

Late Complications of Allogenic Stem Cells Transplantation in Leukaemia

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Abstract

BACKGROUND: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) can cure leukaemia. However, long term complications of post transplantation interfere with the patients' full recovery. The objective of this review was to identify the various long term complications and to assess their individual prevalences.

METHODS: Electronic databases including PubMed, Google Scholar and Cochrane were searched for years 2004–2017. The keywords used were leukaemia, allogenic stem cell transplantation, prevalence, side effects, long term, delayed, adverse effects, complications and outcome.

RESULTS: A total of ten articles were included for analysis. There were 5 prospective studies, 3 retrospective studies and 2 cross sectional studies. A total of 40,069 patients, (20,189 males and 17,191 females) participated in these 10 studies. The gender of 2689 patients were not disclosed. Most common late complications and prevalence were chronic graft versus host disease (43% at 5 years post HSCT), secondary tumor (21% at 20 years post HSCT), hypothyroidism (11% at 15 years), bronchiolitis obliterans (9.7% at 122 days), cardiovascular disease (7.5% at 15 years) and avascular necrosis (5.4% at 10 years). The prevalence of azoospermia was 71.1% and depression, 18%. For the latter two conditions no time limit was available. Follow up duration ranged from 2 years till 30 years post HSCT.

CONCLUSION: While allogenic stem cell transplantation is an effective cure for leukaemia, the procedure is associated with complications that can have their onset many years after the procedure.

Keywords Allogenic stem cells · Chronic graft · Late complications · Leukaemia

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1 Introduction

About 50,000 haematopoietic stem cells transplantations (HSCT) are performed in the world every year and the number of patients that will undergo this procedure is expected to rise. Allogenic haematopoietic stem cell transplantation is becoming more and more common with each passing day [1, 2].

This type of transplantation is a rather astonishingly effective remedy available for both cancerous and non-cancerous diseases affecting the bone marrow [3]. This procedure can be performed for both non-cancerous conditions such as severe aplastic anemia as well as cancerous

conditions such as leukaemia, myelomas and lymphomas, both Hodgkins and Non Hodgkins.

Patients have been followed for up to 30 years post transplantation procedure and have actually been found to be cured of leukaemia [3]. Improvements in the treatment of the post-transplant patient has led to better survival rates after this procedure. Although recipients of allogenic HSCT enjoy remission and control of the leukaemia, being either acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), acute lymphocytic leukaemia (ALL) or chronic lymphocytic leukaemia (CLL), it may not be associated with the return to healthy baseline levels of pre-disease state [3]. The complications of the procedure experienced by survivors is definitely substantial and impacts their health and function. Escaping death because of the disease is no longer a concern but just the beginning of a whole host of possible problems [3]. For resumption of health, physical and physiological normality should be the end point that the clinician should aim for.

Nivision et al. [4] from Australia elicited that the patient's survival was found to be 99.5% of the normal population 10 years after HSCT. It has been highlighted that those living 5 years after allogenic HSCT without any recurrence had a high chance of surviving a further 15 years although death rate remained higher than the rest of the population [4]. Current papers state that death post HSCT is due to other malignancies, recurrent disease attributed to immunocompromised health, infections such as toxoplasmosis, chronic GVHD, lung, heart and vessel problems [5]. Infections frequently occur in the acute post-transplant period due to not just bacteria, but viruses and fungi as well.

Allo-HSCT patients had twice the chance than their immediate relatives to develop a chronic health condition and if they had cGVHD, they were 4.7 times more likely to develop a condition that could lead to death [5].

Information regarding the complications of HSCT is heterogenous. Information needs to be integrated so it can be transplanted into practical care for the patient. The clinician needs to understand the complications to initiate appropriate and a precise management pertaining to the care of the patient. The objectives of this review paper are to identify and understand the complications pursuant to allogenic stem cell therapy in leukemia patients, mostly focusing on adults, to assess the prevalence of these side effects.

The term long-term refers to 2 years and more post HSCT. Previous studies have described complications arising 2 years post transplantation as late onset or delayed [3].

Chronic side effects focused on in this structured literature review include graft versus host disease (GVHD), immune system disruption, secondary cancers [3]. Data on

other side effects were also collected in this review. Post-transplant allogenic patients usually enjoy fair health. However, this procedure may be associated with numerous complications for some patients due to side effects that occur after 2 years. Data about the complications in the literature is varied and conflicting, hence the clinician needs to identify and integrate this information. The present study embarked to answer the following questions:

What the side effects associated with allogenic stem cells in the treatment of leukaemia are and how prevalent these side effects are. This study will be beneficial to both the doctor and the patient. The results from this study might be helpful for doctors to implement appropriate strategies to either prevent or manage the side effects of allogenic HSCT. On the other hand, outcome of this study might be useful as educational materials for patients to be more aware of the complications of HSCT.

2 Materials and methods

The type of study was as a structured literature review. The inclusion criteria included patients who had allogenic transplantation performed as treatment for leukaemia. More than half the sample must have primary disease as leukaemia. It must also be either a clinical trial (case control, cohort, randomized control trial) involving delayed adverse effects regarding allogenic stem cell transplantation. The literature had to be in English and involve only human subjects. The papers should have been published between 2004 and 2017. Full text must be available.

The exclusion criteria were allogenic stem cell transplantations for non-malignant conditions as the primary disease and less than 2 years follow up post-transplant. A preliminary search using electronic databases and articles were searched on online databases using the keywords separately to ensure as many studies as possible were assessed. Relevant papers on the reference list of the viewed papers and other papers citing the viewed papers were also searched and reviewed. Refined search and Literature Selection Abstracts of the articles with titles relating to the study topics were viewed and relevant articles were downloaded for references. Literature selections was done based on inclusion and exclusion criteria. The keywords were leukaemia, allogenic stem cell transplantation, prevalence, side effects, long term, delayed, adverse effects, complications and outcome. The journal search was conducted at Pubmed, Cochrane and Google Scholar. Abstracts of the articles retrieved from the database search were reviewed carefully. Those articles that were clearly not eligible for inclusion criteria were left out. The selected list was discussed with the supervisor and conflicts were resolved after much discussion.

3 Results

Using different keywords, a total of 18,057 articles were retrieved. After reviewing the titles and abstracts, only 10 articles were relevance to the objectives of this review (Fig. 1). The full details of each selected article are summarized in Tables 1 and 2.

4 Discussion

A variety of complications have been reported in the 10 selected studies. These were included; GVHD, bronchiolitis obliterans avascular necrosis, cardiovascular disorders, azoospermia, secondary tumors, depression, and hypothyroidism. Table 3 and Fig. 2 schematically summarize the different steps that may be considered as risk factors for long term complications of allo-HSCT.

One of the important principles of a conditioning regimen is that reduced intensity conditioning has a better outcome compared to total body irradiation and is safer for those patients who are older and medically unwell [7, 8]. Using reduced intensity conditioning, where both low doses of chemotherapy and irradiation are used to destroy the host bone marrow, full destruction does not occur, instead a state of mixed chimerism exists whereby the host and donor cells co-exist. The benefit is due to the graft versus tumor effect [7, 8].

4.1 Graft versus host disease

Chronic graft-versus-host disease (cGVHD) is the most common late complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT) as stated by Hingman and Vogelsang [24]. In another study, a prevalence of 43% cGVHD after allo-HSCT was reported [6]. Our value seems to be lower than other published studies. A study by Mielcarek et al. [25] reported a much higher prevalence of 73%. Skert et al. [26] noted that 75% of patients developed cGVHD after allo-HSCT. Both acute and chronic GVHD are more common after PBSCT than BMT, and this may also be associated with lower rates of malignant relapse [27]. The magnitude of the transfused T cell load may explain the differences in cGVHD risk [27].

4.2 Secondary tumors

The prevalence of secondary tumors was 21% at 20 years and composed mainly of squamous cell cancer, sarcoma, melanoma and breast cancer. A very early study by Kolb et al. [28] that included more than 1000 patients transplanted before December 1985, showed that the incidence of secondary malignancies ranged from 3.5% at 10 years and 12.8% at 15 years, and this is 3.8-fold higher than that of an age-matched control population. This figure was recently updated and it showed that the incidence of secondary malignancies continued to increase with longer

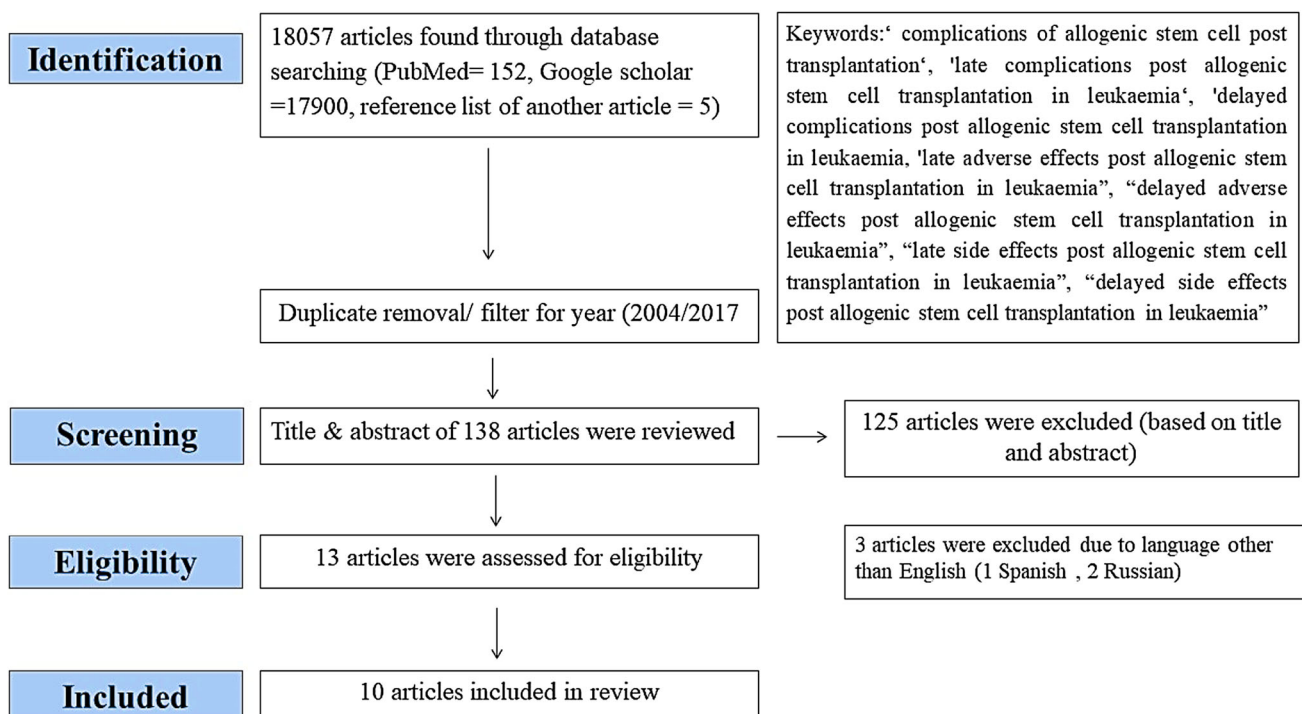


Fig. 1 Flow diagram of articles selection process

Table 1 Summary of articles on the different types of late complications of allogenic hematopoietic stem cell transplantation

Type of transplant	Source of stem cells	Donor characteristics	Follow up duration	Study design	No. of patient with leukemia/total (n)	Author/year
1. Allogenic	BM = 5 PBSC = 269	Related = 118 MUD = 156	3 years	Prospective	AML = 274 n = 274	Boglarka et al. [6]
2. Allogenic	N/A	Related = 2645 Mismatched related = 169 Unrelated = 494 Unknown = 29	25 years	Prospective	ALL = 1364 CML = 1060 n = 3337	Friedman et al. [7]
3. Allogenic	BM = 52 PBSC = 92	Related = 95 MUD = 49	2 years	Cross sectional	AML = 47 CML = 28 ALL = 18 n = 144	Yoshihara et al. [8]
4. Allogenic and autologous	N/A	N/A	9 years	Retrospective	AML-79 CML = 75 ALL = 51 n = 265	Tichelli et al. [9]
5. Allogenic and autologous	N/A	Allogenic Related = 627 Unrelated = 20	8.2 years	Retrospective	AML-335 CML = 230 ALL = 178 n = 1346	Campbell et al. [10]
6. Allogenic	BM = 28 PBSC = 11	Matched related = 32 MUD = 7 Mismatched related = 0	9 years	Cross sectional	AML-17 CML = 11 ALL = 4 n = 39	Rovo et al. [11]
7. Allogenic	BM = All patients	Matched related = 22,661	5 years	Prospective	AML-7461 CML = 7594 ALL = 5516 n = 28,874	Rizzo et al. [2]
8. Allogenic	N/A	Matched related = 102	10 years	Prospective	CML = 102 n = 102	Robin et al. [12]
9. Allogenic	BM 1319 PBSC 1096	Related Unrelated	30 years	Prospective	AML-852 CML = 498 ALL = 299 CMML = 17 n = 2415	Michelis et al. [13]
10. Allogenic	PBSC 1752 BM1337 Both PBSC& BM 29 Cord Blood 43 Unknown = 112	Syngenic 43 Matched related 2160 Mismatched related 159 Matched unrelated donor 808 Mismatched unrelated donor 103	2.8 years	Retrospective	AML-1110 CML = 636 ALL = 536 Other leukaemias = 43 n = 3273	Vajdic et al. [14]

BM bone marrow, PBSC peripheral blood stem cell, MUD matched unrelated donor

follow-up time compared with age-matched control population [29]. This fact is concordant with the findings in our literature review.

4.3 Bronchiolitis obliterans (BO)

BO occurred in 9.7% of the patients in the study by Boglarka et al. [6]. However, the prevalence of BO varied

Table 2 Specification of HSCT treatment

Age at HSCT	Type of complication and prevalence	Type of conditioning	Time of onset after HSCT	Characteristics of affected patients	Reference
Mean age 60 years (range 5–74 years)	cGVHD 5 years post HSCT 43%	RIC TBI 2Gy-28 TBI 2 Gy and FLU-246	Acute GVHD developed at a median of 42 days after HSCT	Had non T cell depleted BM Female donors PBSC mobilized SC History of aGVHD	Boglarka et al. [6]
Mean age 28.1 years	Breast cancer 1.56%	TBI-1070 noTBI-2162 Unknown-1050	12.5 years (5.7–24.8 years)		Friedman et al. [7]
Older than 55 years	Bronchiolitis obliterans 9.7%	MA = 96 RIC = 48	Median time from HSCT to onset of symptoms was 122 days	Symptoms of all 14 patients were cough, dyspnoea and wheezing	Yoshihara et al. [8]
Median age = 39 years	CVS problems 7.5% at 15 years post HSCT 22% at 25 years post HSCT	TBI = 229/265	N/A	More risk factors predisposed to more arterial events Older age at HSCT Undergoing allogenic HSCT Myeloid neoplasm as primary disease	Tichelli et al. [9]
Median age 34 years (range 7 month to 69 years)	3.7% developed avascular necrosis of bone (AVN) at post HSCT 5 years and 5.4% at post HSCT 10 years After allogenic matched related donor 5.57% developed AVN	TBI	N/A	Tend to be male Undergoing allogenic HSCT was a risk factor Exposure to the specific chemotherapeutic factors were not risk factors for AVN	Campbell et al. [10]
Median age 25 years	Azoospermia Oligospermia 71.8%	TBI = 33 RIC = 3	NA	Presence of cGVHD Presence of spermatogenesis was depicted by longer interval since HSCT	Rovo et al. [11]
Median age 27 years	SCC Sarcoma Melanoma Breast cancer 0.65% developed solid tumors	NO TBI	N/A	Occur more in males Twice as common compared to general population Young age at exposure predicts Non SCC occurrence Presence of cGVHD increased risk of tumor	Rizzo et al. [2]
Median age 37 years	Second cancer 21% at 20 years Cataracts 25% at 15 years Hypothyroidism 11% at 15 year Depression 18% Bone and joints 6.86% had late malignancies	TBI = 37	Cancers occur 106 months after HSCT. Cataracts occur 31 months after HSCT. Depression occurred more in those with chronic GVHD Osteonecrosis occurred more in female < 40 years.	No risk factors were identified	Robin et al. [12]

Table 2 continued

Age at HSCT	Type of complication and prevalence	Type of conditioning	Time of onset after HSCT	Characteristics of affected patients	Reference
Median age 43 years	Secondary malignancies 8.7% (209/2415) 58/209 developed non metastatic squamous cell carcinoma and basal cell carcinoma	TBI = 577 TBI 200–500 = 1240 TBI > 500 = 598	Median time of onset was 80 months	Older age at HSCT was a risk factor for secondary malignancies TBI dose, graft source and donor type did not have any significant impact on the development of secondary malignancies	Michelis et al. [13]
Median age 40.4 years	Secondary malignancies 79 second primary Cancers in 76 out of 3273 patients.	Limited field irradiation 2 Low dose TBI 762 High dose TBI 252 Unknown dose TBI 477	3.54 years after HSCT The risk of Melanoma was increased first year post HSCT Lip and tongue cancer elevated all time beyond the first year Soft tissue sarcomas were observed within 4 years Risk of brain, thyroid cancer and non-Hodgkins lymphoma was increased in the first year after HSCT	Risk of cancer was elevated in those who developed cGVHD Risk was not related to the source of the stem cells or whether radiation based conditioning was received	Vajdic et al. [14]

CVS cardiovascular system, TBI total body radiation, MA myeloablation, RIC reduced intensity conditioning, Gy gray, FLU fludarabine, SCC squamous cell carcinoma

Table 3 Risk factors for common late complications of allo-HSCT

Late complications	Risk factors
cGVHD	(a) Donor characteristics Matched sibling donor is better than matched unrelated donor and is in turn better than haplo-identical unmatched donor [15] Gender Males make better donors than previously pregnant females [16] (b) Graft source/characteristics Umbilical cord blood is associated with less risk due to immunological immaturity of T cells. [17, 18] PBSCT associated with higher risk than BMT [19] (c) Stem cells manipulation with T cell depleted better than T cell replete [20] (e) Cytomegalovirus status [21]
Secondary malignancies	(a) Prior therapy: chemotherapy/radiotherapy [22] (b) Conditioning regimen: myelo ablative/reduced intensity conditioning [22]
Organ toxicity	(a) Prior therapy: chemotherapy/radiotherapy [22]. (b) Conditioning regimen: myeloablative/reduced intensity conditioning [22] (c) Post-transplant immunosuppression with busulphan and methotrexate are risk factors for the development of BO [23]
Infertility	(a) Total body irradiation predisposes to infertility [22]

within a wide range as low as 2–3% in a study by Chien et al. [30], 5.5% in a study by Brandon et al. [31], and these values increase to 14% when BO is associated with cGVHD [31]. According to Brandon et al. [31] the presence of cGVHD is said to increase the risk tenfold. In the study by Brandon et al. the median time from procedure to

attaining the spirometric definition for bronchiolitis obliterans syndrome was 439 days (range 274–1690). While most previously identified risk factors were not significantly associated with bronchiolitis obliterans, not being Caucasian ($p = 0.014$), lower circulating IgG levels ($p = 0.010$) and the presence of cGVHD ($p < 0.001$) were

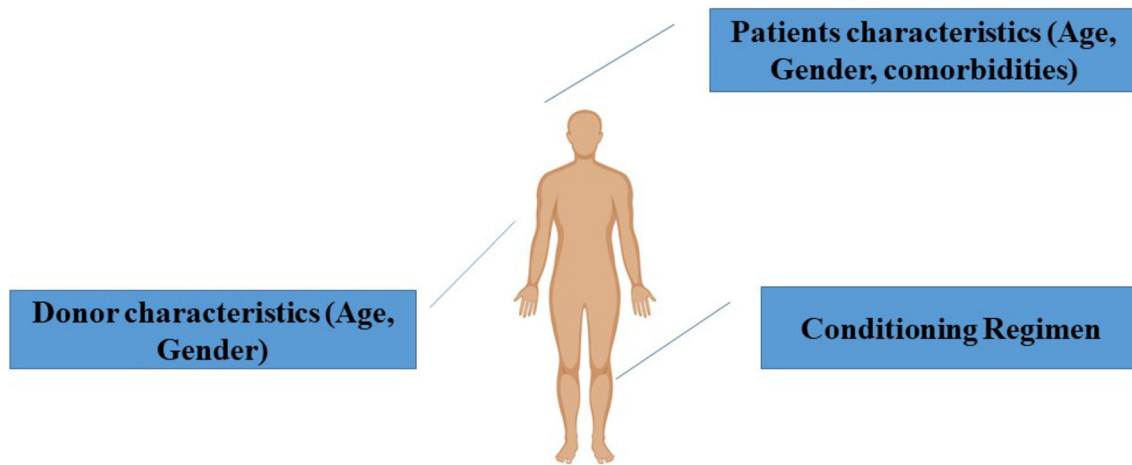


Fig. 2 Different elements that may be considered as risk factors for long-term side effects after allo-HSCT

associated with an increase in risk. Bronchiolitis obliterans syndrome conferred a 1.6 fold increase in risk for mortality after diagnosis [31]. Spirometric monitoring of high-risk patients with cGVHD might allow early diagnosis and treatment for this frequently fatal disease.

4.4 Avascular necrosis (AVN)

In the study by Campbell et al. [10] the prevalence of AVN was 3.7%, 5 years post HSCT and 5.4%, 10 years post HSCT. The incidence according to Weisman et al. can range from 6.3% at initial evaluation and 11.8% for long-term survivors [32]. The mean time from procedure to detection of the condition was 13 months [32]. According to Robin et al. [2] this condition was seen more in younger women less than 40 years of age.

4.5 Cardiovascular side effects

The prevalence of cardiovascular side effects was 7.5% at 15 years post HSCT and was 22% at 25 years post HSCT. Allogeneic recipients with hypertension were found to have a 2.5-fold increased risk of a cardiovascular event, while those with diabetes had a 2.3-fold increased risk [9].

4.6 Azoospermia and oligospermia

The above complication occurred at a prevalence of 72% in the study by Rovo et al. [11].

4.7 Depression

Was associated with the concurrent presence of cGVHD. The prevalence of this condition was 18%.

5 Conclusion

As it could be seen allogeneic HSCT is a good therapy for leukaemia but it has multiple associated late complications that debilitate the patient. The therapy will be more effective if these side effects are better managed. Most common late complications and prevalence were chronic graft versus host disease 43% at 5 years post HSCT, secondary tumor 21% at 20 years post HSCT, hypothyroidism 11% at 15 years, bronchiolitis obliterans 9.7% at 122 days, cardiovascular disease 7.5% at 15 years and avascular necrosis 5.4% at 10 years. Azoospermia was 71.1%. Depression was 18%. For the latter 2 condition no time limit was available. Follow up duration ranged from 2 years post HSCT to 30 years. It was very evident that cGVHD occurred concurrently with a variety of conditions such as bronchiolitis obliterans, atherosclerosis and avascular necrosis. Based on this literature review, it could be presumed that controlling the occurrence of cGVHD through using more matched and donor related transplantations will improve the outcome of allogeneic transplantation. This issue must definitely be addressed as more individuals would opt for this procedure. This review study concludes that while allogeneic HSCT is an effective cure for leukaemia, the procedure is associated with side effects that can have their onset years after the procedure.

6 Limitations

Some of the limitations are that there were no randomized control trials among our selected studies.

There was only one paper for most of the various types of complications except for secondary tumors where there

were five. The sample of patients included in the studies suffered from all kinds of blood disorders such as aplastic anemia and myelofibrosis, not just leukaemia. Concerning leukaemia per say there are four kinds of leukaemia. These are a heterogeneous group of disorders. Most of the studies did not differentiate between the various types of leukaemias nor did they differentiate between HSCT given for malignant and benign conditions. As for the ethnicity, of the sample population they were mostly Caucasian and the findings cannot be generalized to other ethnicities.

7 Future recommendations

Firstly, similar studies should be carried out in the East as Asians are genetically different from Caucasians. Secondly, more studies should be carried out to ascertain each of the above complications in greater details. Thirdly, there should be more randomized control trials, which are the gold standard in research. Furthermore, different types of leukaemia should be studied individually as they are etiologically and histologically different from each other. At present, most of the studies have clumped the patients with various diagnoses together. In addition, after attempts to decrease the co-occurrence of cGVHD, the investigation should be done to explore if the prevalence of the other complications is decreased.

Author's contribution Associate Professor Dr. Sharmilla Kanagasundram acquisition, interpretation and analysis, drafting article and revising it for intellectual content. Associate Professor Farhanaz Amini concept and design of study and revising it for intellectual content.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical statement There are no animal experiments carried out for this article.

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