Hospital and outpatient models for Hematopoietic Stem Cell Transplantation: A systematic review of comparative studies for health outcomes, experience of care and costs

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Abstract

The number of Hematopoietic Stem Cell Transplantations has risen in the past 20 years. The practice of outpatient Hematopoietic Stem Cell Transplantation programs is increasing in an attempt to improve the quality of patient care and reduce the demand for hospital admission. A systematic review of 29 comparative studies between in-hospital and outpatient treatment of Hematopoietic Stem Cell Transplantation, with no restriction by outpatient regime was conducted. This study aims to analyse the current evidence on the effects of the outpatient model on patient-centred outcomes, comparing both in-hospital and outpatient models for autologous and allogeneic HSCT using the Triple Aim framework: health outcomes, costs and experience of care. We found evidence on improved health outcomes and quality of life, on enhanced safety and effectiveness and on reduced overall costs and hospital stays, with similar results on overall survival rates comparing both models for autologous and allogeneic patients. We also found that the outpatient Hematopoietic Stem Cell Transplantation is a safe practice as well as less costly, it requires fewer days of hospital stay both for autologous and allogeneic transplantations. Under a situation of an increasing number of transplants, rising healthcare costs and shortages of hospital capacity, incorporating outpatient models could improve the quality of care for people requiring Hematopoietic Stem Cell Transplantation programs.
Introduction

Hematopoietic Stem Cell Transplant (HSCT) involves the administration of hematopoietic stem cells in patients with dysfunctional or depleted bone marrow. The two major transplant approaches are the autologous (using the patient’s own hematopoietic stem cells), and the allogeneic ones (using related- or unrelated-donor hematopoietic stem cells) [1]. HSCT practice is a highly specialized and resource-intensive medical procedure [2,3]. Especially allogeneic-HSCT is associated with higher occurrence of adverse events such as graft vs. host disease (GVHD), higher incidence of acute renal failure and infectious events [4,5].

The number of HSCTs has increased constantly in the past 20 years, mainly due significant changes in the practice of HSCT. These changes included new anti-microbial agents, wider use of graft and donor types, indications in allogeneic HSCT such as genetic disorders or immunodeficiencies, autologous transplantation for autoimmune diseases, new GVHD prophylaxis and therapeutic strategies, and increased use of biomarkers to both diagnose and guide GVHD therapy. Some authors have shown the number of HSCT patients treated has grown from 4,751 to 17,155 (an increase of 360%) and from 12,199 to 23,945 (an increase of 196%) with allogeneic and autologous HSCT, respectively [6].

To date, most of the high dose therapy and the subsequent supportive care while awaiting hematopoietic recovery have been entirely performed in hospital settings, with a stay of approximately 14 days for autologous HSCT and 30 days for allogeneic HSCT. This can cause a decline in their functional capacity and exposure to nosocomial infections, especially relevant for allogeneic transplant patients when receiving immunosuppression [7,8]. Furthermore, recent studies show that more than half of total charges billed per HSCT correspond to hospital admission costs [9], with its important effect on health care systems.

In a context of a burgeoning incidence of onco-hematological and neurodegenerative diseases, and restricted healthcare resources [10,11], new care and treatment approaches have been tested. The outpatient alternative model of care, is a healthcare modality that administers specialized medical care to patients in their homes, for illnesses that would usually require hospitalization. Previous studies have shown that the outpatient model makes little or no difference in mortality and readmission rates, and that it improves patients’ experience of care, previous studies have shown that the outpatient model makes little or no difference in mortality and can avoid hospital readmission, reducing both clinical and economic burdens [7,12–14].

Since it was first reported by Jagannath et al. in 1997 [15], the outpatient model in the practice of HSCT has also been recognized for its positive results in terms of effectiveness and safety [15–19]. Improvement of anti-microbial prophylaxis and therapy, prevention of oral mucositis, the use of reduced intensity conditioning regimens and high-resolution HLA typing together with the development of ambulatory bone marrow transplantation (HSCT) units have enabled the establishment of outpatient HSCT programs [19].

Their main advantages include shorter hospital stays, lower risk of nosocomial infections, and increased comfort for patients [7,17]. Nevertheless, associated risks with outpatient modalities have been reported in the literature, such as the high frequency of hospital readmissions due to fever and infections related to neutropenia [17,19], as well as the higher occurrence of adverse events, such as graft vs. host disease (GVHD), [19].

Although numerous research has focused on studying the impact of outpatient model in HSCT [7,20], to the best of our knowledge, overall comparative effects have not yet been systematically reviewed. This study aims to analyse the current evidence on the effects of the outpatient model on patient-centred outcomes, comparing both in-hospital and outpatient models for autologous and allogeneic HSCT using the Triple Aim framework: health
outcomes, costs and experience of care. In doing so, we aim to provide an overview of the body of literature published until May 2020. As far as we know, this is the most comprehensive systematic review on this topic that seeks to understand the impact of the outpatient model in HCST from the public, patient, provider and payer perspective.

Although autologous and allogeneic transplants correspond to different types according to clinical characteristics and treatments, a general perspective has been prioritized in this review, with the purpose of identifying more specific lines of comparison so that they can be continued in future studies. The results of this review may be useful in the design of controlled clinical studies aimed at comparing HSCT alternatives, as well as to advance the comparability of methods for estimating health outcomes and costs. From the perspective of health management, the results of this review can be used as a reference to explore innovative options in treatments that require HSCT. For the purpose of uniformity, in the text we use outpatient to refer to all the alternatives that identify this type of outpatient treatment.

Methods

A systematic review to identify studies comparing outpatient and hospital HSCT care models was conducted. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to report our findings [21].

Data sources and searches

The search was conducted in the PUBMED and Google Scholar databases, with no time or language restrictions. The search for published articles was made using a combination of appropriate keywords, MeSH and non-MeSH index terms. The search strategy details are available in S1 File. The last update was carried out on May 17th, 2020. We did not apply any previous protocol.

Inclusion and exclusion criteria

We looked for comparative studies between outpatient and in-hospital, with two different groups of patients undergoing autologous and/or allogeneic HSCT. We sought models of care that aimed to avoid or reduce hospitalisation duration under one of the following categories: 1) admission avoidance programs that provided active treatment in the patient’s home or community houses; 2) schemes that facilitated early discharge from hospital; and 3) patients receiving care in an outpatient setting and avoiding admission to hospital. No filter by medical condition or diagnoses for HSCT was considered. We included all outpatient regimes. 4) Only comparative studies with the existence of a control group were eligible. 5) Reported outcomes on at least one of the dimensions of the Triple Aim framework [22]: health outcomes, experience of care, and costs. The exclusion criteria were: 1) studies focusing on pediatric patients; 2) non primary studies, excluding: systematic reviews and meta-analysis, books, theses, PhD dissertations, conference articles, and working papers.

Study selection

Two authors independently screened titles and abstracts for eligibility followed by full-text review for inclusion. The articles were reviewed and disagreements resolved through discussion and/or involvement of a third researcher. The initial database search generated 149 references. These were assessed for relevance based on the title, and when the information provided in the title was inconclusive, the abstract was consulted. After title and abstract revision, 95 references were identified as relevant to full-text review against the inclusion and
exclusion criteria. During full-text screening, 66 studies were identified as not suitable and were discarded. The authors agreed on more than 80% of the included papers, a third reviewer was consulted for discrepancies, leaving 29 included studies in this paper. The PRISMA Flow Diagram is available in S1 Fig and the PRISMA checklist in S2 Checklist.

Data extraction
Details pertaining to author, publication year, country, study characteristics and design, study sample, outpatient interventions scheme, and reported outcomes were extracted using Microsoft Excel.

Data synthesis and presentation
We applied the Triple Aim [22] framework to sort results in each of its three categories. Since clinical characteristics of autologous and allogeneic HSCT cases differ, data on outcomes were classified separately for each. We presented the most frequently reported Triple Aim framework outcomes in the included papers.

Results
Of the 149 peer-reviewed studies, 29 studies were included: 17 for autologous transplants, 9 for allogeneic transplants and two publications covering both [4,23], which are reported in both tables. One study did not specify type of transplant [24], and it was classified within the allogeneic group (Tables 1 and 2).

From the analysed papers, 57% of autologous papers and 90% of allogeneic analysed reported on at least one health outcomes, the most frequent were: overall survival, progression free survival and mortality rates. Concerning experience of care, safety and effectiveness outcomes were the most reported ones, in 63% and 83% of the autologous and allogeneic studies respectively. However, patient satisfaction only appeared in three studies out of the total 29. Lastly, data were also found on hospitalisations days and overall costs, in 14 autologous studies and 12 allogeneic studies (Tables 3 and 4).

Result analysis according to the Triple Aim framework
Even though, patient selection can affect differences in mortality after 100 days time frame, autologous patients results show that mortality rates without recurrence of the disease at one year are similar when comparing inpatient and outpatient HSCT [25]. Likewise, greater survival at two [26] and four years [8] has been found in the outpatient model. Similar overall survival rates have also been reported [16,17,27,28] (Table 5).

For allogeneic patients (Table 6), the rates of mortality without recurrence of the disease at one year are similar when comparing inpatient and outpatient models [5,19,29,30] for allogeneic HSCT. Lower mortality at 100 days time [4] and at 5 years time [31] has also been reported. Greater survival at four years (8), and statistically significant longer survival at five years has also been found in the outpatient model [31].

With respect to quality of life results, in the autologous studies, the psychological, physical, social and financial well-being has been reported with higher scores in the outpatient model [17].

In parallel, other studies have indicated that the QoL is rather similar for both care models [27,32,33]. Summers [34], reported there were no differences between the groups at any of the time intervals after transplant, and for both groups QoL was rated lowest at day 4–6, with improvements at day 12–16. In the allogeneic cases, quality of life measurements have also
been reported to be similar in patients who underwent outpatient HSCT compared to inpatient HSCT after three months [23].

**Experience of care**

Incidence of neutropenic fever, mucositis, cumulative Graft versus Host Disease (GVHD), as well as median time to neutrophil recovery and median time to platelet recovery are some of the recurrent reported variables (Tables 7 and 8).

### Table 1. Characteristics of studies focused on autologous transplants.

| First Author | Year | Country | Study design | Outpatient regime | Total patients (n) | Inpatient care Model patients (n) | Outpatient care patients (n) |
|--------------|------|---------|--------------|-------------------|-------------------|-------------------------------|-------------------------------|
| Jagannath    | 1997 | USA     | Multi Center Case Control Comparison | Outpatient Clinic | 251               | 160                           | 91                           |
| Meisenberg   | 1998 | USA     | Single Center Prospective Case Control Comparison | Outpatient Clinic | 20                | 28 (46 partial)               |                               |
| Herrmann     | 1999 | Australia | Single Center Prospective Case Control Comparison | Outpatient Clinic | 139               | 88                            | 51                           |
| Summers      | 2000 | Canada  | Multi Center Observational Study | Outpatient Clinic | 41                | 20                            | 21                           |
| Frey         | 2002 | USA     | Single Center Prospective Trial | Outpatient Clinic | 47                | 26                            | 21                           |
| Fernández-Avilés | 2006 | Spain   | Single Center Prospective Case Control Comparison | At home | 100               | 50                            | 50                           |
| Stiff        | 2006 | USA     | Single Center Retrospective Case Control Comparison | Outpatient Clinic | 132               | 32                            | 100                          |
| McDiarmid*   | 2010 | Canada  | Single Center Retrospective Case Control Comparison | Outpatient Clinic | 671               | 163                           | 508                          |
| Faucher et al | 2012 | France  | Multi Center Randomized Study | Outpatient Clinic | 95                | 65                            | 30                           |
| Holbro et al | 2013 | Canada  | Single Center Retrospective Study | Outpatient Clinic | 180               | 89                            | 91                           |
| Graff        | 2015 | USA     | Single Center Retrospective Cohort Study | Outpatient Clinic | 230               | 135                           | 95                           |
| Paul         | 2015 | USA     | Single Center Retrospective Case Control Comparison | At home | 301               | 219                           | 82                           |
| Cantu-Rodriguez* | 2016 | Mexico  | Observational,longitudinal, and prospective study | Outpatient Clinic | 25                | 6                             | 19                           |
| Abid         | 2017 | Singapore | Single Center Prospective Case Control Comparison | Outpatient Clinic | 21                | 11                            | 10                           |
| Shah         | 2017 | USA     | Single Center Retrospective Study | Outpatient Clinic | 1,046             | 669                           | 377                          |
| Obiozor      | 2017 | USA     | Single Center Retrospective Study | Outpatient Clinic | 3 groups          | 273                           | 175                          |
| Martino      | 2017 | Italy   | Single Center Activity Based Costing Analysis | Outpatient Clinic | ND                | ND                            | ND                           |
| Martino      | 2018 | Italy   | Prospective Observational Longitudinal Cohort Study | Outpatient Clinic | 140               | 76                            | 64                           |
| Dunavin      | 2020 | USA     | Multi Center Retrospective Cohort Study | Outpatient Clinic | 1,640             | 1,445                         | 195                          |

Source: Compiled by authors based on included references.

*: This article analyses both allogeneic and autologous,
ND: Not determined.

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For autologous patients the frequency of infections has been reported to be lower (with statistical significance) in the outpatient model [4,9], although similar frequency of infections has also been reported in some papers for both models of care [25,27].

In particular, the frequency of neutropenic fever has been shown to be lower in the outpatient option [17]. A similar frequency has also been reported in both options [25,35]. Frequency of mucositis has also been reported to be similar when comparing inpatient and outpatient HSCT [17,25,27,32].

In allogeneic HSCT, the frequency of neutropenic fever has been shown to be lower in the outpatient option [19,30]. In all the works except in [36], the differences were significant. The lowest frequency of neutropenic fever in patients with outpatient HSTC (8.5%) was reported in [30]. Furthermore, in the outpatient HSCT model, the frequency of mucositis is shown to be six times lower than in hospitalized patients [30]. A similar frequency has also been reported when comparing inpatient and outpatient HSCT [17,25,27,32]. With respect to the acute incidence of transplant rejection or GVHD, it has been reported to be significantly lower in the home modality [8]. Once again, similar incidence has also been reported in the two models of care [24,29,30,37]. The higher frequency of oral nutrition in the outpatient model has been associated with lower probability of GVHD [31].

Patient satisfaction has been reported in a limited number of papers. Gutierrez Garcia et al. [19] reported that patients in hospital experience more stress than those with outpatient care, causing release of inflammatory cytokines. The outpatient care model has also received

### Table 2. Characteristics of studies focused on allogeneic transplants.

| First Author          | Year | Country | Study design                                      | Outpatient regime | Total patients (n) | Inpatient care model patients (n) | Outpatient care HaH patients (n) |
|-----------------------|------|---------|--------------------------------------------------|-------------------|--------------------|----------------------------------|----------------------------------|
| Rizzo **              | 1999 | USA     | Nonrandomized prospective cohort study           | Outpatient Clinic | 132                | 115                              | 17                               |
| Svhahn                | 2000 | Sweden  | Single Center Prospective Case Control Comparison | At home           | 33                 | 11                               | 22                               |
| Svhahn                | 2005 | Sweden  | Single Center Prospective Case Control Comparison | At home           | 90                 | 54                               | 36                               |
| Nicolau               | 2007 | Brazil  | Single Center Retrospective Case Control Comparison | At home           | 100                | 49                               | 51                               |
| Svhahn                | 2008 | Sweden  | Single Center Prospective Case Control Comparison | At home           | 152                | 76                               | 76                               |
| McDiarmid*            | 2010 | Canada  | Single Center Retrospective Case Control Comparison | Outpatient Clinic | 392                | 196                              | 196                              |
| Ringden               | 2013 | Sweden  | Single Center Retrospective Case Control Comparison | At home           | 292                | 146                              | 146                              |
| Granot                | 2015 | EUA     | Single Center Prospective Case Control Comparison | Outpatient Clinic | 1,037              | 548                              | 489                              |
| Cantu-Rodriguez *     | 2016 | Mexico  | Single Center Retrospective Case Control Comparison | At home           | 32                 | 19                               | 13                               |
| Lisenko               | 2017 | Germany | A retrospective single-centre analysis            | Outpatient Clinic | 128                | 65                               | 63                               |
| Guru                  | 2019 | USA     | Single Center Retrospective Case Control Comparison | Outpatient Clinic | 151                | 116                              | 35                               |
| Gutierrez-García      | 2020 | Spain   | Single Center Retrospective Case Control Comparison | At home           | 80                 | 39                               | 41                               |

Source: Compiled by authors based on included references

*: This article analyses both allogeneic and autologous
**: Does not specify type of transplant.
### Table 3. Summary of the Triple Aim dimensions tackled on autologous studies.

| First Author      | Year | Country | Health outcomes | Experience of care | Cost | Hospital Stay |
|-------------------|------|---------|-----------------|-------------------|------|--------------|
| Jagannath         | 1997 | USA     | x               |                   | x    | x            |
| Meisenberg        | 1998 | USA     | x               | x                 | x    | x            |
| Herrmann          | 1999 | Australia | x            |                   | x    | x            |
| Summers           | 2000 | Canada  | x               |                   | x    | x            |
| Frey              | 2002 | USA     | x               | x                 | x    | x            |
| Fernández-Avilés  | 2006 | Spain   | x               | x                 | x    | x            |
| Stiff             | 2006 | USA     | x               |                   | x    | x            |
| McDiarmid         | 2010 | Canada  | x               |                   | x    | x            |
| Faucher           | 2012 | France  | x               |                   | x    | x            |
| Holbro            | 2013 | Canada  | X               | x                 | x    | x            |
| Graff             | 2015 | USA     | X               |                   | x    | x            |
| Paul              | 2015 | USA     | x               |                   | x    | x            |
| Cantu-Rodriguez   | 2015 | Mexico  | x               |                   | x    | x            |
| Abid              | 2017 | Singapur | x              | x                 | x    | x            |
| Shah              | 2017 | USA     | x               |                   | x    | x            |
| Obiozor           | 2017 | USA     | x               |                   | x    | x            |
| Martino           | 2017 | Italy   | x               |                   | x    | x            |
| Owattanapanich    | 2018 | Various | x               |                   | x    | x            |
| Martino           | 2018 | Italy   | x               |                   | x    | x            |
| Koo               | 2019 | USA     | x               |                   | x    | x            |
| Dunavin           | 2020 | USA     | x               |                   | x    | x            |

Source: Compiled by authors based on included references.

*: This article analyses both allogeneic and autologous,
**: This article does not specify type of transplant.

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### Table 4. Summary of Triple Aim dimensions tackled on allogeneic studies.

| First Author       | Year | Country | Health outcomes | Experience of care | Cost | Hospital Stay |
|--------------------|------|---------|-----------------|-------------------|------|--------------|
| Rizzo **           | 1999 | USA     | x               |                   | x    | x            |
| Svahn              | 2000 | Sweden  |                 |                   | x    | x            |
| Svahn              | 2005 | Sweden  | x               | x                 | x    | x            |
| Nicolau            | 2007 | Brazil  | x               | x                 | x    | x            |
| Svahn              | 2008 | Sweden  | x               |                   | x    | x            |
| McDiarmid *        | 2010 | Canada  | x               | x                 | x    | x            |
| Ringden            | 2013 | Sweden  | x               |                   | x    | x            |
| Granot             | 2015 | USA     | x               |                   | x    | x            |
| Cantu-Rodriguez *  | 2015 | Mexico  | x               |                   | x    | x            |
| Lisenko            | 2017 | Germany | X               |                   | x    | x            |
| Guru               | 2019 | USA     | x               |                   | x    | x            |
| Gutiérrez-García   | 2020 | Spain   | x               | x                 | x    | x            |

Source: Compiled by authors based on included references.

*: This article analyses both allogeneic and autologous,
**: This article does not specify type of transplant.

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positive results [30], where the patient satisfaction score reported was 1.3 out of 6, one being excellent. Fernández-Avilés et al. [17] invited thirty patients and caregivers to complete an anonymous questionnaire after the entire procedure was completed, with 95% of them indicating that they would choose to receive outpatient autologous HSCT again and that they would recommend the procedure to a fellow patient. Other studies [38] have also described favourable feedback from outpatient autologous patients on their experience of care.

Cost of health care

Regarding costs, this research shows that the outpatient model is less costly than the inpatient care model. It is important to note that these results are derived from comparative studies in which at least one of the options corresponded to the treatment considered as standard.

Table 5. Summary of results of health outcomes for autologous HSCT patients.

| First Author       | Year | Nonrelapse mortality in 1 year (NMR) | Transplant related mortality (TRM) | Two year progression free-survival (PFS) | Overall Survival 1 year (OS1) | Overall Survival 2 year (OS2) |
|--------------------|------|--------------------------------------|-----------------------------------|------------------------------------------|------------------------------|------------------------------|
| Meisenberg         | 1998 | Similar (without years)               |                                   |                                          |                              |                              |
| Frey               | 2002 | Similar in both: 3 years              |                                   |                                          |                              |                              |
| Fernández-Avilés   | 2006 | Similar in both: 3 years              |                                   |                                          |                              |                              |
| Faucher            | 2012 | Similar in both: 10 years             |                                   |                                          |                              |                              |
| Graff              | 2015 | Out: 0% In: 1.5%, (NS)                | Out: 62% In: 54%, (NS)            | Out:97% In: 91%, (NS)                   | Out: 83% In: 80%, (NS)       |                              |
| Paul               | 2015 | Out: 0% vs In: 1.8% 100 days          |                                   |                                          |                              |                              |
| Shah               | 2017 |                                     |                                   |                                          |                              | Out: greater (Sig)           |

Source: Compiled by authors based on included references.

* NRM: Non Relapse Mortality, TRM: Transplant Related, Mortality, OS: Overall Survival, PFS: Progression Free Survival, NS: Non Significative and Sig: Significant.

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Table 6. Summary of results of health outcomes for allogeneic HSCT patients.

| First Author      | Year | Nonrelapse mortality in 1 year (NMR) | Transplant related mortality (TRM) | One year progression free-survival (PFS) | Overall Survival 1 year (OS1) |
|-------------------|------|--------------------------------------|-----------------------------------|------------------------------------------|------------------------------|
| Svahn             | 2005 | Out: 13% In: 44%, (Sig)              |                                   | Out: 63% In: 44%, (Sig). At four years’ time |
| Nicolau           | 2007 | Similar in both groups               |                                   |                                          |                              |
| Svahn             | 2008 |                                     |                                   | Out 65% In: 47% (Sig). At five years     |                              |
| McDiarmid         | 2010 | Out: 14.1%, lower (Sig). 100 days    |                                   |                                          |                              |
| Ringden           | 2013 | Similar in both groups               |                                   |                                          |                              |
| Granot            | 2015 | Out:13% In: 26%, (Sig). At five years time |                                   |                                          |                              |
| Guru              | 2019 | Out: 3.2% In: 10.8%, (NS)            | Out: 63.6% In: 64.4%, (NS)        | Out: 82.8% In: 73.8%, (NS). 1 year is assumed |
| Gutiérrez-García  | 2020 | Similar in both groups               |                                   |                                          |                              |

Source: Compiled by authors based on included references.

* NRM: Non Relapse Mortality, TRM: Transplant Related, Mortality, OS: Overall Survival, PFS: Progression Free Survival, NS: Non Significative and Sig: Significant.

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The hospital stay is shown to be shorter in the outpatient care model for both autologous (Table 9) and for allogeneic transplants (Table 10). In autologous transplants, all studies, 8 out of 8, report a reduction of the length of hospital stay in the outpatient model, ranging from a 3 days reduction, up to 17 days difference. In the allogeneic patients (Table 10), 3 out of 4 studies report a reduction of up to 11 days in hospital stay, only one study [19], reflects an increase of two additional days on average, in the outpatient model.

Ten research articles were found to compare costs between outpatient and inpatient care model for autologous HSCT patients (Table 11), all of them reported a positive reduction in favour of the outpatient model, ranging from a 19.32% [28], to a 46.48% [17] reduction of costs. In the case of the allogeneic HSCT patients, two authors recently studied costs, both of them report a favourable scenario for the outpatient model, showing a 11.37% [30] and a 27.17% [19] overall cost reduction.

**Discussion**

This systematic review of 29 comparative studies demonstrates that the outpatient model -in its different forms– have several benefits for healthcare organizations and patients. This paper is the first to comprehensively synthesize the current evidence from the Triple Aim perspective.

Pooled data from selected articles reveal that mortality rates without recurrence of the disease at one year are similar when comparing inpatient and outpatient HSCT. In the allogeneic case, the outpatient model has demonstrated a significantly lower mortality at 100 days [4] and at 5 years [39], and a significantly lower transplant-related mortality [8]. These results conform with the existing literature, having Ritchie [40] found that outpatient HSCT was not associated with increased morbidity.

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**Table 7. Summary of safety and effectiveness results for autologous HSCT patients.**

| First Author | Year | Neutropenic Fever | Fever | Infections | Mucositis | Neutro reco | Platelet reco | Non-hemat | Time of engraftment | Karnofsky Performance Status |
|--------------|------|------------------|-------|------------|-----------|------------|--------------|------------|---------------------|-----------------------------|
| Jagannath    | 1997 | NS               |       |            |           |            |              |            |                     |                             |
| Herrmann     | 1999 | Similar          |       |            | Out: No septic shock, Less infections (NS) |           |              |            |                     |                             |
| Frey         | 2002 | NS               |       |            |           |            |              |            |                     |                             |
| Fernández-Avilés | 2006 | Out: 76%, In: 96% (Sig) | Out: 2 days, In: 6 days (Sig) | NS           |          |            |              |            |                     |                             |
| Stiff        | 2006 | NS               |       |            |           |            |              |            | Equal               |                             |
| Graff        | 2015 | Similar          |       |            | NS        |            |              |            |                     |                             |
| Paul         | 2015 | Out: 22%, In 46% (Sig) |       |            |           |            |              |            |                     |                             |
| Abid         | 2017 | NS               |       |            |           |            |              |            |                     |                             |
| Obiozor      | 2017 | NS               |       |            |           |            |              |            | Out: greater        |                             |
| Martino      | 2018 | NS               |       |            |           |            |              |            |                     |                             |

Source: Compiled by authors based on included references.
*GVHD = Graft versus Host Disease,
NS = Non Significant, Sig = Significant, In = Inpatient and Out = Outpatient.

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Analysis on the QoL revealed no conclusive results on the impact of the outpatient model in HSCT. Significant improvement in QoL has been reported for the autologous [17] and allogeneic transplants [19,36]. However, other studies demonstrated no differences in reported QoL between both care models. This is an area that requires further research, as other authors have indicated [17]. However, there is also a need to use other data bases with publications more related to quality of life.

Table 8. Summary of safety and effectiveness results for allogeneic HSCT patients.

| First Author | Year | Neutropenic Fever | Infections (I) or Bacteremia (B) | Mucositis | RPN | Incidence GVHD | Cumulative GVHD | Days to discharge | Oral nutrition |
|--------------|------|-------------------|----------------------------------|-----------|-----|----------------|-----------------|-----------------|---------------|
| SVahn        | 2000 | 30                | Out: 3 days, In: 44% in stage II-IV | NS        |     | Out: 17%, In: 52% |               | Out: 35 median  | Out: Less days of parenteral nutrition (Sig) |
| SVahn        | 2005 | 32                | (B) Out: 3 patients In: 9 patients, (Sig) |          |     | Out: 17%, In: 52% |               |                 |               |
| Niclaou      | 2007 |                   | NS                               |           |     |                 |                 |                 |               |
| SVahn        | 2008 | 35                |                                  |           |     |                 |                 | Out: greater    |               |
| McDiarmid    | 2010 |                   | (I) Out: Less difference (Sig)   |           |     |                 |                 |                 |               |
| Ringden      | 2013 |                   |                                  |           |     |                 |                 | Out: 15% outpatient Others: 32–44% |               |
| Lisenko      | 2017 |                   | Out: 57%, In: 86% (NS)           | NS        |     |                 |                 |                 |               |
| Guru         | 2019 |                   | Out: 8,5%, In: 25,8% (sig)      | (I) NS    |     | Out: 8,5%, In: 50,8% (Sig) |               |                 |               |
| Gutierrez-Garcia | 2020 |                   | Out: 32%, In 90% (sig)          | NS        |     |                 |                 | Out: 10%, In: 29% (Sig) |               |

Source: data published on reviewed articles.
*GVHD = Graft versus Host Disease, RPN = Requiered Parenteral Nutrition, NS = Non Significative, Sig = Significant, In = Inpatient and Out = Outpatient.

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Table 9. Duration of hospital stay for autologous HSCT (in days).

| First Author | Year | Inpatient (days) | Outpatient (days) | Difference |
|--------------|------|------------------|-------------------|------------|
| Jagannath    | 1997 | 15               | 9                 | 6          |
| Meisenberg   | 1998 | 17.3             | 2.7               | 14.6       |
| Fernandez-Aviles | 2006 | 17             | 0                 | 17         |
| McDiarmid    | 2010 | 24               | 21                | 3          |
| Faucher      | 2012 | 12               | 9                 | 3          |
| Graff        | 2015 | 19.2             | 5.4               | 13.8       |
| Paul         | 2015 | 18               | 9                 | 9          |
| Abid         | 2017 | 18.3             | 6.9               | 11.4       |

Source: Calculations based on data reported in publications.

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When looking at safety and effectiveness, the outpatient option scores higher in both autologous and allogeneic cases. Numerous studies show the frequency of neutropenic fever, the appearance of mucositis and the frequency of infections to be lower in the outpatient option [17,25,27,32], although there have also been studies reporting no differences [35]. The higher frequency of oral nutrition in the outpatient model has been associated with lower probability of side effects [29], which is in line with results from other clinical trials [41,42]. Furthermore, Owatanapach et al. [7] found that patients who underwent a HSCT in an outpatient setting actually had a significantly lower risk of developing infectious complications, including 56% reduced odds of developing febrile neutropenia and 60% reduced odds of developing septicemia.

Regarding costs, this research shows that the outpatient model is less costly than the inpatient model. According to our estimated average, the number of days of hospital stay in the outpatient model is 55% and 19% less than the hospital-based model, in the autologous and allogeneic cases, respectively. As Martino et al. explain, this leads to ease of hospital bed shortage and shorter wait times [43]. The average reduction in charges or costs with respect to the hospital-based care model is 33.42% and 19.27% for autologous and allogeneic transplants, respectively. These data on reduction of costs are highly relevant as the HSCT is a resource-intensive and costly intervention. Data from Guru et al. [30], revealed the average national cost for the allogeneic HSCT ranged over 267,000 U.S. dollars in the United States. Reviews in this field also show outpatient autologous HSCT is associated with a significantly reduced bed occupancy [40].

However, there are some limitations to these findings. Firstly, there is considerable variability among studies. When looking at length of hospital stay, indications for hospitalization of

| First Author | Year | Inpatient | Outpatient | Difference |
|--------------|------|-----------|------------|------------|
| Nicolau      | 2007 | 28        | 17         | 11         |
| McDiarmid    | 2010 | 40        | 35         | 5          |
| Lisenko      | 2017 | 22        | 21         | 1          |
| Gutierrez    | 2020 | 30        | 32         | -2         |

Source: Calculations based on data reported in publications.

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Table 11. Reduction of costs (percentage) between outpatient and inpatient care model for autologous HSCT patients.

| First Author      | Year | % reduction |
|-------------------|------|-------------|
| Jagannath         | 1997 | 26.40%      |
| Meisenberg        | 1998 | 34.32%      |
| Frey              | 2002 | 28.37%      |
| Fernández-Avilés  | 2006 | 46.48%      |
| Faucher           | 2012 | 19.32%      |
| Holbro            | 2013 | 31.36%      |
| Abid              | 2017 | 32.72%      |
| Shah              | 2017 | 29.70%      |
| Martino           | 2017 | 42.34%      |
| Dunavin           | 2020 | 43.15%      |

Source: Calculations based on data reported in publications

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outpatients differ between studies. As other investigators point out, further research should adopt common definitions of hospital-outpatient care or collect and report data on clinical components more explicitly to facilitate comparisons across models [12]. Secondly, early discharge, and comprehensive or total hospital at home programmes were all considered for the purpose of this review. As some authors suggest, this may make the comparison and generalisation of results more difficult [27,28]. Thirdly, only one randomised clinical trial was found [28], exposing several limitations for the comparison analysis due to the variability in study designs and patient selection criteria. Indicating the set of clinical variables could have been the deciding factor for clinicians when choosing an inpatient versus an outpatient strategy, which can affect the results [26,28,44]. Martino et al. [45], elaborated Italian consensus guidelines in 2016 to homogenize and bridge gaps in these aspects of outpatient HSCT. Lastly, some individual studies express their limitation in the generalizability of their cost analysis results due to context factors. It should be noted that only the costs included by the authors of the papers are reported in our analysis. A further more detailed analysis of the methodology of cost analysis can be very useful to agree on better options for cost comparison. The complexity in the definition and practice of cost analysis of hematopoietic stem cell transplantation programs has been reported by Al-Hashmi et al 2020 [46].

Considering the above limitations, we propose that future research should: firstly, take a look from a management perspective and propose homogeneous study designs and protocols for clinical trials in Hospital and outpatient models for Hematopoietic Stem Cell Transplantation (HSCT); secondly, when studying costs, these type of innovations require the consideration of multiple perspectives, beyond clinical aspects, and as such, opportunity cost and calculate cost such as staff resources, or the role of a caregiver, which are needed to implement such a new model of care and lastly, focus on making further formal assessment of the experience of care of patients, family and caregivers. There is a clear gap in gathering and publishing this knowledge which can be used to evaluate and improve the management of outpatient schemes.

This research is the first to compare the published results on HSCT between in-hospital and outpatient models in peer-reviewed journals, while bringing a unique perspective to the current body of literature, looking at the integrated impact on health outcomes, experience of care and cost. Limited by the heterogeneity among papers, this study concludes that the outpatient HSCT is safe and effective and its main advantages include significant cost reduction, decrease in length of hospitalization, alleviating constraints on chronic bed shortage, and facilitating patient convenience.

**Supporting information**

S1 Checklist. PRISMA 2009 checklist I.
(TIF)

S2 Checklist. PRISMA 2009 checklist II.
(TIF)

S3 Checklist. PRISMA 2009 checklist III.
(TIF)

S1 Fig. PRISMA diagram.
(TIF)

S1 File. Descriptor combination.
(TIF)
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References

1. Khaddour K, Hana CK, Mewawaalla P. Hematopoietic Stem Cell Transplantation. StatPearls. Treasure Island (FL): StatPearls Publishing; 2021. http://www.ncbi.nlm.nih.gov/books/NBK536951/.
2. Broder MS, Quock TP, Chang E, Reddy SR, Agarwal-Hashmi R, Arai S, et al. The Cost of Hematopoietic Stem-Cell Transplantation in the United States. Am Health Drug Benefits. 2017; 10: 366–374. PMID: 29263771
3. Blommestein HM, Verelst SGR, Huijgens PC, Blijlevens NMA, Cornelissen JJ, Uyl-de Groot CA. Real-world costs of autologous and allogeneic stem cell transplantations for haematological diseases: a multicentre study. Ann Hematol. 2012; 91: 1945–1952. https://doi.org/10.1007/s00277-012-1530-2 PMID: 22864761
4. McDiarmid S, Hutton B, Atkins H, Bence-Bruckler I, Bredeson C, Sabri E, et al. Performing autologous and allogeneic hematopoietic SCT in the outpatient setting: effects on infectious complications and early transplant outcomes. Bone Marrow Transplant. 2010; 45: 1220–1226. https://doi.org/10.1038/bmt.2009.330 PMID: 19946343
5. Ringdén O, Remberger M, Holmberg K, Edeskog C, Wikström M, Eriksson B, et al. Many Days at Home during Neutropenia after Allogeneic Hematopoietic Stem Cell Transplantation Correlates with Low Incidence of Acute Graft-versus-Host Disease. Biol Blood Marrow Transplant. 2013; 19: 314–320. https://doi.org/10.1016/j.bbmt.2012.10.011 PMID: 23089563
6. Passweg JR, Baldomero H, Basak GW, Chabannon C, Corbacioglu S, Duarte R, et al. The EBMT activity survey report 2017: a focus on autologeneic HCT for nonmalignant indications and on the use of non-HCT cell therapies. Bone Marrow Transplant. 2019; 54: 1575–1585. https://doi.org/10.1038/s41409-019-0465-9 PMID: 30728439
7. Owattanapanich W, Suphadirekkul K, Kunacheewa C, Ungprasert P, Prayongratana K. Risk of febrile neutropenia among patients with multiple myeloma or lymphoma who undergo inpatient versus outpatient autologous stem cell transplantation: a systematic review and meta-analysis. BMC Cancer. 2018; 18: 1126. https://doi.org/10.1186/s12885-018-5054-6 PMID: 30445930
8. Svahn BM, Ringdén O, Remberger M. Long-term follow-up of patients treated at home during the panmyelopenic phase after autologeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2005; 36: 511–516. https://doi.org/10.1038/sj.bmt.1705096 PMID: 16025151
9. Bentley Phillips. 2017 U.S. organ and tissue transplant cost estimates and discussion. Milliman Res Rep. 2017; 20.
10. Bazinet A, Popradi G. A general practitioner’s guide to hematopoietic stem-cell transplantation. Curr Oncol Tor Ont. 2019; 26: 187–191. https://doi.org/10.3747/co.26.5033 PMID: 31285655
11. Haematopoietic stem cell transplantation: COVID-19 rapid guideline summary—Hospital Healthcare EuropeHospital Healthcare Europe. [cited 5 May 2021]. https://hospitalhealthcare.com/covid-19-haematopoietic-stem-cell-transplantation-covid-19-rapid-guideline-summary/.
12. Leff B. Defining and disseminating the hospital-at-home model. CMAJ Can Med Assoc J. 2009; 180: 156–157. https://doi.org/10.1503/cmaj.081891 PMID: 19153385

13. Gonçalves-Bradley DC, Iliffe S, Doll HA, Broad J, Gladman J, Langhorne P, et al. Early discharge hospital at home. Cochrane Database Syst Rev. 2017; 6: CD000356. https://doi.org/10.1002/14651858.CD000356.pub4 PMID: 28651296

14. Shepperd S, Iliffe S, Doll HA, Clarke MJ, Kalra L, Wilson AD, et al. Admission avoidance hospital at home. Cochrane Database Syst Rev. 2018; 9: CD007491. https://doi.org/10.1002/14651858.CD007491.pub2 PMID: 27583824

15. Jagannath S, Vesole D, Zhang M, Desikan K, Copeland N, Jagannath M, et al. Feasibility and cost-effectiveness of outpatient autotransplants in multiple myeloma. Bone Marrow Transplant. 1997; 20: 445–450. https://doi.org/10.1038/sj.bmt.1700901 PMID: 9313876

16. Meisenberg B, Ferran K, Hollenbach K, Brehm T, Jollon J, Piro L. Reduced charges and costs associated with outpatient autologous stem cell transplantation. Bone Marrow Transplant. 1998; 21: 927–932. https://doi.org/10.1038/sj.bmt.1701191 PMID: 9613786

17. Fernández-Avilés F, Carreras E, Urbano-Ispizua A, Rovira M, Martínez C, Gaya A, et al. Case-Control Comparison of At-Home to Total Hospital Care for Autologous Stem-Cell Transplantation for Hematologic Malignancies. J Clin Oncol. 2006; 24: 4855–4861. https://doi.org/10.1200/JCO.2006.06.4238 PMID: 17001069

18. Glück S, des Rochers C, Cano C, Dorrean M, Germond C, Gill K, et al. High-dose chemotherapy followed by autologous blood cell transplantation: a safe and effective outpatient approach. Bone Marrow Transplant. 1997; 20: 431–434. https://doi.org/10.1038/sj.bmt.1700901 PMID: 9313874

19. Gutiérrez-García G, Rovira M, Arab N, Gallego C, Sánchez J, Ángeles Álvarez M, et al. A reproducible and safe at-home autologous hematopoietic cell transplantation program: first experience in Central and Southern Europe. Bone Marrow Transplant. 2020; 55: 965–973. https://doi.org/10.1038/s41409-019-0768-x PMID: 31932656

20. van Tiel FH, Harbers MM, Kessels AG, Schouten HC. Home care versus hospital care of patients with hematological malignancies and chemotherapy-induced cytopenia. Ann Oncol Off J Eur Soc Med Oncol. 2005; 16: 195–205. https://doi.org/10.1093/annonc/mdi042 PMID: 15668270

21. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009; 6: e1000097. https://doi.org/10.1371/journal.pmed.1000097 PMID: 19621072

22. Berwick DM, Nolan TW, Whittington J. The Triple Aim: Care, Health, And Cost. Health Aff (Millwood). 2008; 27: 759–769. https://doi.org/10.1377/hlthaff.27.3.759 PMID: 18474969

23. Cantú-Rodríguez OG, Sánchez-Cárdenas M, Treviño-Montemayor OR, Gutiérrez-Agüerre CH, Tarín-Arzaga L, Jaime-Perez JC, et al. Impact of outpatient non-myeloablative hematopoietic stem cell transplantation in quality of life vs. conventional therapy, Psychol Health Med. 2016; 21: 10–19. https://doi.org/10.1080/13548506.2015.1054843 PMID: 26125120

24. Rizzo JD, Vogelsang GB, Krumm S, Frink B, Mock V, Bass EB. Outpatient-Based Bone Marrow Transplantation for Hematologic Malignancies: Cost Saving or Cost Shifting? J Clin Oncol. 1999; 17: 2811–2811. https://doi.org/10.1200/JCO.1999.06.4238 PMID: 10561357

25. Graff TM, Singavi AK, Schmidt W, Eastwood D, Drobsky WR, Horowitz M, et al. Safety of outpatient autologous hematopoietic cell transplantation for multiple myeloma and lymphoma. Bone Marrow Transplant. 2015; 50: 947–953. https://doi.org/10.1038/bmt.2015.46 PMID: 25867651

26. Shah N, Cornelison AM, Saliba R, Ahmed S, Nieto YL, Bashir Q, et al. Inpatient vs outpatient autologous hematopoietic stem cell transplantation for multiple myeloma. Eur J Haematol. 2017; 99: 532–535. https://doi.org/10.1111/ejh.12970 PMID: 28895206

27. Frey P, Stinson T, Sistoon A, Knight S, Ferdman E, Traynor A, et al. Lack of caregivers limits use of outpatient hematopoietic stem cell transplant program. Bone Marrow Transplant. 2002; 30: 741–748. https://doi.org/10.1038/sj.bmt.1703676 PMID: 12439696

28. Faucher C, Le Corroller Soriano AG, Esterni B, Vey N, Stoppa AM, Chabannon C, et al. Randomized study of early hospital discharge following autologous blood SCT: medical outcomes and hospital costs. Bone Marrow Transplant. 2012; 47: 549–555. https://doi.org/10.1038/bmt.2011.126 PMID: 21725375

29. Nicolau JE, de Melo LMMP, Sturaro D, Saboya R, Dulley FL. Evaluation of early hospital discharge after autologous bone marrow transplantation for chronic myeloid leukemia. Sao Paulo Med J. 2007; 125: 174–179. https://doi.org/10.1590/s1516-31802007000300009 PMID: 17923943

30. Guru Murthy GS, Hari PN, Szabo A, Pasquini M, Narra R, Khan M, et al. Outcomes of Reduced-Intensity Conditioning Autologous Hematopoietic Cell Transplantation Performed in the Inpatient versus Outpatient Setting. Biol Blood Marrow Transplant. 2019; 25: 827–833. https://doi.org/10.1016/j.bbmt.2018.12.069 PMID: 30572109
31. Svahn B-M, Remberger M, Heijbel M, Martell E, Wikström M, Eriksson B, et al. Case-Control Comparison of At-Home and Hospital Care for Allogeneic Hematopoietic Stem-Cell Transplantation: The Role of Oral Nutrition. Transplantation. 2008; 85: 1000–1007. https://doi.org/10.1097/TP.0b013e31816a3267 PMID: 18408581

32. Stiff P, Mumbry P, Milner L, Rodriguez T, Parthswarthy M, Kiley K, et al. Autologous hematopoietic stem cell transplants that utilize total body irradiation can safely be carried out entirely on an outpatient basis. Bone Marrow Transplant. 2006; 38: 757–764. https://doi.org/10.1038/sj.bmt.1705525 PMID: 17057729

33. Martino M, Console G, Russo L, Melia'do' A, Meliambro N, Moscato T, et al. Autologous Stem Cell Transplantation in Patients With Multiple Myeloma: An Activity-based Costing Analysis, Comparing a Total Inpatient Model Versus an Early Discharge Model. Clin Lymphoma Myeloma Leuk. 2017; 17: 506–512. https://doi.org/10.1016/j.clml.2017.05.018 PMID: 28647402

34. Summers N, Dawe U, Stewart D. A comparison of inpatient and outpatient ASCT. Bone Marrow Transplant. 2000; 26: 389–395. https://doi.org/10.1038/sj.bmt.1702534 PMID: 10982285

35. Abid MB, Christopher D, Abid MA, Poon ML, Tan LK, Koh LP, et al. Safety and cost-effectiveness of outpatient autologous transplantation for multiple myeloma in Asia: single-center perspective from Singapore. Bone Marrow Transplant. 2017; 52: 1044–1046. https://doi.org/10.1038/bmt.2017.77 PMID: 28481354

36. Lisenco K, Sauer S, Bruckner T, Egerer G, Goldschmidt H, Hillengass J, et al. High-dose chemotherapy and autologous stem cell transplantation of patients with multiple myeloma in an outpatient setting. BMC Cancer. 2017; 17: 151. https://doi.org/10.1186/s12885-017-3137-4 PMID: 28226122

37. Svahn B-M, Bjurman B, Myrbeck K, Aschan J, Ringdén O. Is it safe to treat allogeneic stem cell transplant recipients at home during the pancytopenic phase? A pilot trial. Bone Marrow Transplant. 2000; 26: 1057–1060. https://doi.org/10.1038/sj.bmt.1702672 PMID: 11108303

38. Holbro A, Ahmad I, Cohen S, Roy J, Lachance S, Chagnon M, et al. Safety and Cost-Effectiveness of Outpatient Autologous Stem Cell Transplantation in Patients with Multiple Myeloma. Biol Blood Marrow Transplant. 2013; 19: 547–551. https://doi.org/10.1016/j.bbmt.2012.12.006 PMID: 23253556

39. Granot N, Storer BE, Cooper JP, Flowers ME, Sandmaier BM, Storb R. Allogeneic Hematopoietic Cell Transplantation in the Outpatient Setting. Biol Blood Marrow Transplant. 2019; 25: 2152–2159. https://doi.org/10.1016/j.bbmt.2019.06.025 PMID: 31255743

40. Ritchie L. Outpatient stem cell transplant: effectiveness and implications. Br J Community Nurs. 2005; 10: 14–20. https://doi.org/10.12968/bjcn.2005.10.17325 PMID: 15750495

41. Russell JA, Chaudhry A, Booth K, Brown C, Woodman RC, Valentine K, et al. Early outcomes after allogeneic stem cell transplantation for leukemia and myelodysplasia without protective isolation: a 10-year experience. Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2000; 6: 109–114. https://doi.org/10.1016/s1083-8791(00)70073-5 PMID: 10741619

42. Leger C, Sabloff M, McDiarmid S, Bence-Bruckler I, Atkins H, Bredeson C, et al. Outpatient autologous hematopoietic stem cell transplantation for patients with relapsed follicular lymphoma. Ann Hematol. 2006; 85: 723–729. https://doi.org/10.1007/s00277-006-0149-6 PMID: 16832675

43. Martino M, Ciavarella S, De Summa S, Russo L, Meliambro N, Imbalzano L, et al. A Comparative Assessment of Quality of Life in Patients with Multiple Myeloma Undergoing Autologous Stem Cell Transplantation Through an Outpatient and Inpatient Model. Bone Marrow Transplant J Am Soc Blood Marrow Transplant. 2018; 24: 608–613. https://doi.org/10.1016/j.bbmt.2017.09.021 PMID: 29032271

44. Paul TM, Liu SV, Chong EA, Luger SM, Porter DL, Schuster SJ, et al. Outpatient Autologous Stem Cell Transplantation for Patients With Myeloma. Clin Lymphoma Myeloma Leuk. 2015; 15: 536–540. https://doi.org/10.1016/j.clml.2015.05.006 PMID: 26141214

45. Martino M, Lemoli RM, Girmenia C, Castagna L, Bruno B, Cavallo F, et al. Italian consensus conference for the outpatient autologous stem cell transplantation management in multiple myeloma. Bone Marrow Transplant. 2016; 51: 1032–1040. https://doi.org/10.1038/bmt.2016.79 PMID: 27042841

46. Al-Hashmi H, Alsagheir A, Estanislao A, Bacal J, Alshebah A, Alblowe B, et al. Establishing hematopoietic stem cell transplant programs; overcoming cost through collaboration. Bone Marrow Transplant. 2020; 55: 695–697. https://doi.org/10.1038/s41409-020-0793-9 PMID: 31965055