An evaluation of thrombocytopenia cases in the hematology clinic of the Ankara Numune Training and Research Hospital

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Background Thrombocytopenia is a major disease that requires the referral of outpatient and hospitalized patients to hematology specialists.

Objectives The present study aims to evaluate the laboratory and transfusion statuses of adult patients admitted to our hospital and receiving outpatient/inpatient treatment and diagnosed with thrombocytopenia ($<100\times10^9$/l).

Design Single-center, retrospective, laboratory-based study.

Patients and methods In the study, after obtaining permission of the hospital's Non-Invasive Clinical Research Ethics Committee, the information of patients diagnosed with thrombocytopenia (platelet count $<100\times10^9$/l) and who were examined and treated in the outpatient/inpatient settings between 2008 and 2010 were retrospectively analyzed using patient files and the hospital electronic database.

Sample size A total of 1020 patients diagnosed with thrombocytopenia.

Results The patients were divided into groups according to the most common diagnoses for diseases associated with thrombocytopenia (hematological malignancy, disseminated intravascular coagulation (DIC)-sepsis, immune thrombocytopenia (ITP), infection, and chronic liver disease (*n*=708). Chemotherapy-induced, drug-induced, nutritional (B12, folate deficiency, etc.), OKIT, pregnancy-induced thrombocytopenias and other less common causes of thrombocytopenia were evaluated in a separate group (*n*=312). It was found that female patients were more frequently diagnosed with ITP (71.7 vs. 28.3%). Sex distributions were similar in other groups. The highest mean age (71 years: 50/80) was observed in patients with DIC-sepsis, whereas the lowest mean age was found in patients with ITP (40 years: 30/57) (P<0.001). It was found that the most frequent need for transfusion developed in patients diagnosed with acute myeloid leukemia, acute lymphoblastic leukemia, and aplastic anemia.

Conclusion In this study, it was determined that the prevalence of thrombocytopenia was highest in patients diagnosed with hematological malignancy, ITP, and DIC-sepsis, respectively. In cases of hematological malignancy, the need for replacement of blood products is considered to be inevitable during the treatment process of the underlying disease compared with other clinical conditions.

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Introduction

Thrombocytopenia is defined as a condition where the platelet count is below 150×10^9/l. It may present in addition to another pathology or be directly related to an underlying hematological condition. It is an important condition that requires referral of patients to hematology specialists. As a result of its uncommon life-threatening risks, thrombocytopenia needs to be rapidly evaluated with a wide differential diagnosis and emergency intervention. There are many medical conditions that cause thrombocytopenia in adults. Thrombocytes, the coagulation system, and vascular endothelium are the three main factors responsible for thrombocytopenia. Recognition of the individual platelet depletion mechanism helps to classify thrombocytopenic diseases and explain differences in their clinical features [1].

In adult thrombocytopenia patients, a rapid assessment should be made to exclude the underlying treatable conditions, and then the need for treatment should be evaluated to reduce the risk of bleeding. The transfusion dose depends on the current and expected platelet counts before and after transfusion in the absence of active bleeding in patients. With the transfusion of blood or blood components, many lives can be saved, while some lives can sometimes be lost due to transfusions. Physicians should understand the indications, contraindications, and side effects of treatment very well before making the decision for transfusion.

On the basis of this information, the present study aims to evaluate the laboratory and transfusion statuses of adult patients admitted to our hospital and diagnosed with outpatient/inpatient thrombocytopenia ($<100\times10^9$/l).

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Patients and methods

Study design

In the study, after obtaining the permission of the hospital's Non-Invasive Clinical Research Ethics Committee, the information of patients diagnosed with thrombocytopenia (platelet count $<100\times10^9$/l) and who were examined and treated in outpatient/inpatient settings between 2008 and 2010 were retrospectively analyzed using patient files and the hospital automation system. This study was initiated after the approval of the local Ethics Committee of the Ankara Numune Training and Research Hospital (05.01.2008 NEAH/19).

Patient information included in the study such as age, sex, date of application, hemoglobin (Hb), thrombocyte, and International Normalized Ratio (INR) values at the time of application, laboratory tests performed on the patient, type of blood products transfused (erythrocyte suspension, thrombocyte, and fresh frozen plasma), unit amount, and indications for transfusion were recorded.

Peripheral disseminations of all patients were evaluated by staining with Giemsa stain. Patients with suspected primary bone marrow malignancy or bone infiltration were evaluated by bone marrow aspiration and biopsy. Differential diagnoses were made by examining routine biochemistry examinations in all cases and autoantibodies (rheumatoid factor, antinuclear antibody, and anti-dsDNA) for rheumatological diseases [Sjögren's syndrome and systemic lupus erythematosus (SLE)] in some patients. Cytomegalovirus IgM (CMV IgM), Epstein-Barr virus IgM (EBV IgM), and hepatitis serology were studied by ELISA method in suspected cases for infectious agents that may play a role in the etiology of thrombocytopenia. Patients, who presented with bleeding complaints, were grouped as subcutaneous hemorrhage, mucosal bleeding, and intraorgan hemorrhage. Hemogram values of the patients at the time of diagnosis and during follow-up were recorded.

Statistical analysis

The SPSS 26.0 (IBM Corporation, Armonk, New York, USA) program was used in the analysis of variables. The compatibility of univariate data to normal distribution was evaluated using the Shapiro–Wilk Francia test. While the Kruskal–Wallis H test was used with the Monte Carlo simulation results in comparing more than two groups with each other according to quantitative data; Dunn's test was used for post hoc analyzes. In comparing categorical variables with each other, the Pearson χ^2 test was used together with the Monte Carlo simulation technique. Column proportions were compared with each other and expressed according to the Benjamini–Hochberg corrected P value results. Quantitative variables were expressed as median (percentile 25/percentile 75) in the tables, while categorical variables were shown as n (%). Variables were analyzed at a 95% confidence level, and a P value of less than 0.05 was considered significant.

Results

A total of 1020 patients with a diagnosis of thrombocytopenia ($<100\times10^9$/l) followed up in our clinic were included in the present study. Patients were divided into groups according to their diagnoses for the most common diseases associated with thrombocytopenia (hematological malignancy, disseminated intravascular coagulation (DIC)-sepsis, immune thrombocytopenia (ITP), infection, and chronic liver disease – total number: 708). Chemotherapy-induced thrombocytopenia (CIT), drug-induced, nutritional (B12, folate deficiency, etc.), OKIT, pregnancy-induced thrombocytopenias and other less common causes of thrombocytopenia were evaluated in a separate group (n=312) (Table 1).

Thrombocytopenias associated with DIC-sepsis [thrombotic microangiopathies (TMA) and others], hematological malignancies, ITP, infection, and chronic liver diseases (liver cirrhosis) were evaluated. The frequency of thrombocytopenia was more common in female patients (310 vs. 398). When the groups were evaluated in terms of sex distribution, it was observed that a diagnosis of ITP was more common in female patients (71.7 vs. 28.3%). Sex distributions were similar in other groups (Table 1).

The highest mean age was seen in patients with DIC-sepsis, while the lowest mean age was in patients diagnosed with ITP (P<0.001). The mean ages of the patients diagnosed with hematological malignancy, infection, and chronic liver disease were similar. Leukocyte and mean corpuscular volume (MCV) levels of patients diagnosed with hematological malignancy and DIC-sepsis were similar to those with DIC-sepsis but were higher than other groups (P<0.001) (Table 1).

Patients were grouped according to the severity of thrombocytopenia levels. It was noticed that more than half of the patients had platelet counts of between 50 and 100×10^9/l. The majority of patients (94%) with a platelet level less than 10×10^9/l consisted of patients with ITP and hematological malignancy. Platelet levels of patients with chronic liver disease were found to be more than 10×10^9/l and generally above the level of more than 50×10^9/l (Table 2).

Table 1 Patient groups who most commonly have thrombocytopenia

	DIC-sepsis (A) (*N*=123) [*n* (%)]	Hematological malignancy (B) (*N*=231) [*n* (%)]	ITP (C) (*N*=173) [*n* (%)]	Infection (D) (*N*=81) [*n* (%)]	Chronic liver disease (E) (*N*=100) [*n* (%)]	*P*
Sex						<0.001[c]
Female	62 (50.4)	108 (46.8)	124 (71.7)[ABD]	37 (45.7)	67 (67)	
Male	61 (49.6)[CE]	123 (53.2)[CE]	49 (28.3)	44 (54.3)[CE]	33 (33)	
	Median (q1/q3)	Median (q1/q3)	Median (q1/q3)	Median (q1/q3)	Median (q1/q3)	
Age	71 (50/80)[BCDE]	56 (39/69)[C]	40 (30/57)[E]	52 (33/64)	56.5 (48/64.5)	<0.001[k]
WBCx10 ^{3}	10.7 (5.1/17.1)[BDE]	5.1 (2.6/15.5)[CDE]	7.1 (5.6/9.3)[DE]	3.3 (1.9/6.1)	3.35 (2.45/5.05)	<0.001[k]
HGB	9.8 (8.5/11.6)[CDE]	8.7 (6.9/10.7)[CDE]	13.2 (12.1/14.4)[E]	12.1 (10.1/14.2)	11.7 (9.3/13.4)	<0.001[k]
HCT	29.1 (25/33.4)[CDE]	25.5 (20.1/32.3)[CDE]	38.6 (35.6/42.5)[DE]	35.9 (30.1/40.3)	35.2 (28/39)	<0.001[k]
MCV	87 (84/90)[BC]	90 (86/98)[CDE]	86 (81/88)[E]	88 (84/91)	89 (80/96)	<0.001[k]
PLTx10^3	56 (33/80)[A]	52 (19/74)[E]	42 (21/68)[DE]	67 (29/86)	72 (52.5/83.5)	<0.001[k]
MPV	9.3 (8.5/9.9)[B]C	7.7 (6.9/8.6)[CDE]	10.3 (9.3/11.2)[DE]	8.9 (7.9/9.7)	8.9 (8.1/9.8)	<0.001[k]
PDW	17.2 (16.3/18)	17.3 (16.4/18.2)[C]	16.7 (16.1/17.8)[E]	17.1 (16.4/18)	17.5 (16.9/18)	0.004[k]

DIC, disseminated intravascular coagulation; HCT, hematocrit; HGB, hemoglobin; ITP, immune thrombocytopenia; MCV, mean corpuscular volume; WBC, white blood cell. [c]Pearson χ^2 test (Monte Carlo, exact); post-hoc test: Benjamini–Hochberg correction. [k]Kruskal–Wallis test (Monte Carlo), post-hoc test: Dunn's test, q1: percentile 25, q3: percentile 75. [A B C D E] expresses significance according to related groups.

Table 2 Classification of patient groups according to hematological results

	DIC-sepsis (A) (*N*=123) [*n* (%)]	Hematological malignancy (B) (*N*=231) [*n* (%)]	ITP (C) (*N*=173) [*n* (%)]	Infection (D) (*N*=81) [*n* (%)]	Chronic liver disease (E) (*N*=100) [*n* (%)]	*P*
PLT						<0.001[c]
<10.000	2 (1.6)	26 (11.3)[ADE]	21 (12.1)[ADE]	1 (1.2)	0	
10.000–20.000	16 (13.0)	32 (13.9)	19 (11.0)	11 (13.6)	5 (5.0)[ABE]	
20.000–50.000	34 (27.6)	50 (21.6)[CE]	57 (32.9)	18 (22.2)	18 (18.0)	
≥50.000	71 (57.7)[C]	123 (53.2)	76 (43.9)[D]	51 (63.0)	77 (77.0)[ABCD]	
HGB						<0.001[c]
≤7	15 (12.2)[CD]	66 (28.6)[ACDE]	4 (2.3)	3 (3.7)	9 (9.0)[C]	
7–9	25 (20.3)[C]	60 (26.0)[CDE]	8 (4.6)	9 (11.1)	12 (12.0)[C]	
≥9	83 (67.5)[B]	105 (45.5)	161 (93.1)[ABDE]	69 (85.2)[AB]	79 (79.0)[B]	
Hospitalization status						<0.001[c]
Inpatient	121 (98.4)[BCDE]	150 (64.9)[C]	47 (27.2)	67 (82.7)[BCE]	54 (54)	
Outpatient	2 (1.6)	81 (35.1)[AD]	126 (72.8)[ABDE]	14 (17.3)[A]	46 (46)	
State of bleeding						<0.001[c]
Absent	80 (65)	163 (70.6)	124 (71.7)	64 (79)[A]	89 (89)[ABC]	
Minor	15 (12.2)[E]	42 (18.2)[DE]	37 (21.4)[ADE]	6 (7.4)	3 (3)	
Major	28 (22.8)[BCE]	26 (11.3)	12 (6.9)	11 (13.6)	8 (8)	
PT						<0.001[c]
Normal	44 (35.8)	189 (81.8)[ADE]	172 (99.4)[ABDE]	53 (65.4)[AE]	36 (36)	
Extended	79 (64.2)[BCD]	42 (18.2)[C]	1 (0.6)	28 (34.6)[BC]	64 (64)	
INR						<0.001[c]
Normal	45 (36.6)	192 (83.1)[AE]	172 (99.4)[ABDE]	61 (75.3)[AE]	43 (43)	
Increased	78 (63.4)[BCD]	39 (16.9)[C]	1 (0.6)	20 (24.7)[C]	57 (57)	
APTT						<0.001[c]
Normal	44 (35.8)	190 (82.3)[ADE]	172 (99.4)[ABDE]	53 (65.4)[AE]	36 (36)	
Extended	79 (64.2)[BCD]	41 (17.7)[C]	1 (0.6)	28 (34.6)[BC]	64 (64)	
D-dimer						<0.001[c]
Normal	66 (53.7)	224 (97)[A]	173 (100)[A]	80 (98.8)[A]	99 (99)	
High	57 (46.3)[BCDE]	7 (3)	0	1 (1.2)	1 (1)	
Fibrinogen						<0.001c
Normal	83 (67.5)	213 (92.2)[ADE]	172 (99.4)[ABDE]	65 (80.2)[A]	82 (82)	
Low	40 (32.5)[BCDE]	18 (7.8)[C]	1 (0.6)	16 (19.8)[BC]	18 (18)	

APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; INR, International Normalized Ratio; ITP, immune thrombocytopenia; PT, prothrombin time. [c]Pearson χ^2 test (Monte Carlo, exact); post-hoc test: Benjamini–Hochberg correction. [k]Kruskal–Wallis Test (Monte Carlo), post-hoc test: Dunn's Test, q1: percentile 25, q3: percentile 75. [A B C D E] expresses significance according to related groups.

Bone marrow aspiration and biopsy were performed in a total of 100 (14.2%) patients. To evaluate the etiology of thrombocytopenia, it was determined that 31 (17.9%) of the patients with ITP and 53 (22.9%) of the patients with a diagnosis of hematological malignancy had a bone marrow aspiration biopsy. The majority of patients diagnosed with chronic liver disease, DIC-sepsis, and infection did not require bone marrow biopsy (Table 3).

The transfusion statuses of patients with hematological malignancy are summarized in Table 4. It was found that the most frequent need for transfusion developed in patients diagnosed with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and aplastic anemia. However, hematological malignancies that resulted in the least need for transfusion were chronic lymphocytic leukemia (CLL) and chronic myeloid leukaemia (CML) (Table 4).

In this study, the distribution of the other 312 patients with a platelet level of less than or equal to 100×10^9/l and with different diagnoses is given in Table 5. A total of 82 (8%) patients were not included in the classification because thrombocytopenia was not fully defined. The incidence of pseudothrombocytopenia was found to be 4.6% in all patients. While the frequency of pregnancy-induced thrombocytopenia was 1.5%, the frequency of HELLP syndrome was 0.49%. A total of 52 (5.1%) patients developed CIT and 39 (3.8%) patients developed nonchemotherapy drug-induced thrombocytopenia (DITP). While the development of thrombocytopenia due to vitamin B12 deficiency was observed in 31 (3%) patients, the incidence of heparin-induced thrombocytopenia was 1.4% (Table 5).

The patients with the lowest Hb (<7 g/dl) levels in the study were most frequently those with hematological malignancy and DIC-sepsis. The majority of patients

Table 3 Evaluation of hematological and coagulation results of patients

	DIC-sepsis (A) (*N*=123) [*n* (%)]	Hematological malignancy (B) (*N*=231) [*n* (%)]	ITP (C) (*N*=173) [*n* (%)]	Infection (D) (*N*=81) [*n* (%)]	Chronic liver disease (E) (*N*=100) [*n* (%)]	*P*
Bone marrow biopsy						<0.001[c]
–	119 (96.7)[BCE]	178 (77.1)	142 (82.1)	79 (97.5)[BCE]	90 (90)	
+	4 (3.3)	53 (22.9)[ADE]	31 (17.9)[AD]	2 (2.5)	10 (10)	
Plt transfusion						<0.001[c]
–	82 (66.7)	140 (60.6)	149 (86.1)[ABD]	59 (72.8)[B]	89 (89)	
+	41 (33.3)[CE]	91 (39.4)[CDE]	24 (13.9)	22 (27.2)C[E]	11 (11)	
ES transfusion						<0.001c
–	65 (52.8)	97 (42)	165 (95.4)[ABDE]	68 (84)[AB]	86 (86)	
+	58 (47.2)[CDE]	134 (58)[CDE]	8 (4.6)	13 (16)C	14 (14)	
TDP transfusion						<0.001c
–	61 (49.6)	217 (93.9)[ADE]	173 (100)[ABDE]	60 (74.1)[A]	87 (87)	
+	62 (50.4)[BCDE]	14 (6.1)	0	21 (25.9)[BCE]	13 (13)	
Exitus						<0.001c
–	41 (33.3)	187 (81)[A]	172 (99.4)[ABD]	71 (87.7)[A]	97 (97)	
+	82 (66.7)[BCDE]	44 (19)[CE]	1 (0.6)	10 (12.3)C[E]	3 (3)	

DIC, disseminated intravascular coagulation; ITP, immune thrombocytopenia. [c]Pearson χ^2 test (Monte Carlo, exact); post-hoc test: Benjamini–Hochberg correction. [k]Kruskal–Wallis test (Monte Carlo), post-hoc test: Dunn's test, q1: percentile 25, q3: percentile 75. [A B C D E] expresses significance according to related groups.

Table 4 Hematological malignancies transfused with blood products

Hematological malignancy	Plt transfusion [*n* (%)]	ES transfusion [*n* (%)]	TDP transfusion [*n* (%)]
Acute myeloid leukemia	52 (57.1)	57 (42.5)	9 (64.3)
Acute lymphoblastic leukemia	14 (15.4)	14 (10.4)	3 (21.4)
Aplastic anemia	11 (12.1)	9 (6.7)	0
Myelodysplastic syndrome	8 (8.8)	24 (17.9)	1 (7.1)
Multiple myeloma	3 (3.3)	10 (7.5)	0
Non-Hodgkin's lymphoma	1 (1.1)	10 (7.5)	0
Hodgkin's disease	1 (1.1)	2 (1.5)	1 (7.1)
Idiopathic myelofibrosis	1 (1.1)	2 (1.5)	0
Chronic lymphocytic leukemia	0	3 (2.2)	0
Chronic myeloid leukemia	0	3 (2.2)	0

Table 5 Other causes of thrombocytopenia

Causes of thrombocytopenia (others)	*n* (%)
Unclassified	82 (8.0)
KT-induced thrombocytopenia	52 (5.1)
Pseudothrombocytopenia	47 (4.6)
Drug-induced thrombocytopenia	39 (3.8)
B12 deficiency	31 (3.0)
Pregnancy-induced thrombocytopenia	15 (1.5)
HIT	14 (1.4)
Solid organ malignancies	14 (1.4)
OKIT patient	13 (1.3)
HELLP syndrome	5 (0.49)
Total (others)[a]	312 (30.6)
All Patients[b]	1020 (100.0)

HIT, heparin-induced thrombocytopenia. [a]Distribution rates in the other groups were given. [b]All patients in the study were taken as a reference.

(85.2 and 93.1%) with infection and ITP-induced thrombocytopenia had Hb levels more than 9 g/dl (Table 2).

With respect to the hospitalization statuses of the patients, more than half were inpatient, except for ITP patients, and the highest hospitalization rates were observed in DIC-sepsis and infection patients. When the patients were evaluated according to the presence of bleeding, the most common rate of major bleeding was in patients with a diagnosis of DIC-sepsis (22.8%), while patients with ITP and hematological malignancies had minor bleeding more frequently (Table 2).

Approximately two-thirds of the patients in the DIC-sepsis group were found to have an increase in PZ, INR, and activated partial thromboplastin time (APTT), while 57 (46.3%) patients had high D-dimer levels, and 40 (32.5%) patients were found to have low fibrinogen. A total of 16 (19.8%) patients with thrombocytopenia due to infection had low fibrinogen. Coagulation parameters were determined at normal levels in most of the patients in the other groups (Table 2).

Discussion

There are many medical conditions that cause thrombocytopenia in adults. The most common of these are DITP and infection-induced thrombocytopenia, hematological malignancies, and ITP. In hospitalized patients, the most common causes of severe thrombocytopenia are expected to be myelosuppression or drug-induced [2]. The point prevalence of thrombocytopenia in hospitals is higher than in the general population.

ITP is the most common cause of severe isolated thrombocytopenia in the general population and thrombocytopenia in patients referred to hematology services. It is considered to be an exclusion diagnosis, and care should always be taken in terms of alternative diagnoses to the ITP clinic, especially in atypical applications or if the expected response to first-line treatment is not seen [3]. Although a typical ITP patient will usually be held to be a young woman, in fact, large databases such as the UK-based General Practice Database point to a bimodal distribution of age at diagnosis. There is a young female peak followed by an older male peak, and this second peak incidence is prominent in male patients over 60 years of age [4]. In this study, the most common causes of thrombocytopenia were determined in the order of frequency as hematological malignancies (*n*=231, 22.7%), ITP (*n*=173, 17%), DIC-sepsis (*n*=123, 12.1%), chronic liver disease (*n*=100, 9.8%), and infection-induced thrombocytopenia (*n*=81, 7.9%).

In the differential diagnosis of thrombocytopenia in patients presenting with thrombocytopenia in advanced age, the increased incidence of clonal hematopoietic disorders in addition to ITP should be kept in mind. Therefore, for all patients over the age of 60 years with thrombocytopenia, routine bone marrow examination and imaging (computed tomography neck, chest, abdomen, and pelvis) are recommended for all elderly patients who do not respond to primary ITP treatment [2,3].

Accordingly, in this study, it was determined that patients except those with ITP were older and the group with the highest mean age was patients with DIC-sepsis. Although there is no significant difference in the development of thrombocytopenia in terms of age and sex distributions, female sex is expected to be more frequent, especially in the development of ITP, where autoimmune processes are dominant. Similarly, in this study, it was determined that an ITP diagnosis was more common in female patients (female : male, 2.53 : 1). Sex distributions were similar in other groups.

DIC is a dynamic process and although laboratory tests are useful, they only provide a snapshot of the clinical picture at a particular moment. The presence of thrombocytopenia is sensitive (but not specific) to disseminated intravascular coagulation and is a feature seen in ~98% of cases of diffuse intravascular coagulation [5]. Prothrombin time or APTT is prolonged at some point during the course of the disease only in about half of the cases of widespread intravascular coagulation, and therefore a normal laboratory coagulation profile does not exclude this diagnosis [5]. It is generally recommended to monitor fibrinogen levels. However, since fibrinogen is an acute phase, its levels in the DIC table may be normal [5].

In this study, patients diagnosed with DIC-sepsis and infection-induced thrombocytopenia had the highest hospitalization rates, as expected. While an increase in PZ, INR, and APTT was detected in approximately two-thirds of the patients in the DIC-sepsis group, increased D-dimer levels were found in 57 (46.3%) patients and decreased fibrinogen in 40 (32.5%) patients. Low fibrinogen was found in 16 (19.8%) of the patients with thrombocytopenia due to infection. Coagulation parameters were at normal levels in most of the patients in the other groups.

Thrombocytopenia is a common hematological disorder in patients with chronic liver disease. The pathophysiology of thrombocytopenia in chronic liver disease has long been associated with the hypersplenism hypothesis. Portal hypertension causes aggregation and sequestration of the corpuscular components of the blood, especially platelets, in the enlarged and obstructed spleen. Other important mechanisms include bone marrow suppression with toxic substances such as alcohol or viral infection, and immunological removal of platelets from the circulation [6]. In this study, chronic liver disease with thrombocytopenia seems to be an important cause of thrombocytopenia.

Drug-induced thrombocytopenia

Although the risk of any DITP is low, a lack of awareness, polypharmacy, potential alternative diagnoses, and the absence and underreporting of standardized routine tests may mean that DITP is not adequately recognized [7,8]. In typical DITP, several different mechanisms have been identified, most commonly characterized by severe thrombocytopenia due to the clearance and/or destruction of platelets sensitized by a drug-induced antibody. Patients with typical DITP often bleed when it is symptomatic, and the diagnosis is often difficult to confirm biologically because detection of drug-induced antibodies in the patient's serum or plasma is usually not possible [9].

Chemotherapy-induced thrombocytopenia

CIT refers to the inhibitory effect of anti-tumor chemotherapy drugs on the bone marrow, and especially on megakaryocytes, resulting in a platelet count of less than 100×10^9/l in peripheral blood. Clinically, CIT is a common dose-limiting toxic reaction of chemotherapeutic drugs and can cause dose reductions, dose delays, or even treatment discontinuation. Severe thrombocytopenia can cause spontaneous bleeding of important organs, affecting clinical efficacy and patient survival. The degree of thrombocytopenia is related to the category, dosage, chemotherapeutic cycle, dose form, and auxiliary measurements of chemotherapy drugs, as well as individual differences of the patients. Furthermore, when the same drug is administered for different organ tumors, the severity of bone marrow suppression and thrombocytopenia differs [10]. Incidence rates of thrombocytopenia vary according to the tumor type. Preliminary data analyzes from the Link Doc database from January 2016 to June 2017 show that the incidence rate of CIT is more than 40% in liver cancer, 3.7% in breast cancer, and 10–20% in other cancers. Regarding the chemotherapy regimen, the incidence of CIT is higher in platinum-containing chemotherapy regimens for many cancers, including lung cancer and gynecologic cancer [10]. While CIT was detected in 52 (5.1%) patients showing a point incidence in the records including the period in which the present study was conducted, it is predicted that these rates may rise to levels similar to the literature in the continuous follow-up of patients with cancer.

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia is an immunological complication that is more likely to occur in hospitalized patients and for which heparin therapy is unique. New thrombocytopenia is determined by the score of the confirmed pretest probability scoring system (4T score) in a patient receiving heparin therapy, especially in the presence of progressive or new thrombosis [11]. Until the result is obtained, it is recommended to discontinue heparin and initiate alternative nonheparin anticoagulation.

Pregnancy-induced thrombocytopenia

Pregnancy-induced thrombocytopenia is the second most common hematological disorder after anemia. Although the platelet count does not change much in pregnant female patients compared with nonpregnant female patients, there is a slight decrease during pregnancy. Thrombocytopenia develops in 5–10% of female patients during pregnancy or in the postpartum period [11]. In most cases, it is an incidental disorder. However, it can also provide a clue for coexisting systemic or pregnancy-induced pathologies. Acute fatty liver of pregnancy and preeclampsia/eclampsia/HELLP syndrome (hemolysis, high liver enzymes, low platelets) are types of pregnancy-induced TMA.

Management of pregnancy-induced thrombocytopenia focuses on the underlying cause. Platelet transfusion is generally not required to achieve a specific goal and is only for patients who are bleeding. Local hospital policies govern the platelet count target, and it varies widely between institutions. However, it is recommended that a hematologist be included in the management of pregnancy-induced thrombocytopenia, especially if the platelet count is less than or equal to 70×10^9/l or a coexisting bleeding disorder is detected

[11]. In this study, the frequency of pregnancy-induced thrombocytopenia was found to be 1.5%, while the frequency of HELLP syndrome was determined to be 0.49%.

DIC-induced thrombocytopenia

Platelets have emerged as versatile effectors of an immune-mediated response beyond hemostasis. The contribution of platelets in the defense against inflammation, tissue integrity, and infections has significantly expanded the range of their roles in health and disease states [11]. Thrombocytopenia is a common finding in patients hospitalized with severe sepsis, DIC, and septic shock. Patients with thrombocytopenia have more major bleeding episodes, an increased incidence of acute kidney injury, and an increased duration of ICU-stay [12]. Multiple mechanisms play a role in thrombocytopenia during septic shock, including endothelial dysfunction/coagulopathy, hemodilution, and impaired thrombopoiesis [12].

Blood and blood product transfusion

Since the first blood transfusion trial in the 17th century, whole blood transfusion, only packed red blood cells (RBC), platelets, rare white blood cells, frozen plasma, and plasma-derived products have been used for blood transfusion. Platelets play an integral role in hemostasis in their response to vascular damage. Platelet concentrates are commonly used in patients with severe thrombocytopenia. Transfusion need may develop in patients who had hematological malignancy, bone marrow failure, or other immune and nonimmune thrombocytopenia due to platelet destruction.

Platelet transfusion

When the platelet count is less than 50×10^9/l, bleeding occurs on the skin and mucosa, and patients carry some significant risks during surgery and invasive traumatic examination. Although it has been observed that the bleeding rate increases as the platelet count decreases, a clear threshold for a serious increase in bleeding has not been shown. While there is a high risk of spontaneous bleeding when the platelet count is less than 20×10^9/l, this risk is extremely high when the platelet count is less than 10×10^9/l [13]. The risk of bleeding is generally related to the degree of thrombocytopenia [12], and other important patient-specific features such as vascular risk factors, age [12], and the use of antiplatelet or anticoagulant therapy should be evaluated. When the patients in the present study were evaluated according to the presence of bleeding, it was seen that the most frequent major bleeding rate was in patients with a diagnosis of DIC-sepsis (22.8%), and patients with ITP and hematological malignancies had a higher frequency of minor bleeding.

In the absence of active bleeding in patients, the transfusion dose depends on the current and expected platelet counts before and after transfusion. Usually, an adult receives one therapeutic dose at a time. When patients have active bleeding, the dosage is determined according to the severity of the bleeding and the hemostatic effect of the transfusion. The relevant standard dose is often given according to the degree of thrombocytopenia and one full dose of transfusion is administered at a time (1 U of apheresis platelets or 6 U of random platelet suspension). Patients in this study were grouped according to the severity of their platelet levels to evaluate the distribution of transfusion. It was noteworthy that more than half of the patients had platelet counts of between 50 and 100×10^9/l. It was determined that most of the patients in the less than 10×10^9/l group (47 : 50, 94%) consisted of patients diagnosed with ITP and hematological malignancy. The platelet levels of patients with chronic liver disease were more than 10×10^9/l and generally above the level of more than 50×10^9/l.

ES transfusion

RBC transfusion indications are present when there is severe symptomatology or evidence of end organ damage, periods of severe anemia, and when it improves oxygen transport capacity. Due to the potential for serious transfusion reactions, lack of evidence for better patient outcomes, and growing concern for worse outcomes, liberal transfusion strategies are no longer recommended for most patients. For many physicians, this is a significant change in practice compared with previous years, and attempts are now being made to reduce the use of ES transfusion as much as possible.

In observational studies and several randomized controlled trials (RCS), two different RBC transfusion strategies were compared ('liberal' transfusion with a Hb threshold of 9 or 10 g/dl and a 'tight' transfusion with a Hb threshold of 7 g/dl) to assess which strategy would be more beneficial [14]. With respect to heterogeneity, although it is not possible to make a one-to-one comparison between studies, it has been stated that there is no significant difference between the two approaches in terms of significant survival and the decrease in hospital stay as a result of these studies [15,16].

Unless a patient has acute bleeding, units can be given slowly, with a reassessment between each unit to prevent overtransfusion. The minimum dose required to correct the deficiency is used in best practice [17]. In this study, it was determined that patients with the lowest Hb (7) levels had hematological malignancies and DIC-sepsis. Most of the patients (85.2 and 93.1%)

with infection and ITP-induced thrombocytopenia had Hb levels more than 9 g/dl.

TDP transfusion

Plasma (TDP) transfusion is indicated for patients with multiple coagulation deficiencies, bleeding, or in those undergoing invasive procedures. These conditions are usually due to warfarin (Coumadin) treatment and can also be found in vitamin K deficiency due to malnutrition. Whenever possible, the use of the four-factor prothrombin complex concentrate is recommended as a first-line therapy according to TDP [18]. Prothrombin complex concentrate has the benefits of a faster INR return without the risk of volume overload and transfusion reactions. TDP can be used for the treatment of specific coagulation/anticoagulant factor deficiencies where factor concentrates are not available. However, patients who are determined to have elevated nontherapeutic prothrombin time and INR, who do not bleed or need an urgently invasive procedure, can be treated more conservatively by the supplementation of vitamin K and/or reduction of the warfarin dose.

Transfusion frequency

The incidence of side effects of platelet transfusion, such as fever, allergy, bacterial contamination, and transfusion-related acute lung injury, is higher in patients with cancer compared with other blood components [19]. In a large retrospective cohort study evaluating the risk of thrombosis associated with blood transfusion requirements, 15 237 (3%) of a total of 504 208 cancer patients hospitalized consecutively between 1995 and 2003 received at least one platelet transfusion in addition to ES. In this study, it was determined that the most common platelet and ES transfusions were performed in hematological malignancies at similar rates. Transfusion was applied to patients most frequently diagnosed with AML, ALL, and aplastic anemia. However, it was determined that the hematological malignancies that developed the least need for transfusion were CLL and CML.

Limitations

The study has some limitations. Because the platelet depletion limit was evaluated as less than 100×10^9/l, the patients included in the study could not be compared with patients with platelet levels of 100–150×10^9/l as stated in the literature. In addition, it was not possible to give a general thrombocytopenia rate in all the patients, who applied to our hospital, because the cross-sectional evaluation was limited to patients diagnosed with thrombocytopenia in our hospital. However, the present study provided an important opportunity to present detailed data on a large number of adult patients and our transfusion strategy. As a result of the implementation of a strict transfusion strategy in patients, it is considered an important finding to have values below the high transfusion rates stated in the literature in previous periods.

Conclusion

When thrombocytopenia is seen in adult patients, a rapid assessment should be made to exclude serious and treatable underlying conditions, and then the need for treatment should be evaluated to reduce the risk of bleeding. If a decision is made to treat thrombocytopenia or severe anemia, the opportunity to review the diagnosis must be seized. The exact distinction between the causes of thrombocytopenia and anemia should be considered in all patients to ensure appropriate diagnosis and treatment. In this study, it was observed that significant platelet and ES transfusion was applied in patients with AML, ALL, and aplastic anemia. Therefore, a continuous review of platelet and ES transfusion strategies in other diseases (DIC, infections, liver disease, and ITP) has positive results in terms of the prognosis of patients; on the other hand, it is important to carefully evaluate the pros and cons of blood product transfusion.

In conclusion, in this study, it was determined that the incidence of thrombocytopenia was quite high, but the frequency of major bleeding and the need for blood transfusion were not similar in all disease groups. In hematological malignancies compared with other clinical conditions, the need for the replacement of blood products is considered to be inevitable during the treatment of the underlying disease. In any decision regarding blood product replacement, strict approach guidelines should be taken into account instead of liberal methods.

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Conflicts of interest

There are no conflicts of interest.

References

1 Nguyen TC, Cruz MA, Carcillo JA. Thrombocytopenia-associated multiple organ failure and acute kidney injury. *Crit Care Clin* 2015; **31**:661–674.

2 Arnold DM, Lim W. A rational approach to the diagnosis and management of thrombocytopenia in the hospitalized patient. *Semin Hematol* 2011; **48**:251–258.

3 Swain F, Bird R. How I approach new onset thrombocytopenia. *Platelets* 2020; **31**:285–290.

4 Marieke Schoonen W, Kucera G, Coalson J, Li L, Rutstein M, Mowat F, *et al*. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. *Br J Haematol* 2009; **145**:235–244.

5 Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. *Br J Haematol* 2009; **145**:24–33.

6 Peck-Radosavljevic M. Thrombocytopenia in chronic liver disease. *Liver Int* 2017; **37**:778–793.

7 Arnold DM, Kukaswadia S, Nazi I, Esmail A, Dewar L, Smith JW, *et al*. A systematic evaluation of laboratory testing for drug-induced immune thrombocytopenia. *J Thromb Haemost* 2013; **11**:169–176.

8 Arnold DM, Nazi I, Warkentin TE, Smith JW, Toltl LJ, George JN, *et al*. Approach to the diagnosis and management of drug-induced immune thrombocytopenia. *Transfus Med Rev* 2013; **27**:137–145.

9 Vayne C, Guéry E-A., Rollin J, Baglo T, Petermann R, Gruel Y. Pathophysiology and diagnosis of drug-induced immune thrombocytopenia. *J Clin Med* 2020; **9**:2212.

10 Tas F, Yildiz I, Kilic L, Ciftci R, Keskin S, Sen F. Same chemotherapy regimen leads to different myelotoxicity in different malignancies. *Am J Ther* 2016; **23**:e670–e679.

11 Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost* 2006; **4**:759–765.

12 Venkata C, Kashyap R, Farmer JC, Afessa B. Thrombocytopenia in adult patients with sepsis: incidence, risk factors, and its association with clinical outcome. *J Intensive Care* 2013; **1**:9.

13 Schiffer CA, Anderson KC, Bennett CL, Bernstein S, Elting LS, Goldsmith M, *et al*. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001; **19**:1519–1538.

14 Hirano Y, Miyoshi Y, Kondo Y, Okamoto K, Tanaka H. Liberal versus restrictive red blood cell transfusion strategy in sepsis or septic shock: a systematic review and meta-analysis of randomized trials. *Crit Care* 2019; **23**:262.

15 Ripollés Melchor J, Casans Francés R, Espinosa Á, Martínez Hurtado E, Navarro Pérez R, Abad Gurumeta A, *et al*. Restrictive versus liberal transfusion strategy for red blood cell transfusion in critically ill patients and in patients with acute coronary syndrome: a systematic review, meta-analysis and trial sequential analysis. *Minerva Anestesiol* 2016; **82**:582–598.

16 Gu W-J., Gu X-P., Wu X-D., Chen H, Kwong JSW, Zhou L-Y., *et al*. Restrictive versus liberal strategy for red blood-cell transfusion: a systematic review and meta-analysis in orthopaedic patients. *J Bone Joint Surg Am* 2018; **100**:686–695.

17 Erickson ML. Indications for transfusion and dosing of blood components. *Clinical principles of transfusion medicine*. United States: Elsevier; 2018. 53–67.

18 Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, *et al*. Evidence-based management of anticoagulant therapy. *Chest* 2012; **141**:e152S–e184S.

19 Katus MC, Szczepiorkowski ZM, Dumont LJ, Dunbar NM. Safety of platelet transfusion: past, present and future. *Vox Sang* 2014; **107**:103–113.