Journal of Shahrekord University of Medical Sciences
doi: 10.34172/jsums.864 2024;26(2):x-x http://j.skums.ac.ir

Review Article

Risk of Transfusion Complication: A Systematic Review of Iranian Literature

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Abstract

Background and aims: Injecting healthy blood on time can save patients' lives; on the other hand, delaying the start of transfusion or injecting unhealthy and wrong blood can cause fatal risks. This study aimed to survey the risks of transfusion events as a systematic review.

Methods: In this systematic review, the data associated with transfusion complications were collected by reviewing the literature published from 2001 to 2023 and indexed in various databases using related keywords. Then, the articles were included according to the inclusion and exclusion criteria. The collected data were recorded in Excel, and conclusions were drawn based on the available data.

Results: The findings of this study revealed that the most important complications in patients who had blood transfusion are alloimmunization against Rh antigens (mainly anti-E, anti-D, anti-C, and anti-c) and anti-Kell alloantibodies, especially in patients with thalassemia. Although some cases of ABO antigens and anti-human leukocyte antigen (HLA) were also reported, allergic and febrile non-hemolytic transfusion reactions (FNHTRs) occurred mainly in the Iranian population.

Conclusion: The results showed that the risks of blood transfusion generally include complications that may be preventable by better pretransfusion assessment and monitoring, and many of them can be prevented by strengthening the hemovigilance system and improving the equipment and skills of the staff. Consequently, most transfusion reactions can be prevented and reduced.

Keywords: Haemovigilance, Adverse transfusion reactions, Human errors

Received: February 28, 2023, **Accepted:** July 25, 2023, **ePublished:** March 26, 2024

Introduction

Injecting healthy blood on time can save patients' lives; on the other hand, delaying the start of transfusion or injecting unhealthy and wrong blood can cause fatal risks. Currently, blood transfusion is considered an organ transplant (1,2). Despite establishing the haemovigilance system in Iran, the complications of blood transfusion have not decreased substantially (3). About more than 2 million units of 2017 blood and blood products are injected annually in Iran. However, despite all the advances in the blood transfusion chain technology and the establishment of the haemovigilance system in medical centers and hospitals, we still observe numerous complications of blood transfusion (4). Accurate and timely reporting of complications through the haemovigilance system with careful monitoring of all stages of the blood transfusion chain prevents the occurrence and repetition of transfusion complications (5). Complications of transfusion are related to immune responses such as allergy, fever, hemolytic reaction, transfusion-associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI) or non-hemolytic transfusion reaction such as sepsis, which can be acute (less than 24 hours) or delayed (over 24 hours). The severity of the symptoms depends on the type and number of the product and the patient's condition (6).

The evaluation of risks of transfusion events can be used in the hemovigilance system, which is an organized system of surveillance in all processes, and the transfusion is intended to assess data to inhibit the appearance or recurrence of adverse complications associated with the use of blood products (7, 8). As such, this systematic review study aimed to survey the risks of transfusion events.

Materials and Methods

We reviewed the scientific articles indexed in electronic databases, published from 2001 to 2023. The search date was done on August 7, 2023. We searched several databases such as PubMed, Scopus, Web of Science, Google Scholar, IranDoc, IranMedex, Magiran, and Medilib for Persian and English publications. In addition, we used keywords such as complications of transfusion, hemolytic reaction, transfusion allergic reaction, risk of transfusion, blood transfusion reactions, blood transfusion side effects, and Iran. Dara were collected from the results of the selected documents.

Studies that investigated blood complications in Iran were included in this survey. The cases whose exact cause of the complication was unclear or overlapped with other complications of the disease and publications published in a language other than Persian and English were excluded from the study.

The studies included in this systematic review were screened according to the review of the authors, and in case of disagreement between them, the disputed issue was settled down through discussion, and a decision was made regarding the inclusion or exclusion of the discussed study.

Mild allergic reactions, severe allergic and anaphylactic reactions, and febrile non-hemolytic transfusion reactions (FNHTRs) mainly occurred due to red blood cell (RBC) injection in women and those aged less than 20 years. All mild allergic patients recovered completely, and five cases of severe allergic reaction and two cases of febrile reaction had a total disability (Table 1).

Results

As Figure 1 illiterates, 38 studies were screened and included in this systematic review (6,11-47). Several studies were excluded as they were irrelevant to the aim of this study (48-50), and the full text of four studies was not available (51-54).

All the conducted records were observational design, and most of the included studies were conducted on thalassemia patients. The results revealed that the risks of blood transfusion generally include complications that may be preventable by better monitoring. Most studies focused on alloimmunization and alloantibodies (Table 2).

Discussion

This study showed that the most important complications in blood transfusion patients are alloimmunization against Rh antigens (mainly anti-E, anti-D, anti-C, and anti-c), ABO alloimmunization, and anti-Kell alloantibodies. In addition, allergic reactions and febrile reactions such as FNHTR were also reported as blood transfusion complications in Iran. Antigens against different types of hepatitis were also reported in the included studies. These data were mainly reported based on observational studies or data extraction-Kellan1 case moving anti-Rh system. red blood cell (RBC) transfusions are frequently given, exclusively in the case of "ABO" and RhD phenotypic compatibility between the recipient and the donor; however, other erythrocyte antigens have been linked to the development of alloantibodies or the so-called alloimmunization process. Exposure to the donor erythrocyte antigens, which are absent in the recipient, is the primary prerequisite for the development of alloimmunization. These antigens can start the formation of antibodies against erythrocytes, resulting in potentially serious transfusion reactions (55-57). In line with the results of this study, another review study also indicated that anti-Kell and anti-Rh systems, specifically anti-E, anti-D, anti-C, and anti-c, are the most common alloantibodies (58). Darvishi et al, in their study, indicated that there was no decrease in the prevalence of alloimmunization among Iranian thalassaemic patients during 1994-2013. Despite D antigen being found in pre-transfusion tests, our population had a high rate of anti-D. It highlights the significance of further research into the data on D variants (59). Another review study

Table 1. Different types of transfusion reactions (6,9,10)

Type of Reaction Definition	Definition
Mild and anaphylactic allergic	Associated with hyperimmunologic reaction to a foreign protein in the blood product. An adverse reaction that is more severe than a mild allergic reaction. This can sometimes happen in people with IgA deficiency who develop alloantibodies to IgA and then receive blood products, including IgA.
TRALI	It results from antibodies in the donor ingredients (human neutrophil antigen or human leukocyte antigen) reacting with antigens in the recipient. Lack of ALI before transfusion and onset of ALI during or within six hours of transfusion cessation with hypoxemia (PaO2/FiO2 300 mmHg and oxygen saturation).
TACO	It happens when the volume of the transfused ingredients causes acute respiratory distress (e.g., orthopnea, dyspnea, and cough). Furthermore, evidence of a positive fluid balance, an elevated BNP, radiographic evidence of pulmonary edema, evidence of left heart failure, and an elevated CVP within 12 hours of the transfusion's termination are observed in hypervolemia results.
AHTR	AHTR is caused by ABO incompatibility. Developed during or within 24 hours of the end of the transfusion, along with the new onset of any of the following signs or symptoms: chills/rigors, back/flank pain, fever, hypotension, hematuria, oliguria/anuria, epistaxis, renal failure, DIC, pain and/or oozing at the IV site, positive DAT for anti-IgG or anti-C3, and positive elution test with alloantibody.
HyTR	HyTR is known as the sudden onset of hypotension right after the start of the transfusion and typically goes away when the transfusion stops. Without any indication of other conditions causing hypotension, hypotension (30 mm Hg drop and 80 mmHg systolic blood pressure) happens during or within an hour of the transfusion ceasing.
TAD	TAD is defined as acute respiratory distress that occurs within 24 hours of the end of a transfusion but does not meet the criteria for an allergic reaction, TACO, or TRALI.
TTI	Within 4 hours of a transfusion, TTI can develop with fever, chills, hypotension, and other symptoms indicative of a bacterial infection.
Alloimmunization	An immune response to foreign antigens following exposure to tissues or cells with different genetic make-up is known as alloimmunization. Although alloimmunization occurs naturally during pregnancy, it frequently happens due to a blood transfusion and/or transplant, which is undesirable.

Note. TRALI: Transfusion-related acute lung injury; TACO: Transfusion-associated circulatory overload; FNHTR: Febrile non-hemolytic transfusion reaction; AHTR: Acute hemolytic transfusion reaction; HyTR: Hypotensive transfusion reaction; TAD: Transfusion-associated dyspnea; TTI: Transfusion-transmitted infection; ALI; Acute lung injury; BNP: Brain natriuretic peptide; CVP: Central venous pressure; DIC; Disseminated intravascular coagulation; DAT: Direct antiglobulin test.

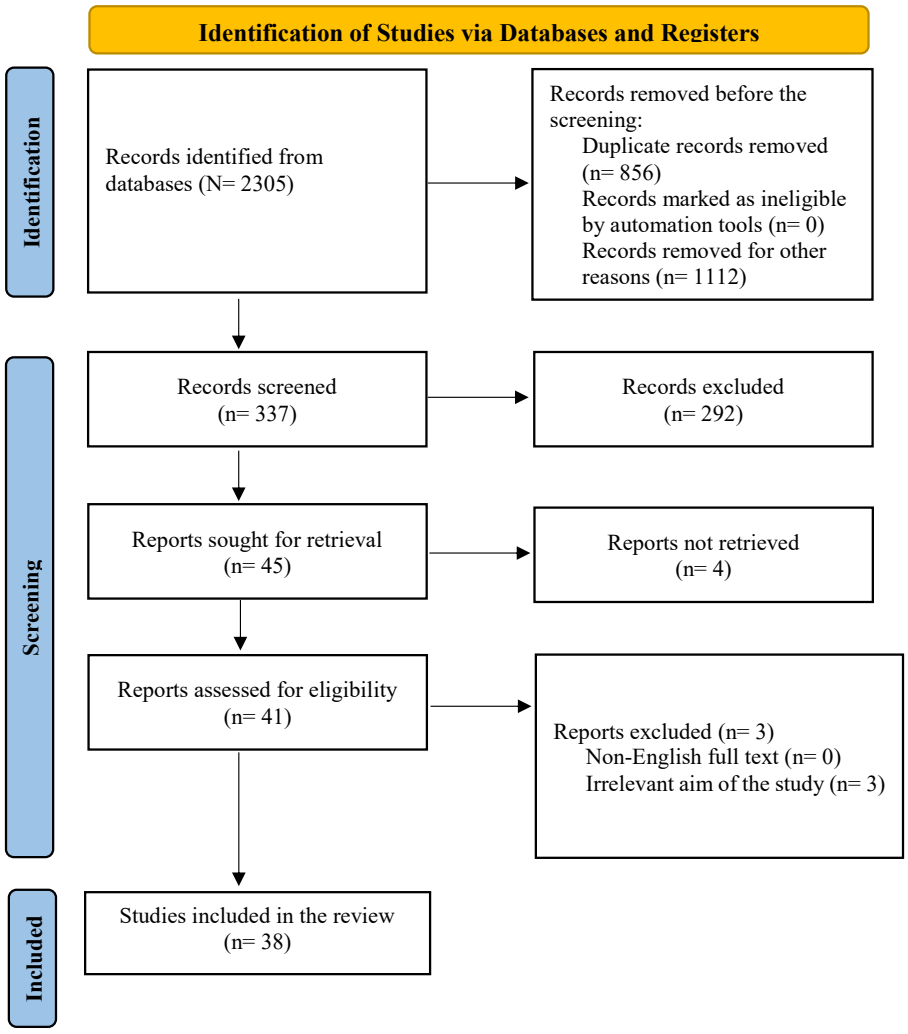

Figure 1. Flowchart of the studies included in this systematic review

in 2012 revealed that the current blood donation rate in Iran is approximately 94% in males between the ages of 25-35, with female donors making up less than 6% of the total. Blood transfusion organization conducts extensive screening of all donated blood for serious transfusion-transmittable infections such as hepatitis B virus (HBV), human immunodeficiency virus (HIV), hepatitis C virus (HCV), and syphilis. In 2011, there were zero percent cases of HBsAg, zero percent of HCV cases, and zero percent of HIV cases in donated blood in blood transfusion organizations (60).

Unwanted complications of blood transfusion are categorized into non-preventable side effects such as post-transfusion purpura, transfusion-transmitted infection, transfusion-associated dyspnea, and acute transfusion reaction. Some complications can be prevented with monitoring. Complications such as alloimmunization, hemolytic transfusion reaction, TRALI, TACO, and transfusion-associated graft vs host disease belong to this category. Some of them are caused by errors such as avoidable, delayed, and under transfusion, anti-D errors, handling and storage errors, and incorrect transfused blood components (5,29).

However, in Iran, with the implementation of the COVID-19 crisis system and consistent coordination between blood transfusion centers throughout the provinces, and compliance with health protocols during the pandemic, the number of blood donations increased (61). Some physicians in Iran injected the fresh frozen plasma of recovered COVID-19 patients into critical COVID-19 patients. Three cases of death were reported, but not confirmed probably due to complications related to the coronavirus, and several cases of recovery were reported (62,63).

When blood transfusions are done properly, it is extremely safe. The observation of transfusion-transmitted infection in heavily transfused thalassemic and hemophilia patients led to concerns about blood transfusion safety to some extent (64). Hemovigilance is considered a recent advancement in the safety of blood transfusion. It is described as surveillance procedures that cover the whole blood transfusion chain from the collection to the follow-up of its recipients to gather and analyze data on unexpected or undesirable events resulting from the therapeutic use of labile blood products and prevent complications in the blood transfusion process (5,65). Hence, the objectives of this system are to identify trends in adverse reactions and unwanted events,

Table 2. Characteristics of studies included in this systematic review

First author	Year	Setting	Sample size	Study population	Mean age	Male/ Female	Findings associated with transfusion reactions
Ahmadi (11)	2001	Kermanshah	142	β-Thalassemia	22.6	187/126	Alloantibodies were developed in 9.2% of the cases. The most alloantibodies were anti-Lua with 61.5% and anti-platelet with 23.1%
Eshghi (12)	2003	Zahedan	163	β-Thalassemia	14.42	96/67	No alloimmunization was seen in the studied group.
Rahgozar (13)	2005	Isfahan	52	β-Thalassemia	18.75	36/16	Alloimmunization included K (27.5%) (12.5%), CW, s, Fyb (5%), S, C, E, e, and M (2.5%) antigens.
Kiani (14)	2006	Lorestan	65	β-Thalassemia	17.63	35/30	Only one case (1.53%) had been alloimmunized.
Karimi (6)	2007	Shiraz	711	β-Thalassemia	NR	366/345	The most prevalent alloantibodies were anti-Kell (50%) > anti-Rh (D) (15.8%) > anti-Rh (E) (10.5%).
Azarkeivan (15)	2008	Tehran	441	β-Thalassemia	22.6	204/207	7 patients (1.6%) had a record of delayed hemolytic disorder, 25 patients (6.1%) developed allergy, and 41 (9.9%) indicated febrile transfusion reaction. Moreover, 369 (88.7%) were HBsAb positive, 117 patients (28.4%) were HCVAb positive, 80 (19.2%) were HBcAb positive, and 3 (0.7%) were HBsAg positive
Shamsian (16)	2008	Tehran	121	β-Thalassemia	19.56	55/66	Direct and indirect antiglobulin were indicated in 5 (62.5%) studied groups.
Ansari (17)	2009	Tehran	80	β-Thalassemia	13.8	37/43	88 patients (19.2%) had febrile reactions during the transfusion, 11.6% of patients had allergic reactions, and 11 patients (2.4%) had hemolytic reactions.
Sadeghian (18)	2009	Mashhad	313	β-Thalassemia	22.6	187/126	Patients showed anti-D (88.88), anti-C (33.3), and anti-E (11.1).
Azarkeivan (19)	2011	Tehran and Qazvin	835	β-Thalassemia	8.35	416/419	Anti-Kell was seen in 34 (33.7%) cases, anti-D in 11 (10.9%) cases, and anti-E in 10 (9.9%) cases.
Obeidi (20)	2011	Bushehr	90	β-Thalassemia	16.96	39/51	Alloantibodies were seen in 9 patients (10%) and 18% of anti-Kell cases.
Kosaryan (21)	2012	Sari	218	β-Thalassemia	19.6	100/118	47% of cases had at least one type of alloantibody, and 40% of patients indicated C, Cw, and Lea.
Yaghobi (22)	2012	Larestan	186	β-Thalassemia	36	80/106	Anti-E2-HGV was detected in 16 of 86 patients, and HCV antibodies were detected in 18 of 86 patients. In addition, HGV viremia was diagnosed in 13 of 86 patients.
Amin (23)	2013	Zahedan	385	β-Thalassemia	13.8	221/164	69 patients (17.9%) were alloimmunized (against Rh and Kell systems),
Mirzaeian (27)	2013	Zahedan	385	β-Thalassemia	22.5	221/164	21 patients (5.5%) indicated autoantibody, and the incidence of alloimmunization was 17.9% (Rh and Kell).
Ghorbani Ali-Abadi (24)	2013	Shiraz	3467	β-Thalassemia	45.4	2189/1298	0.8% of the patients had alloantibody and anti-Kell (23%), anti-E (15%), and anti-C (11%).
Keikhaei (25)	2013	Ahvaz	133	β-Thalassemia	17.5	66/67	Alloantibodies were seen in 25 (18.7%) patients, and 17 (12.7%) had autoantibodies.
Payandeh (28)	2013	Kermanshah	6238	β-Thalassemia	45	32/27	59 (0.94%) cases showed transfusion reactions. Allergic reactions which were revealed with various skin disorders, including rashes and pruritus (49.2%), FNHTR (37.2%), pain (6.8%), and hypotension (6.8%) were seen.
Tahannejad-Asadi (29)	2013	Ahvaz	70	β-Thalassemia	22.5	31/39	6 (8.6%) were detected as unexpected alloantibodies, 3 cases as anti-Kell, 1 as anti-E, and 1 as anti-D.
Khademi (26)	2013	Tehran	3092	Elective surgery	45.8	1114/1978	Alloantibodies were identified in 30 patients, and most of them were anti-E (20.59%), anti-Kell (23.53%), and anti-c (17.56%).
Gharehbaghian (30)	2014	Ardebil	1420	Elective surgery	43.2	842/578	The prevalence of alloantibody (anti-Kell, anti-E, and anti-c) was 0.92% (13 patients).
Azarkeivan (31)	2015	Multicenter (Tehran, Ghazvin, Karaj)	441	β-Thalassemia	14.4	234/207	Alloimmunization (anti-Rh antibodies, anti-Kell, anti-D, and anti-Colton) was found in 50 (11.3%) patients, 37 (74%) patients with one alloantibody, and 8 (16%) with two antibodies.

Table 2. Continued.

First author	Year	Setting	Sample size	Study population	Mean age	Male/ Female	Findings associated with transfusion reactions
Kasraian (32)	2015	Shiraz	741	β-Thalassemia	22.7	359/382	Acute transfusion reactions were seen as 0.06%, 0.11%, 0.10%, and 0.2%, respectively, from 2009 to 2012, which were included in FNHTR, mild, and severe allergic reaction
Vaziri (33)	2015	Yazd	100	β-Thalassemia	16.5	46/54	Only 4 cases (4%) were identified with alloantibodies (One was anti-C and anti-D, while three indicated anti-Kell).
Babaei (34)	2016	Zanjan	75	Blood donors	NR	73/2	Alloantibodies (against K, c, and antigens) were identified in the serum of 6 donors (8%).
Davari (35)	2016	Zanjan	49	β-Thalassemia	18.59	25/24	Alloimmunization was seen in 16.32% with 10 alloantibodies (Mostly against anti-Kell, anti-Rh, E, and c-antigens) identified in 8 patients.
Younesi (36)	2016	Tehran	240	β-Thalassemia	26.5	119/121	Alloantibodies in positive alloantibodies patients were 84.76% (89/105), most of which were anti-Kell and Rh, anti-E, and anti-D. Moreover, HLA antibodies were 65.7%.
Razjou (37)	2017	Tehran	3056	Hematooncological diseases	50	1987/1069	Symptoms of transfusion reaction were identified in 12 (0.4%) patients. Platelet, and septic transfusion reactions, found 3 positive blood cultures.
Eghbali (38)	2019	Markazi province	48	β-Thalassemia	12.5	26/22	13 cases (27.08%) had alloantibodies, 6 cases (12.5%) had autoantibodies, and 7 others (14.58%) had autoantibodies and alloantibodies
Homeirani (39)	2019	Mashhad	516	β-Thalassemia	18.5	245/271	Alloantibodies were detected in 16 (3.1%), and autoantibodies were observed in 21 (4.1%) cases. 2 patients (12.5%) developed Anti-c, E, P1; Anti-c, E, K, and 1 case (6.25%) developed 2 antibodies (anti-D, C), and 4 cases (25%) Anti-D, 3 (18.75%) anti-Kell, 2 (12.5%) Anti-E, 2 (12.5%) Anti-C, 1 (6.25%) Anti-Jka; and 1 (6.25%) Anti-Jkb
Sarihi (40)	2020	All provinces	480	β-Thalassemia	29	187/239	Antibodies against E and D antigens were seen in all provinces. Alloantibody anti-Kpa was mostly detected in the western region, anti-E was most prevalent in the southeastern region, and anti-Kell antibody reached 37.7% in the western area.
Amiri (41)	2021	Hamadan	116	Blood recipients patients	23.47	36/80	Allergic reactions were the most prevalent complication in 63 cases (53.4%), followed by FNHTR in 28 cases (24.1%).
Ebrahimisadr (42)	2021	Tehran	184	β-Thalassemia	NR	66/118	116 (63%) patients had alloimmunization, and most of them (12) were anti-Kell (13%), 11 anti-D (5.98%), and 10 anti-E (5.4%).
Hashemzadeh (43)	2022	Tabriz	308	Heart surgeries patients	54.34	296/12	None of the patients indicated hemostatic complications such as cardiac arrhythmia or hemodynamic instability.
Kasraian (44)	2022	Shiraz	650	β-Thalassemia	21.28	322/328	The most prevalent alloantibodies were anti-Kell (50%), anti-D (26%), and anti-E (15.4%).
Seirfar (45)	2022	Kerman	95	Blood recipients patients	NR	49/46	148 (0.92%) patients with blood complications were observed.
Koochakzadeh (46)	2023	Tehran	195	β-Thalassemia	21.37	100/95	The incidence of alloantibody was 21.88% (6.73-37.02) in Rh+and 15.34% (9.75-20.93) in Rh- patients. Moreover, the prevalence of alloantibody was 26.67% in blood type AB, 13.46% in blood type A, 14.29% in blood type B, and 17.44% in blood type O.
Mobasheri (47)	2023	Birjand	68	β-Thalassemia	13.67	35/33	The alloimmunization was 2.9%, and the most prevalent alloantibodies were anti-Rh systems (1 case) and anti-Kell (1 case).

Note. NR; Not reported; HBsAb: Hepatitis B virus surface antibody; HCVAb: Hepatitis C virus antibody, HBcAb; Hepatitis B core antibody total; HBsAg: Hepatitis B surface antigen; Anti (D, C, E): Antigens (D, C, E); HGV: Hepatitis G virus; FNHTR: Febrile non-hemolytic transfusion reaction; HLA: Human leukocyte antigen.

which will assist the compilation of instructions and transfusion policy, identify practice-related development areas and research, increase the awareness of transfusion risks, serve as an early warning system for new side-effects, and enhance patient safety during transfusion (5). Avoiding unnecessary blood transfusions and upholding a transfusion-restrictive strategy are the best ways to prevent transfusion reactions. Furthermore, the hemovigilance reporting system should be contacted if any symptom appears within 24 hours of a blood transfusion and is thought to be a transfusion reaction. Early detection, prompt interruption of the transfusion, early consultation with a hematologist and even an ICU section, and fluid resuscitation are all necessary to manage

blood transfusion reactions (66).

The studies' small sample size, limitations in investigating allergic reactions and infectious complications of blood transfusion, and lack of studies on different populations were the limitations of the conducted studies. Moreover, most studies focused on alloimmunization. This is probably due to the low number or absence of other complications in patients with thalassemia and other blood recipients.

Conclusion

This study revealed that the most important complications in patients with blood transfusion are alloimmunization against Rh antigens (mainly anti-E, anti-D, anti-C, and anti-c) and anti-Kell alloantibodies, especially in patients with thalassemia. However, some cases of ABO antigens and anti-human leukocyte antigens were also reported, so most transfusion reactions can be prevented and improved by accurate monitoring. For safe transfusion when setting up the transfusion, it is important to consider safety donation (Transfusion is considered an organ transplant), appropriate transfusion decision and documentation, focusing on patients, effective communications, training, and increasing knowledge of personnel involved in transfusion. Therefore, unnecessary blood transfusions should be avoided, and by increasing the knowledge and information, disclosure of the relevant information by staff, and developing the haemovigilance system, the statistics of complications can be reported in real terms. The application of advanced technology in blood transfusion screening, donor selection, voluntary donations, and sepsis during blood transfusion is crucial to precipitating the transmission.

Authors' Contribution

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Supervision: Noormohammad Arefian and Abolfazl Azizi Farsani.
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Writing–review & editing: Faranak Behnaz and Abolfazl Azizi Farsani.

Competing Interests

The authors declare no conflict of interests.

Ethical Approval

Not applicable.

Funding

None.

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