presentation was 11.68 (±1.75) g/dl .

Moreover, figuring the main causes of TP we have found that (hypersplenism, DIC, post-treatment / chemotherapy, ITP, aplastic anemia, leishmaniasis, congenital / hereditary, autoimmune, lymphoma, malaria, SLE) cause severe platelet deficiency as it was found that the average platelet count of the sample was less than 20000 ul.

5.3-The results of The clinical history presentation

Concerning the clinical history presentation we found that fever was the most common symptom among the majority of patients (199) 88.1%, fatigue (111) 49.10%, pallor (107) 47.3%, perspiration (102) 45.1%, others clinical findings (109) 41%, hepatomegaly (84) 37.2%, loss of Weight (78) 34.5%, splenomegaly (77) 34.1%, prodromal disease (66) 29.2%, bone pain (27) 11.9%, skin rash (24) 10.9%, Recent live vaccine and Lymphadenopathy (23) 10.2%, arthralgia (21) 9.3%, altered consciousness (21) 9.3%, when comparing these results with a study published by In the study by (Parul Gupta, 2015)[173] showed that the most common presenting symptom was fever in 100% of cases followed by myalgia in 56.25% of cases , chills and rigor was found in 53.12% of cases, dehydration in 40.62% of cases followed by pallor in 15% of cases, jaundice in 11.25% of cases, and Hypotension in 9.37% of cases, Hepatomegaly in 8.12% and splenomegaly in 6.87%, Pleural effusion in 6.25% of cases is depicted, another study done Khodaija Mahvish, 2021)[169] the common clinical features were fever followed by body ache (60.8%), headache (55.8%) and joint pain (48.8%).

Regarding bleeding presentation, our study showed that, the majority of the admitted patients with TP hadn't bleeding tendency (155)×68.6%, however they had low platelet count, that's mean they were discovered accidentally, whereas about one third of patients had bleeding tendency in the form of spontaneous hemorrhage (58) 25.7%, followed by Post-Surgery/ Trauma (13) 5.8%. This bleeding was presented as ecchymosis/petechiae/purpura or mucosal mucosa in most bleeding tendency forms of 28.3% followed by epistaxis 21.7% then hematuria 6.2%, gingival hemorrhage, hematemesis 4.9% , bleeding typical puncture sites, hematemesis 3.5% and hemoptysis 1.3%, these results were different to a study published by (Mousumi Kar,2015)[176] in which showed that most common bleeding tendency forms was gum bleeding (39.3%) followed by epistaxis (25%), then petechiae (10.7%), Purpura (10.7%), Hematuria (7.1%) and ecchymosis in (3.6%), another study done by (Isha Bhatia and others, 2022)[175] showed that petechiae was the most common bleeding manifestation (63%)

5.4-The results of aetiology of thrombocytopenia

In current study shows that the most common causes of thrombocytopenia among the sample were infections, for 95 patients (42%), 58 (25.7%) malignancy, 57 (24.80%) hematological, 5 (2.2%) Nutritional, 3 (1.3%) autoimmune diseases, 8 (3.5%) of other causes.

These results showed similar findings when compare them with previous studies as a study done by (Isha Bhatia and others, 2022)[175] where the commonest etiology of thrombocytopenia was infectious diseases such as dengue fever (60%), followed by malaria (12%), enteric fever (10%), other undifferentiated viral fevers (10%) and MIS-C (multisystem inflammatory syndrome in children) (4%), immune thrombocytopenic purpura (2%), leukaemia (1%) and hepatitis A.

Another study done by (Khodaija Mahvish, 2021)[169] where the commonest causes of thrombocytopenia were dengue fever (25.8%) followed by unspecified viral illness (17.5%), septicemia (10%), ITP (7.5%), enteric fever (6.67%) and Chikungunya (6.67%) while in a study done by (Bindu T. Nair*, Kuldeep Sharma, Sandeep D. Paimode, 2019)[160] were viral fever (other than dengue and chikungunya), 27.78% (50), followed by Dengue 22.2% (40), enteric fever 12.22% (22), chikungunya 11.11% (20) and malaria 8.33% (15) ,also , In study done by (Gandhi, 2015)[168] malaria was found to be the major cause in 41.07%.8 , Similarly, (Lakum, 2014)[174] also found malaria as the commonesy cause of thrombocytopenia in 46.8% of the cases while in a study done by (Bhalara, 2015)[172] showed dengue (60.8%) as the main etiological element.

Regarding incidence of leukemia, out of 56 cases of this study of acute leukemia, 12.5% were acute leukemia, while 87.5%were ALL, this result differs with results of (Deepshikha Verma, 2022)[163] where it was found that the number of cases of acute leukemia more than the rest of the cancers.

Infection was documented in 42% of all patients with thrombocytopenia, which is the most common identified cause for low platelet. Sources of the infection included: post viral and pneumonia (43.2%), which is the most common infectious disease associated with thrombocytopenia, leishmaniasis (23.2%), malaria(10.5%), meningitis (4.2%), and gastroenteritis (3.2%).

In the study done by (M.Manoj , 2014)[164] the leading cause of thrombocytopenia was malaria. The 2nd leading cause of febrile thrombocytopenia was dengue fever. Typhoid fever accounted for 6% of cases.

5.5-The results of Treatment of thrombocytopenia

In this present study shows that the vast majority of thrombocytopenic pediatric patient (n=219, 82.3%),, treated supportively by (antibiotics 52% , NSAID 69% , platelet transfusion 42%) while who were treated by corticosteroids (n=75 ,27.1%) and immunoglobulins(n = 17, 6.1%) when compare it with a study done by (Mohamed Eltawel, & others, 2018)[171] in which around two third of their population were treated by (n = 52, 64.2%) monitoring/spontaneous recovery and platelet transfusion (n = 9, 11.1%) while immunoglobulins were given in (n = 8, 9.9%), or a combination of both (n = 12, 14.8%).

5.6-The results of outcome of thrombocytopenia

Regarding the outcome of thrombocytopenic children in our study, we found that - among (226) patients with thrombocytopenia - 77 (27%were completely cured, 73 (26.4%) were referred to otherhospitals most probably leukemic children, 29 (10.5%) were (dead), 25 were discharged against medical advice and 13(4.7%) of cases were with unknown outcome. .

Different to other studies ,the mortality rate in this study was counted as (10%) , increasing in male (62%) more than females (36%), also ,this mortality rate had a relationship with age of child in which we found in our study as decreasing the age as increasing the rate , a study published by (Krishnan ,2008)[166] their rate of mortality was higher about (17%) of intensive care admitted pediatrics , while in a study published by (Michael D. Tarantino, 2016)[167] the rate was much lesser about 0.3% mostly in male gender .

An interesting finding in this study we found that all deaths of thrombocytopenic pediatrics had platelet counts of less than 20000 , this tell us that when platelet count decreasing less than 20000 becoming more fetal and need of urgent platelet transfusion for saving the patient this also found in a study published by (Agrawal,2008)[165] in India showing that the mortality was found associated to the admission platelet counts signifying that the predictive power of low platelet counts does take the disease progression in account.

5.7-The results of relationship

- There is relationship between the the platelet count and bleeding tendency.
- There are significant relationships between some etiologies and bleeding tendency
- There is no significance in sex factor regarding the morbidity in these patients with thrombocytopenia.
- There is significance in age factor regarding the morbidity (Autoimmune, ITP, Post Medication/Chemotherapy) in these patient thrombocytopenia.
- There is relationship between the causes of thrombocytopenia and the clinical characteristics.
- There is relationship between the causes of thrombocytopenia and the outcome.

6.0 - Conclusion and Recommendations:

6.1 - Conclusion:

In this study, it was found that, two hundred and twenty-six thrombocytopenic pediatric patients were identified out of 3236 admitted patients recorded during the study period. The incidence for thrombocytopenia in pediatric patients was 7%. The majority of them were 130 males (57.5%) and in the age group of <5 years 143cases (63.3%). The majority of cases accidentally identified by a primary care provider who performs a complete blood count (CBC) for other indications 155 (68.6%), whereas the patients presented with bleeding symptoms were 71cases (26.7%) patients, of whom (n = 64; 90.1%) were ecchymosis followed by epistaxis then hematuria. The most common nonspecific symptoms were fever (n = 199; 88%) followed by fatigability and pallor. The laboratory tests revealed that the majority of patients had severe thrombocytopenia (20000-50000µl) 66 cases (29.2%) followed by very severe (20000µl) 59 cases (26%), whereas about 44.7% of cases has platelet count > 50,000µl of mild and moderate thrombocytopenia. The findings revealed that the most common identified cause for all cases was Infectious diseases (especially post viral) 95 cases (42%) followed by leukemia (24.8%) then anemia (20%). Among the 226 cases of moderate and sever thrombocytopenia, the majority of patients were received supportive treatment in the form of platelets transfusions, antibiotics and NSAID. Out of 226 cases, 94 patients (42%) were required platelets transfusions. Only 17 patients required IV immunoglobulin therapy from a hematologist. The outcomes of the patients were cured 77 cases (27.8%) followed by referred cases 73 patients (26.4%) and died (n = 29; 10.5%5%). There are significance association between age factor and some etiologies including autoimmune, ITP, and post medication . The bleeding tendency was significantly associated with the severity of thrombocytopenia (p value <0.05). There are relationship between the etiology of thrombocytopenia and the clinical characteristics, and outcomes (p value < 0.021).

6.2-Recommendations

- Before conducting any therapeutic intervention on a patient with thrombocytopenia, there are considerations, that should be given related writing a detailed medical history, and proper physical examination to ensure the presence of mild to moderate symptoms, such as fever, fatigue, headache, or muscle pain, especially in the first 24 to 48 hours. Symptoms, including bleeding, bruising, severe headache, abdominal pain, nausea and vomiting, changes in vision, mood swings, shortness of breath, swelling and epistaxis or recurrent infections, are all symptoms that should be urgently evaluated by a doctor.
- A complete CBC and platelet count should be done before any medical intervention.
- The study recommends that, the hospitals and medical care providers for patients with thrombocytopenia need to complete the documentation files and records, in order to reveal more information about the clinical history of the patients with thrombocytopenia.
- The study recommends for researchers in the future to conduct a further studies to identify the factors and causes that lead to platelet deficiency in Yemeni patients.
- Keeping the latest principles and guidelines used in the diagnosis and treatment of the patients with thrombocytopenia.
- The study recommends that, further studies should be done on a large scale population of patients with thrombocytopenia.
- The study recommends that, the ministry of health should provide the public hospitals by modern laboratory devices to facilitate for the pediatrician for appropriate diagnosis.

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Chapter Eight : Appendix :

Appendix-A: Distribution of the sample patients according to the place of birth:

Place of Birth	N	%
Sana'a Governorate	80	35.4%
Dhamar Governorate	23	10.2%
Ibb Governorate	18	8.0%

Al Hudaydah Governorate	14	6.2%
Taiz Governorate	14	6.2%
Hajjah Governorate	13	5.8%
Amran Governorate	12	5.3%
Al-Bayda Governorate	10	4.4%
Al-Jawf Governorate	9	4.0%
Al-Mahwit Governorate	9	4.0%
Saada'a Governorate	9	4.0%
Raymah Governorate	7	3.1%
others	2	0.9%
Al Dhalea Governorate	2	0.9%
Shabwah Governorate	2	0.9%
Marib Governorate	2	0.9%
Total	226	100.0%

Appendix-B : Distribution of the sample patients according to the clinical features

Categories	N	Percent
Fever	199	88.1%
Fatigability	111	49.1%
Pallor	107	47.3%
Sweats	102	45.1%
Hepatomegaly **93**	84	37.2%
Weight loss	78	34.5%
Splenomegaly	77	34.1%
Bleeding symptoms	71	31.4%
Prodromal illness	66	29.2%
Bone pain	27	11.9%
Skin rash	24	10.6%

Recent live vaccine	23	10.2%
Lymphadenopathy	23	10.2%
Arthralgia or arthritis	21	9.3%
Altered consciousness	21	9.3%
Recurrent infection	19	8.4%
Cough	14	6.2%
Abd Distention	13	5.8%
Vomiting	10	4.4%
Odema	10	4.4%
Diarrhea	10	4.4%
Convulsion	10	4.4%
Dyspnea	10	4.4%
Recent viral infection	9	4.0%
Coma	8	3.5%
Recent travel	7	3.1%
Jaundice	6	2.7%
Sudden Cardiac Arrest	5	2.2%
Cyanosis	4	1.8%
Neck Swelling	3	1.3%
Post diet	2	0.9%
Eye Protrution Swelling	1	0.4%
Shock	1	0.4%

Appendix-C : Distribution of the sample patients according to etiological spectrum

Categories **94**	N	Percent
Leukemia's	56	24.8%
Anemia	45	19.9%
Post-Viral / Pneumonia	41	18.1%
Leishmaniasis	22	9.7%

Malaria	10	4.4%
Immune Thrombocytopenic purpura	9	4.0%
Severe Acute Malnutrition	4	1.8%
Meningitis	4	1.8%
Systemic Lupus Erythematosus	3	1.3%
Dengue Fever	3	1.3%
HBV	3	1.3%
AKI / RF	3	1.3%
Gastroenteritis	3	1.3%
Diphtheria	2	0.9%
Post Medication/Chemotherapy	2	0.9%
TB	2	0.9%
Measles	2	0.9%
Lymphoma	2	0.9%
UTI	2	0.9%
Disseminated Intravascular Coagulopathy	2	0.9%
CLD	2	0.9%
CMV	1	0.4%
Kwashiorkor	1	0.4%
TTP	1	0.4%
Down Syndrome	1	0.4%
Total	226	100.0%

Appendix-D :Distribution of leukemic patients:

LEUKEMIAS	Count	N %
Acute lymphoblastic leukemia	49	87.5%
acute myelogenous leukemia	7	12.5%

Total	56	100.0%

Appendix-E: Distribution of the anemic patients

Diagnosis	Categories	N	Percent
ANEMIA	Hemolytic anemia	20	44.40%
	sickle cell crisis	12	26.70%
	Thalassemia	7	15.60%
	Aplastic Anemia	3	6.70%
	Fanconi anemia	2	4.40%
	Hypersplenism	1	2.20%
	Total	45	100.00%

Appendix -F: Distribution of the infected patients

Categories	N	Percent
Post-Viral / Pneumonia	41	43.2%
Leishmaniasis	22	23.2%
Malaria	10	10.5%
Meningitis	4	4.2%
Dengue Fever	3	3.2%
HBV	3	3.2%
Gastroenteritis	3	3.2%
Diphtheria	2	2.1%
TB	2	2.1%
Measles	2	2.1%
UTI	2	2.1%
CMV	1	1.0%
Total	95	100.0%

Appendix-G: Approval of 21 Sep ethical commitee

21SEPTEMBER UNIVERSITY FOR MEDICAL AND APPLIED SCIENCES
UNIVERSITY PRESIDENT

الجمهورية اليمنية
وزارة التعليم العالي والبحث العلمي
جامعة ٢١ سبتمبر للعلوم الطبية والتطبيقية
رئيس الجامعة

الإدارة العامة
السكرتارية
التاريخ
الرقم ٢٢٩

الأستاذ الدكتور/مطهر مرشد
رئيس هيئة مستشفى الثورة العام
المحترم

الموضوع: تسهيل مهمة بحث

تهديكم رئاسة جامعة ٢١ سبتمبر للعلوم الطبية والتطبيقية أطيب تحياتها وتقديرها وإشارة إلى الموضوع أعلاه تكرموا مشكورين بالتوجيه الى من يلزم بتسهيل مهمة بحث طلاب كلية الطب للدفعة الأولى مستوى خامس قسم الأطفال مجموعة (D5b) تحت اشراف د/ محمد عقلان، و د/ خالد الجمرة، لعدد (١٣) طالب بحسب عنوان البحث الموضح قرين اسمائهم:-

م	الاسم	عنوان البحث
١	عصام لطف الله ابو زينه	Prevalence and etiological spectrum of thrombocytopenia among pediatric patients Sana'a city, yemen presented in major hospitals in 2022
٢	علي عبدالملك الجويني	
٣	محمود ناصر الراجحي	
٤	محمد ابراهيم الصيوعي	
٥	عزام عبده الازرقي	
٦	عمار علي الغزالي	
٧	سيماء فرحان الزبيري	
٨	ليلى فرحان الزبيري	
٩	نهى سعيد الميرابي	
١٠	محمد حسين علي سعد	
١١	محمد عبدالوهاب عواض	
١٢	عبدالملك شعلان الفراس	
١٣	احمد صالح الغزالي	

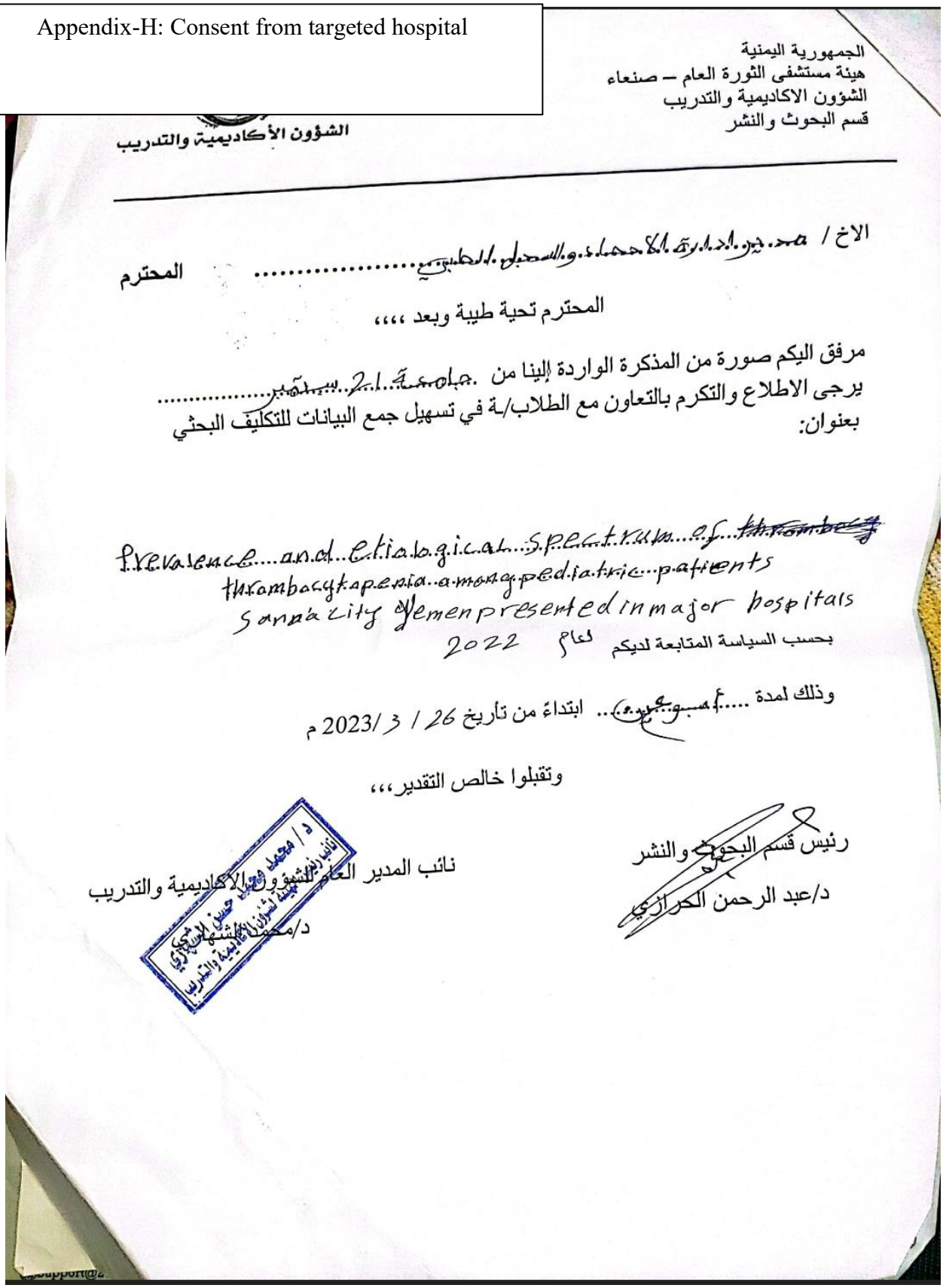
، تفضلوا بقبول خالص تحياتي وعميق احترامي ...

أ.د. دكتور/
مجاهد علي معصار
رئيس الجامعة

Sana'a - Taiz street - Al-Sawad
Tel: (01/692100) Fax: (01/696585) B.O.P: (17021)
Support@21umas.edu.ye

صنعاء - شارع تعز - السواد
تلفون: (٠١/٦٩٢١٠٠) فاكس: (٠١/٦٩٦٥٨٥) ص.ب (١٧٠٢١)
إيميل: Support@21umas.edu.ye

Appendix-H: Consent from targeted hospital



الجمهورية اليمنية
هيئة مستشفى الثورة العام – صنعاء
الشؤون الاكاديمية والتدريب
قسم البحوث والنشر

الشؤون الأكاديمية والتدريب

الاخ / مدير ادارة الاحصاء والسجل الطبي ..... المحترم

المحترم تحية طيبة وبعد ،،،،

مرفق اليكم صورة من المذكرة الواردة إلينا من جامعة 21 سبتمبر .....
يرجى الاطلاع والتكرم بالتعاون مع الطلاب/ـة في تسهيل جمع البيانات للتكليف البحثي
بعنوان:

Prevalence and clinical Spectrum of thrombocytopenia among pediatric patients thrombocytopenia among pediatric patients Sana'a City Yemen presented in major hospitals 2022

بحسب السياسة المتابعة لديكم لعام

وذلك لمدة ..... ابتداءً من تاريخ 26 / 3 /2023 م

وتقبلوا خالص التقدير،،،

رئيس قسم البحوث والنشر
د/عبد الرحمن الكراري

نائب المدير العام للشؤون الاكاديمية والتدريب
د/محمد [illegible]

Appendix -I :Questionnaire

Questionnaire of

Incidence and etiological spectrum of thrombocytopenia among admitted pediatric patients in major hospitals, Sana'a city, Yemen 2022

…… : .DATE OF ADMISION: …/ …/…….. SERIAL No

NAME: …… SEX: ○ MALE ○ FEMALE

..…… :DATE OF BIRTH

AGE (At Diagnosis) : …….. years, ……. months

:PLACE OF BIRTH: …… PLACE OF RESIDENCE ...……

CLINICAL FEATURES

: **Bleeding history**

spontaneous □

postsurgery/ trauma □

accidentally discovered □

: Bleeding tendency

epistaxis □ ecchymosis / petechae / purpura or mucocutaneus □

bleeding from puncture sites □

hematuria □ gingival bleeding □ hematemesis □
hematochezia □ hemoptysis □

heavy menstrual bleeding □ intracranial hemorrhage □

Page 1 of 4 .

Clinicalhistory:

□*prodromalillness*

□*recentviralinfection*

□*recentlivevaccine*

□*recenttravel*

□*postdiet*

□postdrug/poison

□*fever□sweats□weightloss□Recurrentinfection□pallor□arthralgiaorarthritis□Bone pain □Fatigability*

□*Alteredconsciousness□skinrash*

□*lymphadenopathy□hepatomegaly□splenomegaly.*

□***Others:……***

□***Familyhistoryofbleeding***

LabFindingAtDiagnosis:

CBC

HB	TLC	LYMPHOCYTE	ANC	PLTs

Bloodfilmmorphology:……..

Bonemarrowaspiration:……..

OtherspecificIX:……

DIAGNOSIS

CATEGORY:

oINFECTION

oHEMATOLOGICAL

oNUTRITIONAL:……

o***Congenital/inherited***

o***DRUGS/POISON:……***

oAUTOIMMUNE:…….

oMETABOLIC:…….

oMALIGNANCY

oOTHERS:…….

SPECIFICDx:

o*POST-VIRAL*

oMALARIA

oLESHMANIASIS

oInfectious,Others:……..

o*ANEMIA:(iron,B12orFolatedeficiency)……*

o*Hypersplenism*

oVonWillbranddisease

oDIC

oITP

○*NeonatalAutoimmunethrombocytopenia*

○*Neonatalalloimmunethrombocytopenia*

○SLE

○*Inherited/congenitalasWisckot-Aldrichsyndrome*

○APLASTICANEMIA:…….

○LEUKEMIAS:……..

○LYMPHOMA:…….……..

○SOLIDTUMOR:…….…..

○*Postmedication/chemotherapy*

○*OTHERS:……*

Treatment

□*Supportive(antibiotics/PLT/…)*

□*corticosteroid*

□*IVimmunoglobulin*

OUTCOME:

○***CURE***○***DAMA***○***UNKOWN***○***REFFERED*** ○***DEAD***

CAUSEOFDEATH:

○*INFECTION/SEPSIS*○*BLEEDING*○*OTHER*:……

Appendix -J: استبيان عربي

تاريخ دخول المستشفى ..../..../..... رقم الملف .....

الإسم :..... الجنس : ○ ذكر. ○ إنثى

تاريخ الولادة :..... .....

العمر (وقت التشخيص) : ..... سنوات ..... أشهر

مكان الميلاد :..... مكان الإقامة :.....

العلامات و الأعراض السريريه

تاريخ النزيف :

□ تلقائي

□ بعد العملية / إصابة

□ أكتشف بطريقة عرضية / بدون اعراض

الميل للنزيف :

□ رعاف. □ تكدم/ نزف تحت الجلد / بقع حمراء تحت الجلد او الأغشية المخاطيه

□ نزيف من مواضع الوخز والإبر

□ دم مع البول □ نزيف من اللثه. □ قيء دموي. □ دم مع البراز

□ بلغم مع الدم

□ نزيف شديد من الدورة الشهرية. □ نزيف داخل الجمجمة

معدل حدوث قلة الصفيحات الدموية والأسباب المحتمله للمرض بين مرضى

الأطفال المقبولين في المستشفيات الكبرى مدينة صنعاء ، اليمن لعام ٢٠٢٢

التاريخ السريري

□ اعراض مرضية واسعه قبل ظهور المرض

□ لقاح فيروسي حديث

□ لقاح حي حديث

□ سفر حالي قريب

□ بعد الوجبه الغذائيه

□ بعد اخذ دواء / تسمم

□ حمى. □تعرق. □ فقدان وزن. □ عدوى متكررة

□ شحوب الجلد. □ الم او التهاب مفاصل. □ الم عظام

□ إجهاد سريع. □تغير حالة الوعي. □ طفح جلدي

□ تورم العقد الليمفاوية. □تضخم الكبد. □تضخم الطحال

□ **أخرى : .....**

□ **التاريخ المرضي العائلي في النزيف**

النتائج المخبريه وقت التشخيص

فحص الدم العام

HB	TLC	LYMPHOCYTE	ANC	PLTs

شكل شريحة الدم تحت المجهر :.....

عينة نخاع العظم :.....

فحوصات متخصصة أخرى .....

التشخيص

الفئة :

- **عدوى .....**
- **امراض الدم.....**
- **أمراض التغذيه .....**
- **أمراض خلفية/ وراثيه**
- **أدوية / سموم .....**
- **أمراض المناعة الذاتيه.....**
- **أمراض أيضيه .....**
- **اورام سرطانيه**
- **أخرى :.....**

التشخيص الدقيق :

- **بعد عدوى فيروسيه**
- **مرض الملاريا**
- **مرض اللشمانيا**
- **مرض معدي... ..**
- **فقر دم (نقص الحديد ، فيتامين ب١٢ ، حمض الفوليك)**
- **تضخم الطحال**
- **مرض فون**
- **مرض DIC**

- **مرض نقص الصفائح الوراثي**
- **نقص الصفائح الذاتي مناعة في حديثي الولادة**
- **نقص الصفائح بسبب تفاعل المناعه لزمرة الدم في حديثي الولاده**
- **مرض الذئبة الحمراء**
- **مرض خلقي / وراثي**
- **مرض توقف نخاع العظام عن انتاج خلاياء الدم :.....**
- **سرطان الدم : .....**
- **سرطان العقد الليمفاوية : .....**
- **سرطانات صلبه : .....**
- **تفاعل بعد أدوية / علاج كيماوي**

العلاج

- □ تدعيمي (مضادات حيوية / صفائح دمويه/ .....)
- □ أدوية الكورتيكوستيرويد المضادة للالتهابات
- □ اجسام مضادة محاليل وريديه

النتائج

○ تعافي. ○ رفض المريض العلاج. ○غير معروف. ○ تحويل

○ توفي

أسباب الوفاة

○ عدوى/تنتن. ○ نزيف. ○ أخرى :.....