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System dynamics analysis of mortality post allogeneic hematopoietic stem cell transplant

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Abstract

Allogeneic hematopoietic stem cell transplantation is a well-proven treatment for hematologic malignancies and non-malignancies, but it has a high risk of disease recurrence and severe transplant-related morbidity and death. The mortality and long-term survival of post-allogeneic hematopoietic stem cell transplant patients are improving due to improvements in condition procedures, methods, novel medicines, and supportive care practices. Allogeneic hematopoietic stem cell transplant (allo-HCT) findings, nonetheless, still present a chance for recovery. The results of this investigation updated previous research on risk factors for death following allogeneic HCT. We performed a systematic review and meta-analysis to assess mortality post allo-HCT through a comprehensive literature search using PUBMED/MEDLINE, CINAHL, Web of Science, and EMBASE up to April 30, 2023 and extracted clinical outcome data relating to benefits followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search identified 551 studies. Only 12 studies (*n* = 450 patients) met our inclusion criteria. OS rates were the subject of the meta-analysis. The following were the outcomes of heterogeneity tests: According to Chi2=9.14, df=6, P=0.17, and I2=34 percent, the study's data did not appear to be heterogeneous. The OS rate did not differ significantly (P>0.05) using the fixed-effect model analysis. In conclusion, the HSCT must offer the best overall survival, quality of life, and cost outcomes compared to any other treatment strategy. More studies will need a lot of data, and careful data analysis will help get clear data on HSCT outcomes.

Keywords: PRISMA; Post allo-HCT; PUBMED/MEDLINE; HSCT

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Introduction

Long-standing treatment for hematologic and non-hematologic diseases with a high risk of significant transplant-related morbidity and mortality as well as disease relapse is allogeneic hematopoietic stem cell transplantation [1]. The ongoing populace of > 100,000 hematopoietic cell transplantation (HCT) survivors in the USA is projected to increment fivefold by 2030, with 14% of the populace matured < 18 years and 25% with age ≥ 60 years at transplantation [2].

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According to standard definitions [3], the disease status at the time of the transplant was categorized as low, intermediate, or high.

The severity of comorbidities was determined using the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI), with grades ranging from zero to three [4]. The analysis included both myeloablative and reduced-intensity conditioning regiment recipients. Typically, a calcineurin inhibitor like cyclosporine or tacrolimus was used in conjunction with methotrexate or mycophenolate mofetil for graft-versus-host disease (GVHD) prevention. As previously mentioned, [5], standard institutional clinical guidelines were followed when providing supportive care.

The well-known composite endpoints of disease-free survival (DFS), relapse-free survival (RFS), progression-free survival (PFS), and event-free survival (EFS) are combined from post allo-HCT aggregates [6]. According to the National Cancer Institute's dictionary of cancer terms, DFS and RFS are synonymous since there are no international consensus standards for the definition of survival endpoints used in cancer clinical trials [7]. PFS is also defined in a similar way, but it is most useful for patients who are not in complete remission at the beginning of the transplant and is widely used in transplant studies. It's important to note that studies on leukemia patients frequently refer to DFS as "leukemia-free survival" (LFS). Even though the terms "time to disease recurrence/progression or death" (DFS, RFS, and PFS) are almost always used interchangeably, events that are taken into account in EFS may not necessarily include disease recurrence or death. In clinical trials, EFS has been defined differently according to the disease [8]

Late complications include secondary cancers, organ-specific complications, late infections, impairments in quality of life (QOL), psychosocial issues, sexual and fertility concerns, financial toxicity, and integration back into society. Late complications can occur months to years after transplantation. Late non-relapse mortality among transplant survivors is influenced by a number of complications, including cardiovascular complications, end-stage renal disease, and bronchiolitis obliterans [9]. Avascular necrosis, dry eyes, xerostomia, and other complications can have a negative impact on quality of life as well as mortality. Exposures related to transplants can either partially or completely account for the onset of these complications [10]. Pre-transplant treatment exposures, such as disease-specific chemotherapy or radiation, as well as lifestyle factors that can and cannot be changed (such as smoking and hereditary cancer risk factors) can increase the risk [11]. Chemotherapy and total body irradiation (TBI) exposures related to the conditioning regimen are frequently linked to the risk of late complications in all HCT recipients. Chronic GVHD and its treatment are also major contributors to late complication risks among allogeneic HCT recipients. The objective of a systemic analysis study is to identify the dynamics analysis of mortality post-allogeneic hematopoietic stem cell transplant.

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Materials and methods

Search and Selection of Studies

The literature from March 30, 1995, to March 30, 2023, was searched in terms of post-allogenic bone marrow transplant, acute leukemia, systematic review, relapse, and stem cell transplant. We carried out a comprehensive literature search using two major databases—PUBMED/MEDLINE and EMBASE—in accordance with a predefined study protocol, the type of study—whether prospective or retrospective, single-center or multicenter, or registry data—had no bearing on our search. There were 512 published manuscripts among the papers that were screened.

Inclusion criteria

Criteria for literature inclusion; 1) Study design: case-control studies of the treatment of leukemia with Allo-genic BMT. 2) Topics: patients with leukemia who had been given a diagnosis in accordance with the diagnostic criteria according to the type of leukemia [12], and there were no restrictions placed on clinical classification, sex, age, or any other biological characteristics. 3)

Measures of success

Overall survival (OS) rate, disease-free survival (DFS) rate, recurrence rate, acute graft-versus-host disease (GVHD) incidence, and chronic GVHD incidence were all measured.

Exclusion criteria

1) Small sample size; 2) research that has been published multiple times; 3) No case-control studies were carried out. 4) The data cannot be utilized because the report was insufficient. 5) The findings of the research were retold. 6) Case studies.

Data extraction

A bias risk assessment was carried out in this study in accordance with the recommendations in Chapter 5.3 of the Cochrane System Review Manual. 2) Data extraction and literature retrieval: Two researchers (Yousif NG and Alamran FG) carried out an independent literature review. Information was removed, and characteristics were surveyed. A third researcher was included to help with the decision-making process if necessary, and disagreements were discussed and resolved. Excel and the document management software Note Express were utilized in order to manage and extract the research data. The authors of this article were contacted whenever incomplete data were discovered in the literature.

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These were among the extracted data: 1) fundamental facts about the articles: author, date of publication, and number of cases; 2) assistance: scheme, treatment plan; 3) indicators of outcomes: OS rate, DFS rate, recurrence rate, and incidence of both acute and chronic GVHD are all included.

Statistical analysis

The computer program Review Manager (RevMan;) was used in the meta-analysis. The Cochrane Collaboration, version 5.4, 2020). The method was an inverse variance model. The I2 value and Cochran's Q-test were used to measure heterogeneity. A random effect model was used in cases with an I_2 value greater than or equal to 25%; The significance level was set at 0.05 or less.

Results

Study Search

After screening for duplicates and removing 102 articles, a preliminary search of the database yielded 512 articles. Due to the absence of clinical studies, animal studies, and reports written in a language other than English 212 studies were ruled out. Conference abstracts, the lack of full text, the absence of quantitative data, and the incompleteness of the treatment all contributed to the exclusion of 187 additional articles. This meta-analysis included 12 studies for qualitative analysis.
Figure 1 and Table 1 show the preferred Reporting Items for Systematic Reviews and Meta-Analyses study selection flow diagram.

Analyses of the literature's methods

All twelve studies analyzed in this meta-analysis provided a baseline of demographic information for all studies. Random methods and in-depth interventions were covered in great detail in each article. Dissemination stowing away was utilized in a portion of the examination, so there was minimal particular predisposition. There was a slight implementation bias because only seven articles provided in-depth descriptions of the numbers and causes of blindness, withdrawal, and lost follow-up. All of the literature obtained their trial plans to reduce bias. Because some reports identified additional risks, the bias was greater. Figure 2.

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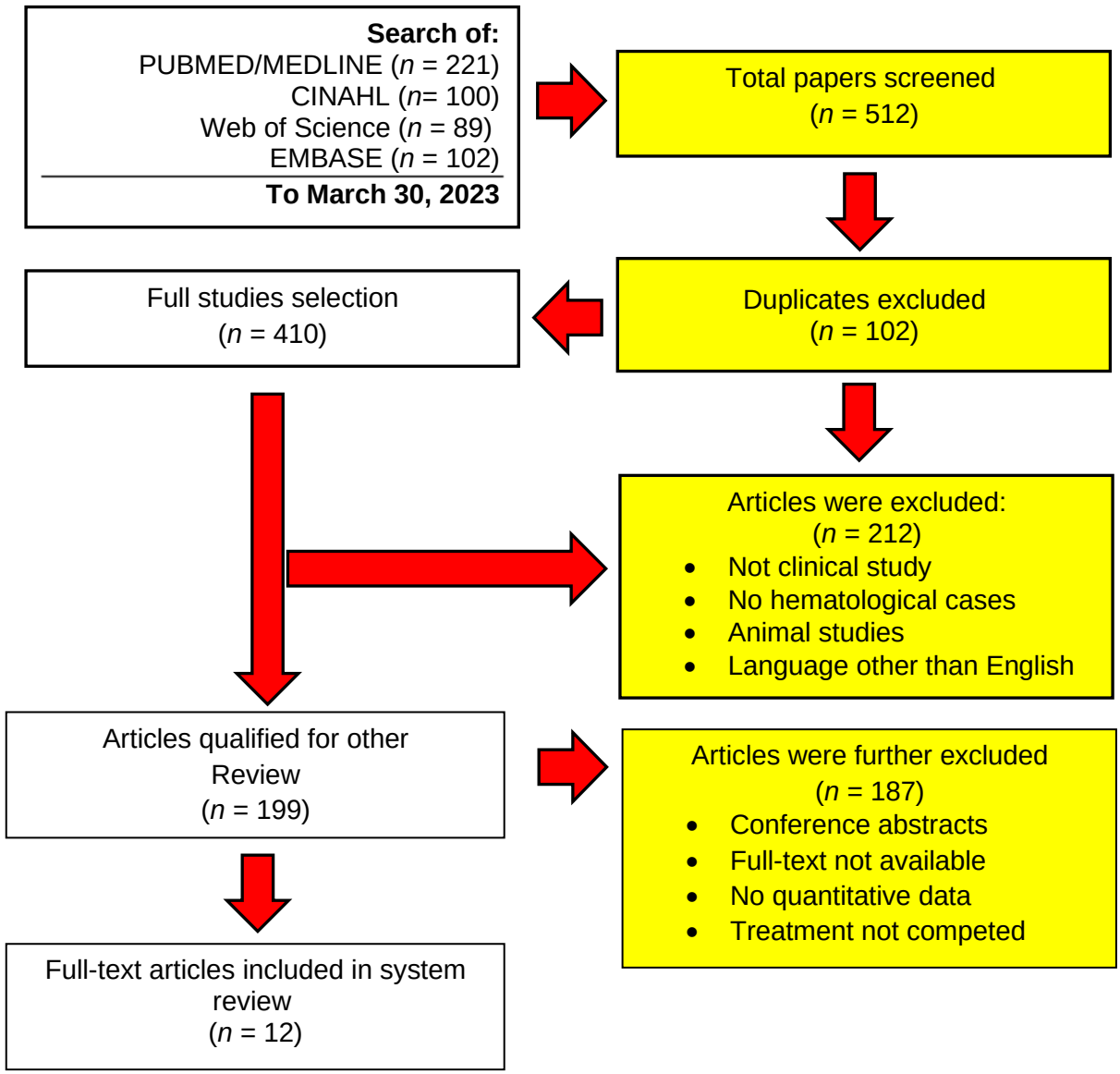

Figure 1.

PRISMA flow diagram of the included studies.

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Table 1.

Patient Characteristics and Outcomes of Eligible Studies

NO	Author(s) and year of publication	Sample size	Median follow-up Years	overall survival rate	Accumulative incidence of recurrence-related mortality
1	Bhatia S, et al. 2021 [12]	4741	10	87.8%	12.2% (95% CI, 9.0%-11.4%)
2	Godara A, et al. 2019 [13]	68,296	13	92.4%	7.6% (95% CI, 3.0%-6.1%)
3	Francisco L, et al. 2016 [14]	2,999	20	86.1%	13.9% (95% CI, 11.0%-13.4%)
4	Wingard JR, et al. 2011 [15]	3,788	10	85%	15% (95% CI, .2.0%-5.2%)
5	Martin PJ, et al. 2010 [16]	7,984	46	80.4%	19.6% (95% CI, 78.1% to 82.6%
6	Holmqvist AS, et al 2011 [17]	1388	14.6	79.3%	20.7% (95% CI, 0.31-0.76
7	Vajdic CM, et al 2016 [18]	3273	10	85%	22.2% (95% CI, 19.7 to 24.9)
8	Gooley TA, et al 2010 [19]	1148	9	84%	16% (95% CI, 1.2–3.4
9	Schechter T, et al 2013 [20]	371	7	79.5%	20.5% ((95% CI, 0.32–0.49
10	Pond GR, et al 2006 [21]	1386	6	98.5%	0.39; 95% CI, 0.17-0.88
11	Arora M, et al 2016 [22]	998	10	82%	10.2% (95% CI, 0.9–2.4)
12	Shankar SM, et al 2007 [23]	845	4,9	98%	2%;(95% CI, 1.2–4.3)

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Figure 2.

Risk of bias assessments for studies in a Cochrane review

Overall survival (OS) rate meta-analysis findings

OS rates were the subject of the meta-analysis. The following were the outcomes of heterogeneity tests: According to Chi2=9.14, df=6, P=0.17, and I2=34 percent, the study's data did not appear to be heterogeneous. The OS rate did not differ significantly (P>0.05) using the fixed-effect model analysis. Figure 3.

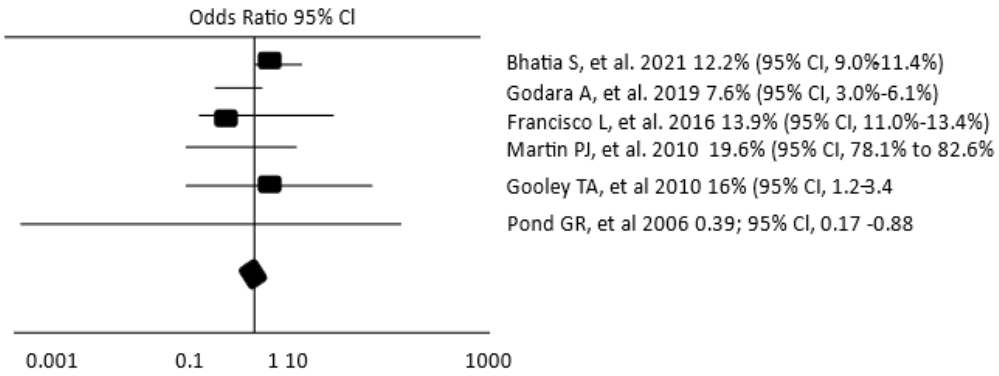

Figure 3.

Risk of bias assessments

Rate of relapse analysis

Following treatment, a meta-analysis was conducted on the rate of relapse. The following were the outcomes of heterogeneity tests: The study's data did not appear to be heterogeneous, with Chi2 = 7.06, df = 4, P = 0.13, and I2 = 43%. The BMT group had a lower recurrence rate (P 0.05) according to the fixed effect model analysis. Look at Figure 4.

Publication bias

A publication bias analysis was carried out, and funnel charts based on the OS rate, DFS rate, incidences of acute and chronic GVHD, and recurrence were created. The funnel charts showed a lot of symmetry and little asymmetry, pointing to the possibility of publication bias in the selected literature due to the heterogeneity and small sample size. Figures 4.

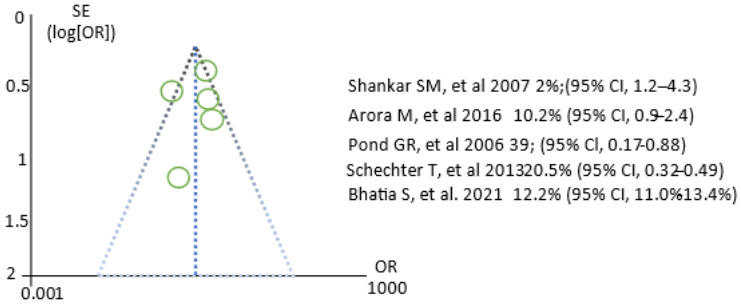

Figure 4.

Rate of relapse analysis

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Discussion

After HCT, mortality rates rise significantly in the first five years, but they remain four to nine times higher than in the general population for at least 25 years [24]. The proportion of mortality among transplantation survivors contrasted and the normal populace rate diminishes with expanding age, as mortality expansions in everyone, except the number of abundances passings per 1,000 man years increments pointedly, particularly following 50 years old. Regardless of age, the excess mortality rate results in an estimated 30% lower life expectancy than the US population. The significant reasons for overabundance passings incorporate repetitive sickness, second malignancies, contaminations, constant GVHD, respiratory infections, and cardiovascular illnesses [25].

The primary objective of this analytical study was to compare long-term survivors' mortality rates to those of the general population following an allogeneic hematopoietic stem cell transplant. Relapse, acute or chronic graft-versus-host disease (GVHD), infection, or other acute or subacute toxicities of HCT account for the majority of deaths following HCT within the first two years [26].

Death after two years is uncommon [27]. The composition of the cohorts, the time between BMT and cohort entry, and the disease status at cohort entry have all varied across studies that have described the risk of late mortality following BMT. Also, previous cohorts have covered different transplant eras and used different methods to figure out vital status [28]. Meaningful comparisons have been impossible due to the disparity between previous studies. However, every study found an increased mortality risk compared to the general population, and the majority of them found that the risk remained elevated for at least 15 years after BMT [4]. After BMT, the mortality risk remained elevated for at least 30 years in our analytic study [29].

In the past ten years, four large studies have described post-allogeneic transplant mortality rates: The first study, known as the Center for International Bone Marrow Transplant Registry (CIBMTR), came to the conclusion that allogeneic HCT survivors who survived for two years have excellent long-term survival prospects. Life expectancy, however, remains lower than anticipated. It is necessary to perform HCT earlier in the disease, control GVHD, enhance immune reconstitution, use less toxic regimens, and prevent and treat late complications [30].

The second study, a nationwide one conducted in Japan, demonstrated that long-term survivors of allogeneic HCT are more likely to die from other causes than the underlying disease that caused HCT [31]. The Blood or Marrow Transplant Survivor Study (BMTSS) [12] is the third study. It found that new transplantation strategies have gradually reduced late allogeneic HCT mortality. Over the four decades examined in this study, all-cause mortality has decreased by 44% for allogeneic HCT recipients and 75% for autologous HCT recipients. Non-relapse mortality demonstrates a decline in risk more than relapse-related mortality.

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In addition, a finding similar to that of other HCT series [12] revealed that late relapse was the leading cause of death among patients who underwent transplantation for cancer, accounting for between 27% and 42% of all deaths. There is a lack of data on adult leukemia survivors who did not receive HCT, but it has been demonstrated that relapse is a significant long-term issue for survivors of childhood and adolescent cancer [4]. Relapse was more common between years 2 and 5 of HCT, but it decreased after five years, making it possible to reduce intensive surveillance for late relapse [6]. The most common cause of relapse following HCT has been found to be advanced or recurrent disease prior to transplantation in a number of studies [12]. Early referral for transplantation would be beneficial to address this challenge in order to identify patients who are suitable candidates for HCT and who are unlikely to be cured by nontransplantation therapy [11].

This study's analytical data revealed that needs to be addressed because transplantation protocols and methods have evolved over time, as have the conditions and comorbidities of patients. In addition, not all patients in all choice studies received the same follow-up and treatment for complications. In addition, improvements have been made in the treatment of relapse following allogeneic HCT and the prevention of post-transplant complications like acute GVHD and infections.

Both transplant teams and public health organizations need to be aware that fatalities can occur many months or years after a transplant [14]. The allocation of resources is necessary for prompt infection detection and treatment. Data collection and analysis are essential components of any transplant therapy, and support includes both [15].

After treatment, the recurrence rate, relapse-related mortality, and non-relapse-related mortality were the subjects of a meta-analysis. Although there was no significant difference between recurrence-related mortality and non-relapse-related mortality ($P>0.05$), the lower recurrence rate in the BMT group suggests that BMT treatment may significantly lower the risk of relapse in AML patients. Specifically, there was no discernible effect on patient mortality, which is in line with the previous analysis's conclusion. The median number of CD34+ cells transplanted and various disease stages are related [32]. The various stages of the disease are not explained in this analysis because there is insufficient data and a small sample size. There were numerous limitations to this study. First, despite the fact that the search scope of this study included a number of authoritative databases, only seven articles were included in the final analysis. The heterogeneity was strong, but there was no detailed subgroup analysis of studies with heterogeneity [33]. This is because the inclusion and exclusion criteria were relatively stringent. Second, the results were constrained by inconsistent follow-up times across all studies. We used a random effect model to examine the article's heterogeneity in light of the preceding. In addition, future research will broaden the scope of the search to lessen publication bias and article heterogeneity.

Conclusion

The HSCT must provide the best overall survival, quality of life, and cost outcomes when compared to any other treatment strategy in light of the most recent advances in new medicine, targeted therapies, and treatment complications. To get clear data on HSCT outcomes, more studies will need a lot of data, and careful data analysis will help.

Funding

No funding was received.

Competing interests

The authors declare no conflict of interest.

Ethics Statement

Not applicable.

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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