ORIGINAL ARTICLE

Frequency of different causes of thrombocytosis among patients presenting to tertiary care hospital.

Masooma Jaffer[1], Omar Shahid[2], Rumaisha Aslam[3], Fatima Saeed[4], Atiqa Arshad[5], Muhammad Touqeer Hanif[6]

ABSTRACT… Objective: To assess the prevalence and underlying causes of thrombocytosis among patients seeking medical attention at a prominent tertiary care facility located in Lahore. Thrombocytosis, characterized by an elevated platelet count, can signify an array of underlying health conditions, and this research seeks to unravel the frequency of these causes within the study population. **Study Design:** Cross-sectional. **Setting:** Department of Pathology, Allama Iqbal Medical College and Jinnah Hospital. **Period:** November 2019 to May 2020. **Methods:** A total of 150 patients were carefully selected from diverse medical specialties, including but not limited to medical, surgical, gynecological, obstetric, gastroenterological, nephrological, and intensive care units. The diagnostic criteria for thrombocytosis were aligned with the operational definition provided by the World Health Organization (platelet count exceeding >450 x 10^9/L) during the stipulated study period. Statistical analysis of gathered data was performed using SPSS version 17.0. **Results:** The findings of the study showcased that infections and iron deficiency emerged as the predominant contributors to thrombocytosis among the adult patient cohort. These factors were trailed by conditions like chronic infections, trauma accompanied by blood loss, and instances of splenectomy. Interestingly, instances of primary thrombocytosis, notably essential thrombocythemia, constituted a mere 2% of the overall sample size, signifying its rarity within this adult population. **Conclusion:** In the realm of thrombocytosis, the research highlights a notable prevalence of secondary thrombocytosis, while primary thrombocytosis remains a considerably infrequent occurrence among adults. The study emphasizes the significance of infections and iron deficiency anemia as the leading triggers for secondary thrombocytosis. Such insights contribute to an improved understanding of the spectrum of conditions associated with elevated platelet counts and may aid clinicians in effectively diagnosing and managing these underlying causes.

Key words: Essential Thrombocytosis, Infections, Iron Deficiency Anemia, Thrombocytosis.

INTRODUCTION

Platelets are minute cellular fragments that stem from megakaryocytes' cytoplasm. The standard range for platelet levels in the bloodstream is 150-450 x 10^9/L. These are the smallest participants in hemostasis.[1] Thrombocytosis, an elevation in circulating platelet count, is commonly stumbled upon as an incidental anomaly during routine blood count assessments for unrelated reasons. This condition is categorized into primary and secondary (reactive) types based on its origin.[2] In the case of secondary thrombocytosis, it emerges as a response to other underlying conditions, such as infections. Notably, markers of acute phase reactions like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are considerably elevated in individuals with reactive thrombocytosis. Conversely, primary thrombocytosis, often known as Essential Thrombocytosis, is typically linked to myeloproliferative disorders and stems from clonal abnormalities.[1] The frequency of thrombocytosis in patients varies from 6% to 15% with Primary and secondary thrombocytosis occurring in about 12.3% and 87.7% of the cases, respectively.[2] Primary thrombocytosis is also associated with higher incidence of thromboembolic and hemorrhagic complication while such complications are less frequently observed with secondary thrombocytosis.

1. MBBS, FCPS, Assistant Professor Hematology, Akhtar Saeed Medical College, Rawalpindi.
2. MBBS, FCPS, Senior Registrar Cardiology, Wazirabad Institute of Cardiology, Wazirabad.
3. MBBS, Demonstrator Pathology, Al–Aleem Medical College, Lahore.
4. MBBS, FCPS, Assistant Professor Hematology, Allama Iqbal Medical College, Lahore.
5. MBBS, M.Phil, Assistant Professor Hematology, Akhtar Saeed Medical & Dental College, Lahore.
6. MLT, M.Phil (Microbiology), Senior Lecturer MLT, College of Allied Health Sciences, Akhtar Saeed Medical & Dental College, Lahore.

Correspondence Address:
Dr. Muhammad Touqeer Hanif
College of Allied Health Sciences,
Akhtar Saeed Medical & Dental College,
Lahore
touqeerhanif001@yahoo.com

However, cases of clinically significant thrombosis have been reported in patients with secondary thrombocytosis as well making this incidentally-observed abnormality clinically significant.[3]

The causes of thrombocytosis have been discussed in studies but with a marked variation in frequency of various causes has been seen. Dinesh et al found the commonest cause of thrombocytosis as infection 34.8%, followed by infection with iron deficiency anemia 28.7%, iron deficiency anemia alone 12.6%.[4] This is in contrast with earlier studies, in which iron deficiency anemia accounted for upto 6% cases only (2). Another study showed frequency of infection as 16.2%, iron deficiency anemia as 17.2% and infection with iron deficiency anemia both as 48.3%.[4] In the study conducted by Ozcan et al., it was observed that approximately 6.3% of patients exhibiting thrombocytosis had their elevated platelet counts attributed to reasons such as splenectomy or tissue injury. This phenomenon was noted for both of these underlying causes.[5] Thus a marked variation has been seen regarding causes of thrombocytosis.[6]

The foundation of this study rests upon the need to comprehensively unravel the prevalence of diverse etiological factors contributing to thrombocytosis within the context of a tertiary care environment. Although thrombocytosis is frequently encountered as an incidental finding, its potential to give rise to significant complications cannot be overlooked. Consequently, a meticulous exploration of the various types and underlying causes of thrombocytosis becomes imperative to foster effective management strategies. In light of the potential complexities associated with thrombocytosis, it becomes increasingly vital to identify and classify the distinct causes of this condition. Such an endeavor not only aids in facilitating tailored therapeutic interventions but also aids in averting potential complications that may arise due to inadequate management. An intriguing facet that drives the significance of this study is the scarcity of local literature addressing this specific aspect, particularly concerning the adult population. This void in knowledge underscores the urgency to undertake research that delves into the prevalence and causal factors of thrombocytosis within the local context. By bridging this gap, the study stands to offer valuable insights into the disease burden borne by the community, specifically concerning the types of thrombocytosis and their associated causes in adults.

The knowledge garnered from this research is poised to have tangible impacts on medical practice. Pathologists and medical consultants stand to benefit significantly from the elucidation of local patterns of thrombocytosis, as this information empowers them to make earlier and more accurate diagnoses. Moreover, armed with this understanding, medical practitioners can adopt more precise and targeted management strategies, ultimately leading to enhanced patient outcomes.

METHODS
Conducted within the esteemed Pathology Department of Allama Iqbal Medical College/ Jinnah Hospital in Lahore, this study embraced a cross-sectional design with the objective of investigating the prevalence and underlying factors of thrombocytosis among patients within a tertiary care framework. The research was conducted in strict accordance with ethical standards and obtained the essential approval from the institutional ethical committee (39th ERB/24.10.19). The study was conducted from November 2019 to May 2020.

Encompassing a diverse range of participants, the study focused on adult patients aged 15 to 70 years, regardless of gender, who presented with a notably elevated platelet count exceeding 450 x 10^9. Utilizing a non-probability consecutive technique for participant selection, the study enrolled a total of 150 patients who met the stringent inclusion criteria. Before inclusion, all participants were meticulously informed about the study's purpose and procedures, and their voluntary participation was secured through the acquisition of informed consent. The utmost regard for confidentiality was ensured to safeguard the privacy of all participants.

Upon the meticulous collection of demographic details such as name, age, and gender, the amassed data was subjected to rigorous analysis using SPSS version 17.0, a reliable statistical tool. To gain a comprehensive understanding of the participant characteristics, the numerical variable 'age' was summarized by determining both its mean and standard deviation. This approach provided valuable insights into the central tendency and dispersion of age within the studied population.

Recognizing the potential influence of various variables, the data underwent stratification based on age, gender, and the particular type of thrombocytosis exhibited by each participant. This meticulous stratification enabled the identification of potential effect modifiers that might impact the observed associations. To assess the relationships between categorical variables, such as gender or type of thrombocytosis, and other relevant factors, the Chi-square test was judiciously applied to the data.

In line with established practices in statistical analysis, the adopted significance level was set at a p-value of less than or equal to 0.05. This threshold was chosen as the critical point for determining statistical significance, ensuring a level of rigor in interpreting the results. The utilization of this significance level was pivotal in discerning whether observed associations were likely to be attributed to chance or if they indeed held genuine statistical significance.

Through the meticulous implementation of this comprehensive methodology, the study sought to unravel the intricate landscape of thrombocytosis and its underlying factors within the context of a tertiary care hospital setting. The integration of ethical considerations, robust participant selection, data collection, and advanced statistical techniques lent a high degree of reliability and validity to the study's findings. Ultimately, this research contributes to the growing body of knowledge in the field, potentially offering valuable insights for clinical practice and future investigative endeavors in hematological disorders.

RESULTS

The study was carried out over a period of 6 months in Jinnah hospital. 150 patients were included from different departments e.g. medical, surgery, gynecology & obstetrics, gastroenterology, nephrology and intensive care units. Patients were diagnosed as having thrombocytosis as per operational definition of WHO. During the study period, 3 cases of Essential thrombocythemia were seen, which accounts for 2% of the total sample size. 98% of the cases were of secondary (reactive) thrombocytosis. group I ranging from 15 years to 30 years of age which accounts for total 48 number of cases(32%). Group II was most frequent which ranges from 31years to 50 years with 61 cases (42%). Group III ranges from 51years to 70 years with 41 cases in total (27%).

Distribution of cases according to severity of thrombocytosis is shown in Table-IV which shows mild thrombocytosis to be most frequent (46.7%), followed by moderate Thrombocytosis (42%) and least frequent was severe Thrombocytosis (11.3%).

Age	Frequency	Percent
15 to 30 years	48	32.0
31 to 50 years	61	40.7
51 to 70 years	41	27.3
Total	150	100.0
Mean=40.40 yrs SD=14.62 Minimum= 16 yrs Maximum = 70 years		

Table-I. Age distribution of subjects

Figure-1. Gender distribution of subjects
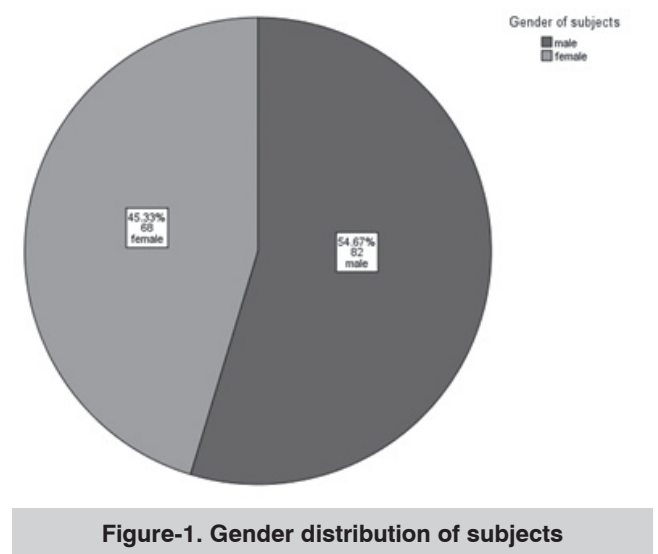
Sr. No	Type of Thrombocytosis	Number of Cases	Percentage
1.	Primary thrombocytosis	03	2%
2.	Secondary thrombocytosis	147	98%

Table-II. Distribution of study population according to type of thrombocytosis (n =150)

Sr.	Severity of thrombocytosis	No. of Cases	Percentage
1.	Mild 450 -700 x 109/L	70	46.7%
2.	Moderate 700 -1000 x 109/L	63	42%
3.	Severe >1000 x 109/μL	17	11.3%

Table-III. Distribution of cases according to severity of thrombocytosis (n=150)

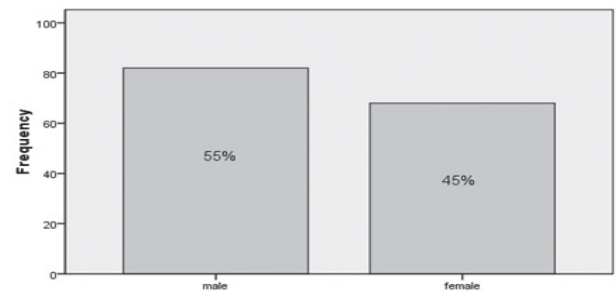| Sr.	Causes	No. of Cases	Percentage
1.	Infection	52	35.4%
2.	Iron deficiency anemia	36	24.5%
3.	Infection + Iron deficiency anemia	38	25.9%
4.	Chronic infection	17	11.6%
5.	Trauma/blood loss	03	2%
6.	Splenectomy	01	0.7%

Table-IV. Distribution of study population according to Reactive causes of thrombocytosis (n =150)

		Type of Thrombocytosis		Total	
		Primary Thrombocytosis	Secondary Thrombocytosis		
Age of subjects	15 to 30 years	0	48	48	Chi- square =1.529 P value=.466
		.0%	32.7%	32.0%	
	31 to 50 years	2	59	61	
		66.7%	40.1%	40.7%	
	51 to 70 years	1	40	41	
		33.3%	27.2%	27.3%	
Total		3	147	150	
		100.0%	100.0%	100.0%	

Table-V. Distribution of thrombocytosis according to age groups (n =150)

Figure-2. Distribution of thrombocytosis according to sex
*Chi-square= .178 P value = .673

DISCUSSION

The prevailing form of thrombocytosis often stems from a reactive response, primarily triggered by elevated levels of circulating cytokines that encourage the production of platelets. Conditions marked by inflammation, vasculitis, allergies, acute and chronic infections, malignancies, hemolysis, as well as instances of iron deficiency and blood loss, collectively contribute to an escalation in platelet count.[7] At times, reactive thrombocytosis can manifest noticeably, and in certain instances, the platelet count might exceed 1000 × 10^9/L. This occurrence, although not uncommon, is predominantly observed subsequent to infections. Additionally, it can emerge in diverse scenarios such as recovery from myelosuppression, instances of iron deficiency, or as a component of the acute phase reaction.[8] Typically, there is indication of ongoing inflammation, often manifested as an elevated erythrocyte sedimentation rate (ESR) or elevated C-reactive protein levels. However, this is not always the case.

		Type of Thrombocytosis		Total	
		Primary Thrombocytosis	Secondary Thrombocytosis		
Severity of Thrombocytosis	Mild Thrombocytosis 450-700x109/l	0	70	70	Chi-square= 4.227 P value = .121
		.0%	47.6%	46.7%	
	moderate thrombocytosis 700-1000x109/l	3	60	63	
		100.0%	40.8%	42.0%	
	severe thrombocytosis >1000x109/l	0	17	17	
		.0%	11.6%	11.3%	
Total		3	147	150	
		100.0%	100.0%	100.0%	

Table-VI. Distribution of study population according to severity of thrombocytosis (n =150)

	Causes of Secondary Thrombpocytosis	Type of Thrombocytosis		Total	
		Primary Thrombocytosis	Secondary Thrombocytosis		
	Primary	3	0	3	Chi- square =150.00 P value=.000
		100.0%	.0%	2.0%	
	infection	0	52	52	
		.0%	35.4%	34.7%	
	iron deficiency anemia	0	36	36	
		.0%	24.5%	24.0%	
	infection + iron deficiency anemia	0	38	38	
		.0%	25.9%	25.3%	
	chronic infection	0	17	17	
		.0%	11.6%	11.3%	
	trauma/blood loss	0	3	3	
		.0%	2.0%	2.0%	
	splenectomy	0	1	1	
		.0%	.7%	.7%	
Total		3	147	150	
		100.0%	100.0%	100.0%	

Table-VII. Distribution of study population according to Reactive causes of thrombocytosis (n =150)

The pivotal player in the development of Reactive Thrombocytosis is the inflammatory cytokine Interleukin-6 (IL-6), owing to its significant involvement in the acute phase response during inflammatory and neoplastic diseases. Another acute phase reactant, C-reactive protein (CRP), is also influenced by IL-6 and is synthesized in the liver. Elevated CRP levels are observed in cases of acute infections and inflammatory conditions.[9,10] In the development of reactive thrombocytosis, IL-6 assumes a significant role by actively promoting megakaryopoiesis. This influence occurs both through direct stimulation and indirectly by enhancing the production of thrombopoietin (Tpo) in the liver. Ishiguro et al. conducted a study investigating the dynamics of IL-6 and Tpo and found that during the initial week of infection, levels of both Tpo and IL-6 reached their highest point. Interestingly, this was observed while platelet levels remained within the normal range. However, in the subsequent second and third weeks, as platelet levels peaked, the levels of Tpo and IL-6 declined.[11] In a research endeavor focusing on individuals with pronounced thrombocytosis (platelet count exceeding 800 x 10^9/L), the prevailing source was identified as infectious diseases, particularly with respiratory tract infections leading the tally.[12] Similarly, in our studied patient group, infectious diseases emerged as the predominant driver of reactive thrombocytosis, with respiratory tract infections standing out as the primary contributor, followed by occurrences in the urinary tract and gastrointestinal system. Notably, the incidence of thrombocytosis was more elevated in individuals afflicted by severe pulmonary tuberculosis in comparison to healthy controls.[13]

It was reported that anemia is a common cause of reactive thrombocytosis.[14,15] In IDA, increased level of erythropoietin has been incriminated to have a possible role in stimulating megakaryopoiesis because of its structural homology with thrombopoietin.[5] Thrombocytosis can also accompany several other hematological malignancies. To rule out chronic myeloid leukemia (CML), the absence of the bcr–abl fusion transcript must be demonstrated. In the case of polycythemia vera (PV), iron deficiency might obscure the usual indicators of elevated red cell mass, although the practical significance of differentiating iron-deficient PV from essential thrombocytosis (ET) is likely minimal. When there is the absence of significant bone marrow fibrosis and distinctive laboratory characteristics like a leucoerythroblastic blood film and splenomegaly, established primary myelofibrosis (PMF) can be ruled out. Drug such as thalidomide increases the

risk of extreme thrombocytosis and probably that of venous thrombosis.[16-18]

CONCLUSION

Secondary thrombocytosis prevails as a frequent occurrence among adults, contrasting with the rarity of primary thrombocytosis. While infectious diseases constitute the most prevalent cause of secondary thrombocytosis, it's imperative to extend scrutiny towards additional factors. Conditions such as iron deficiency anemia, chronic infections, and tissue injury accompanied by blood loss warrant diligent investigation. This holistic approach ensures a comprehensive understanding of thrombocytosis's multifaceted etiology, guiding more effective diagnostic and therapeutic strategies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Masooma Jaffer	Principal Investigator and writer.	
2	Omar Shahid	Co-investigator and writer with initial analysis.	
3	Rumaisha Aslam	Result analysis and writing and review.	
4	Fatima Saeed	Corrections in investigations and writings.	
5	Atiqa Arshad	Critical analysis of results and writing.	
6	Muhammad Touqeer Hanif	End critical corrections and analysis and formatting.	