North Clin Istanb 2021;8(3):261–268
doi: 10.14744/nci.2020.76258

Original Article PEDIATRICS

Retrospective evaluation of acute transfusion reactions in a tertiary hospital in Erzurum, Turkey

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ABSTRACT

OBJECTIVE: Transfusion of blood and blood components is a special type of tissue transplantation, a life-saving treatment. However, besides the benefits of blood product transfusions, there are also some undesirable side effects. In the present study, the frequency and type of transfusion reactions related to blood and blood components were investigated.

METHODS: In this retrospective study, types and the time of occurrence of acute transfusion reaction (ATR), the types of blood and blood components used in our hospital between January 2018 and January 2020 were evaluated for hemovigilance using unit blood products application and side effect reporting forms.

RESULTS: During the 2-year period, 61,636 blood and/or blood components were used in 9334 patients, and 53 of the transfused patients developed ATR. In two patients, ATR developed 2 times and a total of 55 ATR developed. Of the patients who developed ATR, 18 were female and 35 were male, and their ages ranged from 1 month to 85 years. The frequency of ATR was 0.09%, and 47.3% of ATRs were allergic transfusion reactions, 41.8% were febrile non-hemolytic transfusion reactions (FNHTRs), 7.3% were hypotensive transfusion reactions, and 1.8% were transfusion-related lung injury. Fifty-five ATRs were found to be associated with 61.8% erythrocyte suspension, 30.9% with FFP, 5.5% with platelet suspension, and 1.8% with whole blood.

CONCLUSION: There are a limited number of studies evaluating transfusion reaction frequency and reaction types from our country. The most frequent ATR reported in our hospital were mild allergic reactions and FNHTR. The most common side effect of blood product type was erythrocyte suspension. It is important to monitor the transfused patients for undesired reactions during and after the transfusion to determine the frequency, type, risk factors, and safety precautions of the transfusion reactions.

Keywords: Acute transfusion reaction; allergic; FNHTR; hemovigilance.

Cite this article as: *Duzenli Kar Y, Ozkorucu Yildirgan D, Aygun B, Erdogmus D, Altinkaynak K. Retrospective evaluation of acute transfusion reactions in a tertiary hospital in Erzurum, Turkey. North Clin Istanb 2021;8(3):261–268.*

Blood products transfusion is a life-saving treatment that is applied in patients all over the world due to anemia, thrombocytopenia, or coagulation disorders [1]. In addition to the benefits of blood and/or blood component transfusions, there are also some side effects. Adverse reactions (side effects) that occur due to transfusion of blood and blood components are called transfusion reactions [2, 3]. Undesirable side effects ob-

Received: May 09, 2020 *Accepted:* November 04, 2020 *Online:* May 24, 2021

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served during transfusion or within the first 24 h are reported as acute (early) transfusion reactions (ATRs) [4–6]. ATRs are divided into two groups as immunological and non-immunological. While non-immunological reactions result from the physical and chemical properties of the transfused blood component, immunological reactions occur because the transfused erythrocyte, leukocyte, platelet, and plasma proteins cause antibody production in the recipient [5, 6]. While acute immunological transfusion reactions are seen as febrile non-hemolytic transfusion reaction (FNHTR), acute hemolytic reaction, mild allergic reaction, anaphylactic reaction, transfusion-related acute lung injury (TRALI), and acute non-immunological transfusion reactions are seen as bacterial contamination, transfusion-associated circulatory fluid/load overload (TACO), hypotensive transfusion reaction, non-immune hemolytic reaction, hypothermia, and electrolyte imbalance (hypocalcemia, hyperkalemia, and hypokalemia) [5].

The most common side effects associated with transfusions are non-hemolytic transfusion reactions such as FNHTR, which can be seen 1 in 30–400 transfusions, and minor allergic reactions that can occur in 1 in 100–900 transfusions [2]. ATRs are often not severe, but rarely can cause fatal complications such as TRALI and anaphylactic shock. Therefore, it is important to monitor patients during and after transfusion [3].

In our country, a regulation was made by the Ministry of Health and the Turkish Red Crescent with the "Technical Assistance Project for Strengthening the Blood Supply System" supported by the European Union between February 2012 and February 2014 for the purpose of safe blood and blood component supply and traceability. Within the scope of this project, the establishment of National Hemovigilance Centers was supported to collect and evaluate information about the collection of blood and blood components, follow-up of recipients, clinical use of products, and to prevent the occurrence or recurrence of these unexpected or undesirable situations resulting from these procedures, and a National Hemovigilance Guide was created [3]. The blood and blood products needs of our patients are met by the Turkish Red Crescent East Anatolia Region Blood Center through our hospital's transfusion center. Our hospital's hemovigilance unit provides services to evaluate the unexpected or undesired reactions arising from the collection, transportation, and clinical use of blood and blood components and to prevent the occurrence and recurrence of these adverse reactions.

Highlight key points

- Transfusion of blood and blood components is a life-saving treatment.
- The most common side effects associated with transfusions are non-hemolytic transfusion reactions such as FNHTR and minor allergic reactions.
- It is important to monitor transfused patients for undesired reactions during and after the transfusion, to determine the frequency, type, and risk factors of the transfusion reactions and to take safety measures in this regard.

Since transfusions of blood components can cause fatal side effects, to avoid unnecessary transfusions; many studies have been conducted examining transfusion indications, length of stay in intensive care units, and transfusion reactions [5]. In our study, the frequency, types, and occurrence times of acute adverse transfusion reactions related to the use of blood and blood components in our hospital were investigated.

MATERIALS AND METHODS

The patients who underwent blood and blood component transfusion between January 2018 and January 2020 in our hospital were included in the present study. Number of transfused patients, types of blood products transfused (leukocyte-reduced erythrocyte suspension, whole blood, fresh frozen plasma [FFP], and leukocyte-reduced platelet suspension), ATRs developing during or within the first 24 h of transfusion, and the occurrence time of ATR were recorded retrospectively from patient files. The signs and findings related to transfusion were arranged in accordance with the definition of the National Hemovigilance Guide. The ATR was defined as the reactions that developed within the first 24 h from the onset of the transfusion. We classified ATR such as hemolytic reactions, FNHTR, mild allergic reactions, anaphylactoid reactions, bacterial contamination, TRALI, TACO, transfusion-related isolated hypotension, hypothermia, citrate toxicity, and metabolic disorders [4]. Hemolytic reaction is the intravascular destruction of erythrocytes as a result of the reaction of an antigen in the donor's erythrocytes with the antibody in the recipient. It is generally seen as a result of ABO incompatible blood transfusion and development of alloantibodies in patients with frequent transfusion requirements such as thalassemia and sickle cell anemia [4, 5]. It presents with fever, chills, chest pain, abdominal, back and flank pain, nausea/vomiting,

hypotension, pallor, jaundice, oliguria-anuria, diffuse bleeding, and dark urine. In the laboratory findings, decreased hemoglobin, hemoglobinemia, hemoglobinuria, haptoglobin, serum indirect bilirubin, and an increase in lactate dehydrogenase are seen [4]. FNHTR occurs due to the binding of recipient antibodies to donor leukocytes and/or the accumulation of biological molecules such as complement, lipid, and cytokines in blood products [7]. After excluding other causes of fever, such as hemolytic transfusion reaction, bacterial contamination, and fever due to the underlying disease, the diagnosis is made by the presence of severe shivering accompanying fever ≥38°C or 1°C above the pre-transfusion value [4–7]. Mild allergic reactions and anaphylactoid reactions are caused by antibodies in the recipient against proteins in the donor plasma. Mild allergic reactions present with non-life-threatening mucocutaneous signs and symptoms such as itching, maculopapular rash, urticaria, local angioedema, periorbital itching-erythema-edema, and conjunctival edema. Anaphylactoid reactions are a life-threatening side effect affecting the respiratory and/or cardiovascular system as well as the mucocutaneous system. In addition to mucocutaneous system findings, severe clinical findings such as severe bronchospasm, severe hypotension, hypotonia, and respiratory failure are observed in patients [4, 5]. Bacterial contamination occurs due to infection in the donor or contamination of the product during preparation of the blood product. It usually presents with fever (>39°C or >2°C increase from pre-transfusion value), chills, bruising, tachycardia, and changes in blood pressure (hypertension or hypotension) that occur within the first 4 h after the start of transfusion. All other signs of bacterial sepsis can be seen. The diagnosis is made by the growth of the same bacteria in the transfused blood product and in the blood culture taken from the recipient [4, 5, 7]. TRALI occurs during transfusion or within the first 6 h after transfusion in a patient without acute lung injury before transfusion. There is lung damage caused by the interaction of the donor's anti-human leukocyte antigen and anti-human neutrophil antigen and recipient neutrophils. Dyspnea, hypoxia, hypotension, tachycardia, fever, and bilateral infiltrates are seen on anteroposterior chest radiography [4, 5]. TACO is the development of congestive heart failure and pulmonary edema due to volume overload after transfusion. For diagnosis, in addition to symptoms of acute onset or worsening respiratory distress and/or pulmonary edema during transfusion or within the first 12 h after transfusion, additional findings such as cardiovascular system changes (tachycardia, hypertension, jugular venous fullness, and peripheral edema) that cannot be explained by the patient's underlying medical condition, increased weight, improvement in clinical findings after diuretic or dialysis administration, and increased level of B-Type natriuretic peptide (BNP or NT-pro BNP) are required [4]. Transfusion-related isolated hypotension is diagnosed by measuring a decrease to 30 mmHg, or more, or measuring 80 mmHg and below in the systolic blood pressure during transfusion or within 1 h of transfusion [4] due to the increase in bradykinin production, such as the use of negatively loaded leukocyte filters, the use of angiotensin-converting enzyme (ACE) inhibitors, and abnormal bradykinin metabolism [5]. Metabolic disorders, citrate used as an anticoagulant in stored blood products, have calcium binding properties. Therefore, it causes a decrease in serum ionized calcium levels in patients undergoing rapid blood transfusion. In these patients, signs of hypocalcemia such as paresthesia, tetany, arrhythmia, and prolonged QT interval on electrocardiography can be observed. In addition, as the waiting period of the stored blood product increases, it may cause hyperpotasemia due to hemolysis [4, 5].

Statistical Analysis

Statistical analysis was performed using the SPSS version 15.0 statistical software (IBM Corp., Armonk, NY). Categorical variables were presented as frequency and percentage, and numerical variables as mean±SD. The Chi-square was used to test the association between categorical outcome variables. Differences were considered statistically significant with $p<0.05$.

Ethics Committee Approval

Erzurum Regional Training and Research Hospital Clinical Researches Ethics Committee approval was obtained for the study on February 17, 2020 (number: 2020/04-55).

RESULTS

From the records of our hospital's transfusion center, it was determined that 61.636 units of blood and/or blood components were used in 9334 patients between January 2018 and January 2020. Blood and blood components used consisted of 18.015 units of erythrocyte suspension, 4099 units of platelet suspension, 39.153 units of

Table 1. Frequency of acute transfusion reactions

Acute transfusion reactions	Erythrocyte suspension (n)	Whole blood (n)	Fresh frozen plasma (n)	Platelet suspension (n)	Total (n, %)
Total transfusions	18.015	156	39.153	4099	61.636
Mild allergic reactions	11	0	14	1	26 (0.042)
Pediatric	7	0	0	1	
Adults	4	0	14	0	
FNHTR	21	0	2	0	23 (0.037)
Pediatric	4	0	1	0	
Adults	17	0	1	0	
Anaphylactoid reaction	1	0	0	0	1 (0.001)
Pediatric	0	0	0	0	
Adults	0	0	0	0	
Hypotensive reactions	1	0	1	2	4 (0.006)
Pediatric	0	0	0	2	
Adults	1	0	1	0	
TRALI	0	1	0	0	1 (0.001)
Pediatric	0	1	0	0	
Adults	0	0	0	0	

FNHTR: Febrile non-hemolytic transfusion reaction; TRALI: Transfusion-related acute lung injury.

FFP, 156 units of whole blood, and 213 units of cryoprecipitate. It was determined retrospectively that ATR developed in 53 of the transfusion patients from the blood products administration and side effect reporting forms of the Transfusion Center Hemovigilance unit of our hospital. It was observed that ATR developed once in 51 patients, 2 times in two patients (Table 1).

In our study, the frequency of ATR was 0.09%, the frequency of mild allergic reactions was 0.042% (26/61.,636), the frequency of FNHTR was 0.037% (23/61.636), the frequency of hypotensive transfusion reaction was 0.006% (4/61.636), the frequency of anaphylactoid reaction was 0.001% (1/61.636), and TRALI frequency was found to be 0.001% (1/61.636). The frequency of ATR types among all transfusion reactions; mild allergic reaction frequency was 47.3% (26/55), FNHTR frequency 41.8% (23/55), hypotensive transfusion reaction frequency 7.3% (4/55), anaphylactoid reaction frequency 1.81% (1/55), and the frequency of TRALI was found to be 1.81% (1/55). The frequency of ATR is shown in Table 1 according to the type of blood product used. The most common types of ATR were mild allergic reactions and FNHTRs (Table 1). Acute hemolytic reaction did not occur in any of the patients.

According to the hemovigilance records of our hospital, the clinical findings of a patient who developed TRALI occurred at the 15th min of the transfusion, and the clinical findings of a patient who developed anaphylactic reaction at the 20th min of the transfusion, and the clinical findings of four patients who developed hypotensive transfusion reaction at 31.2±22.1 min, and cases reported to develop mild allergic reaction at 57.9±45.2 min, and the cases with FNHTR developed in 43±37.4 min of the transfusion (Table 2). Table 2 shows the ATR occurrence times according to the reaction types.

Of the patients who developed ATR, 18 were female and 35 were male, and their ages ranged from 1 month to 85 years (Fig. 1). Although the frequency of ATR in childhood tends to be more common in boys, there was no statistically significant difference between females and males in all patient population (p=0.762).

The frequency of ATR seen in surgical services in our hospital (ATR number/total transfusion number) was 0.46% (10/2159), 0.24% (7/2915) in child intensive care units, 0.21% (11/5014) in hematology and oncology, 0.21% (3/1380) in pediatrics, 0.15% (6/3846) in the burn unit, 0.09% (9/9225) in internal medicine, and 0.02% (9/37.097) in intensive care units (Table 3).

TABLE 2. The time of occurrence of acute transfusion reactions

Acute transfusion reaction types	Number of cases	Reaction development time (minute) (mean±SD) (min–max)
FNHTR	26	43±37.4 (5–180)
Allergic reaction	23	57.9±45.2 (3–180)
Hypotensive transfusion reaction	4	31.2±22.1 (10–55)
Anaphylactoid reaction	1	20
TRALI	1	15

FNHTR: Febrile non-hemolytic transfusion reaction; TRALI: Transfusion-related acute lung injury.

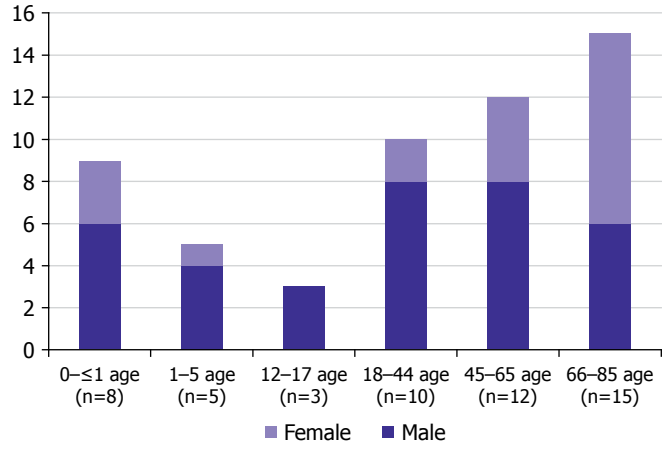

FIGURE 1. Age and gender distribution of patients with acute transfusion reaction.

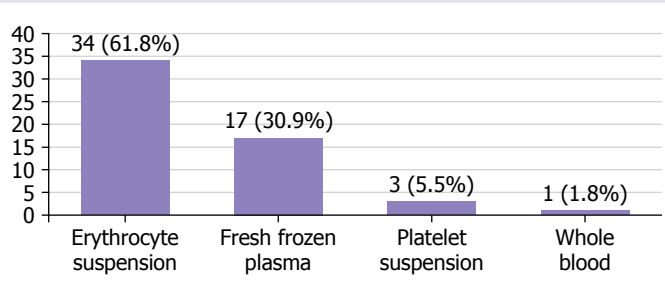

FIGURE 2. Frequency of undesirable reactions by blood component type.

Fifty-five ATRs were found to be associated with 61.8% erythrocyte suspension, 30.9% with FFP, 5.5% with platelet suspension, and 1.8% with whole blood. In Figure 2, the distribution of ATRs according to the types of blood products is given.

TABLE 3. ATR frequency distribution of units

Units	Percentage	ATR/total transfusion (n)
Surgical services	0.46	(10/2159)
Child intensive care units	0.24	(7/2915)
Hematology and oncology	0.21	(11/5014)
Pediatrics	0.21	(3/1380)
Burn unit	0.15	(6/3846)
Internal medicine	0.09	(9/9225)
Intensive care units	0.02	(9/37097)

ATR: Acute transfusion reactions.

DISCUSSION

Transfusion of blood and/or blood components is a special tissue transplant. Therefore, unnecessary transfusion of blood and blood products should be avoided. The monitoring of the process from the preparation of blood products to their administration to the recipient and the unwanted and unexpected reactions that develop in the recipient is of vital importance. In our hospital, 61.636 units of blood and blood components were transfused in 2 years, and 55 (0.09%) ATRs were reported. The incidence of ATR has been reported between 0.032% and 21.3% in the literature [8–14]. In general, the frequency of ATR has been reported more frequently than in our study [8–11, 13]. We believe the reason for this is that transfusion reactions that do not require medical treatment may be underreported due to the high workload of health-care professionals in our country.

In our study, mild allergic reactions (47.3%) and FNHTR (41.8%) were detected as the most common ATR in accordance with the literature. Similar to our study, Sharma et al. [15] allergic transfusion reactions were 65.6%, Kumar et al. [12] 55.3%, Venkatachalapathy et al. [16] 50%, Payandeh et al. [17] 49.2%, Borhany et al. [10] 46.8%, and Sidhu et al. [9] reported that they found it more frequently than FNHTR as 42.2% (Table 4). It has been reported that the incidence of FNHTRs can be reduced significantly with the use of leukocyte-reduced products [18]. Most of the patients with a mild allergic reaction reported having maculopapular rash - flushing, itching, and urticarial rash. In the study conducted by Adkins et al. [19], urticaria, itching, rash, and flushing were reported as the most common minor allergic reaction symptoms and signs, similar to our study. However, one of our patients died due to the development of a serious anaphylactoid reaction at the 20th min of the erythrocyte suspension (Table 2). Although TRALI and TACO have been reported as the most mortal type of reaction among ATR [20], ATR which resulted in our case of mortality was an anaphylactoid reaction. Hypotensive transfusion reactions are seen after conditions that lead to increased bradykinin production, such as the use of negatively charged leukocyte filters, the use of ACE inhibitors, and abnormal bradykinin metabolism. Negatively charged leukocyte filters can activate the kallikrein-kinin system by binding factor XII. Activating factor XII separates pre-kallikrein into kallikrein, while kallikrein degrades high-molecular-weight kininogen, causing bradykinin release. Bradykinin binds to endothelial cells and causes hypotension by vasodilation. Bradykinin is rapidly inactivated by the ACE. Since ACE is inhibited in patients using ACE inhibitors, these patients are more prone to these reactions [21, 22]. We supply blood products with leukocyte displacement to all our patients through the Red Crescent. Four of our patients were using ACE inhibitors, and two of them used leukocyte-reduced thrombocyte suspension, one of them used leukocyte-reduced erythrocyte suspension. Similar to the study of Payandeh et al. [17], the hypotensive transfusion reaction was reported in four patients (Table 4).

Table 4. Transfusion reactions in comparison to other studies

Name of the study, source number	Mild allergic reactions (%)	FNHTR (%)	Anaphylactoid reaction (%)	Hypotensive reactions (%)	Hemolytic reaction (%)	TRALI (%)	TACO (%)	Bacterial contamination (%)	Pulmonary embolism (%)
Current study (n=55)	47.3	41.8	1.81	7.3	NR	0.81	NR	NR	NR
Sharma et al. [15] (n=32)	65.6	28.1	3.1	NR	NR	NR	NR	NR	3.1
Borhany et al. [10] (n=32)	46.8	28	3.1	NR	6.2	3.1	NR	12.5	NR
Sidhu et al. [9] (n=90)	42.2	36.6	1.1	NR	12.2	1.1	4.2	2.2	NR
Gente et al. [25] (n=128)	31.3	46.7	4.3	NR	5.83	2.18	2.9	NR	NR
Ramanathan et al. [24] (n=109)	39.1	52.7	3.6	NR	0.9	0.9	1.8	NR	NR
Payandeh et al. [17] (n=55)	49.2	37.2	NR	6.8	NR	NR	NR	NR	NR
Bassi et al. [26] (n=100)	24	73	NR	1	1	NR	NR	1	NR
Khalid et al. [27] (n=171)	33.9	41.9	0.47	1.4	1.8	NR	NR	0.9	NR
Venkatachalapathy et al. [16] (n=45)	50	43.75	NR	NR	NR	NR	NR	NR	NR
Kumar et al. [12] (n=195)	55.3	35.8	5.1	NR	2.5	0.5	0.5	NR	NR
Mafirakureva et al. [14] (n=212)	33.9	58.5	1.4	0.4	5.2	NR	NR	NR	NR

FNHTR: Febrile non-hemolytic transfusion reaction; TRALI: Transfusion-related acute lung injury; TACO: Transfusion associated circulatory overload; NR: Not reported.

Although TRALIs are noted mostly after plasma transfusion [23] in the literature, in our study TRALI developed after use of whole blood due to the complication of bleeding in one patient after congenital heart disease operation. The frequency of TRALI (1.81%) was similar to Sidhu et al. [9], Ramanathan et al. [24], and Gente et al. [25] (Table 4). This patient had congenital heart disease and after being operated on, the patient was diagnosed with TRALI due to developing a sudden respiratory distress in the 15th min of whole blood infusion in the post-operative period and bilateral infiltrates that did not occur before on chest radiography. While the patient had congenital heart disease and surgery to address this before transfusion, cardiogenic edema was excluded due to sudden onset of these findings after transfusion, the absence of any respiratory distress, and the absence of infiltration on chest X-ray before transfusion.

In our study, 61.8% of all transfusion reactions were reported to be associated with erythrocyte suspension, 30.9% with TDP use, and 5.5% with platelet suspension (Fig. 2). In the study conducted by Ramanathan et al. [24], the percentage of these parameters was 80%, 11.8%, and 6.4%, respectively. Bassi et al. [26] reported that ATR was seen after use of erythrocyte suspension 76%, whole blood 15%, and platelet suspension 8%, Khalid et al. [27] platelet suspension 7%, erythrocyte suspension 87.7%, and FFP 5%, Payandeh et al. [17] erythrocyte suspension 45.7%, FFP 30.5%, and platelet suspension of 20.3%, Sidhu et al. [9] reported that ATR was seen after use of whole blood 47%, erythrocyte suspension 36.1%, FFP 6.3%, and platelet suspension 10.6%. We believe that the reason why ATRs were found to be associated with most common erythrocyte suspension in our study is that our hospital is an "Eastern Anatolia Regional Hospital" in Turkey. This can be explained by the fact that the number of erythrocyte suspensions used is higher than other blood products because of the high number of admission or referral of patients with acute bleeding or in need of surgery, thus, surgical units, intensive care units, burn unit, and palliative care.

The limitations of our study include the retrospective design and single-center experience.

There are a limited number of studies evaluating transfusion reaction frequency and reaction types from our country. The most frequently reported undesirable ATR in our hospital were mild allergic reactions and FNHTR. The most common side effect reported was the use of blood product type erythrocyte suspension. The units that reported ATR most frequently were surgical services and hematology/oncology units. It is important to monitor transfused patients for undesired reactions during and after the transfusion, to determine the frequency, type, and risk factors of the transfusion reactions and to take safety measures in this regard. In addition, we think that each center knows the risk factors in terms of its own transfusion reaction, keeps the records of the Hemovigilance Unit complete, and ensures that all transfusion reactions are diagnosed and followed, not only those requiring immediate medical intervention.

Ethics Committee Approval: The Erzurum Regional Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 17.02.2020, number: 2020/04-55).

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Authorship Contributions: Concept – YDK; Design – YDK; Supervision – YDK; Fundings – YDK, DE; Materials – YDK, DE; Data collection and/or processing – YDK, BA, DOY; Analysis and/or interpretation – YDK, KA; Literature review – YDK; Writing – YDK; Critical review – YDK, KA.

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