Hematopoietic Stem Cell Transplantation versus Immunosuppressive Therapy in Patients with Acquired Severe Aplastic Anemia: A Cost-Effectiveness Analysis

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Abstract

Background

Controversy remains regarding which therapy to initially select for severe aplastic anemia (SAA) patients aged 35-50-years-old. This analysis of cost-effectiveness using a Markov model compared immunosuppressive therapy (IST) with hematopoietic stem cell transplantation (HSCT) in age-stratified patients with SAA.

Methods

In younger patients (aged 18-35-years-old), HSCT yielded 22.67 quality-adjusted life years (QALYs), compared with 12.21 QALYs for IST therapy, offering an expected benefit with HSCT of 10.46 QALY.

Results

The HSCT strategy dominated in younger patients, though it was $146,970 more expensive than IST and the ICER of HSCT to IST was $14,054.19/QALY, which was less than the willingness to pay (WTP) value of $25,397.57/QALY. The IST strategy dominated in older patients because it was $72,009 less expensive than HSCT and yielded 3.24 QALYs more than HSCT. The model was vigorous in the sensitivity analyses of the key variables tested through the plausible ranges that were acquired from costing sources and previously-published literature.

Conclusions

The preferred induction strategy for younger patients with SAA appears to be HSCT and the preferred strategy for older patients is IST, which minimizes cost while maximizing QALYs.

1. Background

Aplastic anemia (AA) is an immune-mediated diseaseinvolving hematopoietic failure. Severe aplastic anemia (SAA) progresses rapidly and has a high mortality. Standard front-line treatment for SAA patients is either hematopoietic stem cell transplantation (HSCT) or immunosuppressive therapy (IST).

Acquired SAA is considered the result of the immune-mediated destruction of hematopoietic cells and, therefore, HSCT may essentiallycure the disease. The overall survival rate of SAA patients receiving HSCT decreases with age due to the increasing possibility of graft failure and graft-versus-host disease (GVHD) [1]. The European Hematopoietic Stem Cell Transplantation Center guidelines state that sibling HSCT is the first choice of treatment for adolescent and young adult SAA patients and that patients between the ages of 35 and 50-years-old should be carefully assessed for complications after transplantation. The long-term cure rate of HLA-matched hematopoietic stem cell transplantation (HSCT) has reached 75%-80% in recent years [2]. The first-line treatment should be HSCT if patients under 35-years-old have HLA-matched relative donors. The upper age limit for HSCT as first-line therapy remains controversial

because the results vary extensively in diverse clinical studies [2]. The latest British Committee for Hematology Standardization recommends an age limit of 50-years-old for the use of HLA-contracted cell donor HSCT and patients aged 35 to 50-years-old need to be carefully assessed for comorbidities to decide whether they are suitable for transplantation [3].

Immunosuppressive therapy (IST) suppresses immune function to reduce abnormal immune responses. The current standard IST first-line therapy is Antithymocyte globulin (ATG) combined with Cyclosporine (CSA). IST is indicated for non-severeaplastic anemia (AA) with blood transfusion dependence, minors lacking HLA-matched relative donors, severe aplastic anemia (SAA) patients with HLA-matched relative donors aged > 35 years, and patients aged > 50 years [4]. The overall survival rate with IST is generally high, with a 5-year survival rate of 60–85% [5]. There is no upper age limit for IST but the mortality rates for patients over 60-years-oldincrease. IST does not cure SAA and there are 3major adverse consequences: no response, relapse, and clonal evolution.

Hematopoietic stem cell transplantation (HSCT) offers the best chance of treatment but it is costly and limited by the incidence of GVHD, especially in elderly patients who lack HLA-matched relative donors. IST is also a first-line therapy that can induce a response in up to 75% of patients [6], but it also has a high relapse rate and can cause secondary clonal diseases, especially in young SAA patients. Therefore, the choice of treatment for patients aged 35 to 50-year-old with SAA is clinically controversial. This study used clinical economics to compare the cost-effectiveness of 2 treatments for patients aged 35-50-years-old with severe aplastic anemia (SAA) and for another group of 18-35-year-old SAA patients at the same time. This study alsoattempted to provide an objective reference for the clinical selection of treatment methods and to investigate the price threshold of the prioritized method, thereby decreasing patients' medical expenses and improving the quality-adjusted life years (QALYs).

2. Methods

2.1 Patients

This study enrolled adult patients who were diagnosed with SAA for the first time and had not received immunosuppressive therapy (IST) or hematopoietic stem cell transplantation (HSCT). The study population was consistent with that from the literature on probabilistic sources. The age distribution of the patients was mostly concentrated in the range of 18-50-years-old. The patients were divided into 2groups, namely the 18-35-years-old and 35-50-years-old groupfor analysis.

The structure of the model

We established a Markov model of 2interventions based on the relevant literature and clinical practice to perform a cost-effectiveness analysis of IST and HSCT for SAA. The incremental cost-effectiveness ratio (ICER) was the principal evaluation index. If the ICER is less than a certain threshold, the therapy is cost-effective; otherwise, it is not. The ICER threshold is conveyed as the willingness to pay (WTP), which

reflects the economic burden of the patient's willingness to bear a quality-adjusted life year (QALY) for treating the disease. We typically used the common GDP per capita for comparison: If ICER < GDP per capita, the increased cost was completely worthwhile and the therapy was very cost-effective. However, if the per capita GDP < ICER < 3 times per capita GDP, the increased cost was acceptable and the therapy was cost-effective.If ICER > 3 times the per capita GDP, the added cost was not worthwhile and the therapy was not cost-effective. Therefore, the WTP value of this study was set to 3 times the Chinese GDP per capita ($25,397.57).

We used the TreeAge Pro 2011 software to build the Markov model to assess the cost-effectiveness of the 2 options. The TreeAge Pro 2014 Suite software is a professional analysis software for building decision trees and Markov models. Two cost-effectiveness analysis models (Figs. 1A and 1B) with 5 states were createdbased on the relevant guidelines and clinical practice of IST and HSCT for severe aplastic anemia (SAA). The models intuitively reflect the mutual transformation association between the states. Patients that choose HSCT may be in 1 of 5 states of ‘healing/death/ineffective (still SAA)/short-term complications/long-term complications’ during the first cycle (after treatment) and transitioning to other states in the second and subsequent cycles. Similarly, patients that choose IST may be in 1 of 5states of ‘CR/PR/death/invalid (still SAA)/serious complications’ in the first cycle (after treatment) and transitionto other states in the second and subsequent cycles. The state of death cannot be transformedinto any other state and is also known as the absorbing state. Transitions between several other states have different probabilities and different states necessitate different medical costs. Each patient can only be in 1 state in any 1cycle. The model cycle of both scenarios was set to 6 months. The model was run for 30 years (at which point most patients had died) to reflect the natural outcome of the disease and the life expectancy of the study population.

2.2 Data

The probability of conversion between the different states of the model derivedfrom an extensive literature search. The inclusion criteria were as follows: (1) The study time ranged from January 1, 1980, to August 1, 2018; (2) Research sample for the initial diagnosis of AA; (3) Sample population that has not received IST/HSCT treatment before; (4) Total sample size > 30 cases; and (5) Studies dividing the sample population into HSCT and IST groups for comparison. HSCT included HLA-matched sibling transplantation, unrelated donor transplantation, and alternative donor HSCT. The exclusion criteria were as follows: (1) A study time frame that was earlier than January 1, 1980; (2) Study-sample age range of < 18 years; (3) Total study-sample size of < 30 cases; and (4) A sample population that had previously received HSCT/IST treatment. Accounting for expert advice and making certain assumptions based on the existing literature and clinical guidelines, we arranged the baseline value of the possibilities (Table 1).

Table 1
Baseline value of the possibilities of HSCT and IST and Primary outcomes of QALYs

	Variables	Baseline(range)(%)		Literature
		18-35y	35-50y	
HSCT	Transplant failure rate	1.5-(0-12.5)	2.8-(0-15.2)	7, 9, 10,11, 13, 14, 15, 17,18
	3-year OS rate	80.1(47–96)	66.7(45-81.5)	2, 7–18
	Short-term complications	13.8(9.1–28.7)	15.4(10.3–34.1)	7–11,13–16
	Long-term complications	19.0(7-27.5)	22.6(8.3–40.2)	7–11,13–16
IST	3-year OS rate	73.9(58.2–86.2)	84.2(69–91)	2,7–18
	CR rate	24.4(10.2–64.3)	26.9(6.5–51.2)	6, 7, 10,11,13, 15
	PR rate	33.0(16.5–68.3)	36.2(18.1–59.4)	6, 9,10,11,13,15
	No-response rate	30.1(4–54)	28.7(10.2–47)	6, 7,9,10,11,13,14,15,17,18
	Serious side-effect	5.3(0-27.3)		7,8,10,11,13, 14, 15
	Relapse rate	7.1(5.1–33)		9, 10,11, 14,17
HSCT	QALYs	22.67	12.87	
	Cost	$202,007.78	$229,724.34	
	ICER			
IST	QALYs	12.21	16.11	
	Cost	$55,037.73	$157,714.99	
	ICER			
Incremental Effectiveness	QALYs	+ 10.46 QALYs	-3.24 QALYs	
	Cost	$146,970.06	$72,009.35	

HSCT: hematopoietic stem cell transplantation; IST: immunosuppressive therapy; OS: overall survival; CR: complete remission; PR: partial remission; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio. For a given variable, the upper row is for the 18–35 year age group, and the lower row is for the 35–50 year age group.

Variables	Baseline(range)(%)	Literature
ICER	$14,054.19/ QALY<$25,397.57/ QALY	-$22,225.11/ QALY

HSCT: hematopoietic stem cell transplantation; IST: immunosuppressive therapy; OS: overall survival; CR: complete remission; PR: partial remission; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio. For a given variable, the upper row is for the 18–35 year age group, and the lower row is for the 35–50 year age group.

2.3 Cost

This study only considered direct medical costs from the perspective of China's health care system. Based on the ICD-10 code, inpatients over 18-years-old admitted to the Huashan Hospital associatedwith Fudan University from January 1, 2009, to January 1, 2019, were selected according to the diagnosis. The screening conditions were limited to the first diagnosis of SAA patients. The treatment cost and follow-up cost were calculated and expert advice was consulted. We used the calculated median cost in the baseline analysis and indirect costs such as loss of labor capacity were not included in this study (Table 2).

Table 2
The main cost of the treatment for SAA

Examination and treatment items	cost (dollar$)
Routine examination (blood routine, liver function, renal function, electrolytes) (once)	16.14(2.86 + 7.14 + 2.57 + 3.57)
Cyclosporine concentration (once)	21.43
Pretransfusion compatibility check (once)	21.43
Bone marrow puncture (once)	38.57
Valacyclovir (0.3 g/tablet)	0.20
Imipenem cilastatin sodium (0.5 g/bottle)	20.96
Voriconazole (200 mg/tablet)	51.96
Vancomycin (0.5 g/bottle)	16.80
Rabbit ATG (25 mg/stick)	371.43
Cyclosporine (25 mg, 50 capsules/box)	34.78
Methylprednisolone (40 mg/stick)	3.69
MTX (1 g/stick)	26.44
CTX (0.2 g/stick)	3.64
Calcium folinate for injection (50 mg/stick)	1.04
Recombinant human granulocyte stimulating factor (75 μg/stick)	6.22
Recombinant thrombopoietin (5000 μl/stick)	155.06
Mycophenolate moretil Capsules (250 mg/tablet)	1.97
Tacrolimus (5 mg/stick)	1.80
Ferric amine (0.5 g/stick)	7.95
Hospitalization + nursing/day	9

The health utility value is the weight of a certain health state comparative to the total health state. It is an index for assessing the satisfaction degree of a certain health condition and is a comprehensive index showingthe health status of the individual. The value ranges from 0–1 and death is scored as 0, while complete health is scored as 1. The health utility values used in this study were resultant from the expert opinion: CR and survival with no complications werefundamentally equivalent to a complete health status and consequently, their health utility value was 1. PR had a slightly lower health utility value of 0.9; the health utility value of short-term complications and long-term complications was 0.5 and 0.6, respectively.The quality of life in patients with SAA and severe complications was greatly affected, with a

health utility value of 0.3 and the health utility value of death was 0. Discounting is the process of converting the cost and health outcomes incurred at different times (years) into cost and health outcomes at the same ‘time point’ at a certain interest rate. A 3% discount rate was used in this study.

This study used quality-adjusted life years (QALYs) to evaluate the health outcomes of the 2 groups, namely, the ‘effects’ in the cost-effectiveness analysis. One QALY is equal to the expected life of the model simulation multiplied by the health utility value during this time.

All procedures followed were according to the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

3. Results

3.1 The cost-effective analysis

The 18 to 35-year-old group and the 35 to 50-year-old group generated very different conclusions based on the results of the 30-year simulation (Table 1). For the 18 to 35-year-old group, hematopoietic stem cell transplantation (HSCT) had a QALY increment of 10.46 QALYs relative to immunosuppressive therapy (IST), with a cost increase of $146,970.06 and an incremental cost-effectiveness ratio (ICER) of $14,054.19/QALY, which was less than the WTP value of $25,397.57. Therefore, the choice of HSCT was more cost-effective than IST for the 18 to 35-year-old population. However, for the 35–50 age group, the HSCT group's QALY increment relative to the IST group was − 3.24 QALYs and the cost increase was $72,009.35. Therefore, HSCT wasnot a cost-effective option, while IST was a more cost-effective option for the 18 to 35-year-old group.

According to the baseline examination of the Markov cohort simulation, the total cost of HSCT and IST always had a large gap, even with the extension of the follow-up period for the 18–35 age group, but the increased effect of HSCT to IST (quality-adjusted life year, QALY) was increasing.Therefore, the ratio of the cost difference to effect difference progressively became smaller (Table 3). As time elapses, HSCT's relatively high health resource input shows a better cost-effectiveness advantage. In the 35–50 age group, the cost of IST was always lower and the QALYs were always more, so IST is always in absolute advantage (Table 3).

Table 3
Baseline analysis of the Markov cohort simulation

Therapy	Time	Cost (dollar$)	QALYs	ICER
18–35 age group				
HSCT	10 years	144,743.55	9.40	28,766.15
IST		49,239.62	6.08	
HSCT	20 years	183,470.77	17.65	18,144.36
IST		53,728.41	10.50	
HSCT	30 years	202,007.78	22.66	14,054.19
IST		55,052.01	12.21	
35–50 age group				
HSCT	10 years	182,963.09	6.29	IST in absolute advantage
IST		120,799.61	8.46	
HSCT	20 years	218,597.89	11.93	
IST		148,734.45	14.95	
HSCT	30 years	229,724.34	12.87	
IST		157,714.99	16.11	

HSCT: hematopoietic stem cell transplantation; IST: immunosuppressive therapy; QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio.

3.2 The probabilistic sensitivity analysis

The probabilistic sensitivity analysis assesses the influence of all model parameters on the analysis results by altering all the set model parameters at the same time. The analysis follows the standard of Monte Carlo simulation, in which the individual can transfer to different states in each cycle according to the transition probability between states. The results are demonstratedin the incremental cost-effect scatter plots (Figs. 1C and 1D) through the simulation of a large number of cohort samples (the probability sensitivity analysis of this study for a Monte Carlo simulation of 1000 sample sizes). The dotted line in the figure is the WTP threshold line and the results of ICER are distributed on both sides of the threshold line. As seen inthe figure, with a threshold of WTP=$25,397 in 65.9% of cases in the 18-35-year age group, HSCT was more cost-effective and in 63.3% of cases in the 35-50-year age group, IST was more cost-effective.

3.3 The threshold analysis

The threshold analysis evaluates when the cost-effective optimal decision is altered to another scheme by changing the variables of the Markov model according to the probability range of the model. The

examination (Table 4) showed that for the 18–35 age group, when the cost of transplantation was no higher than $129,714.29, HSCT was more cost-effective than IST andthe preferred treatment method from the perspective of health economics. Even if the cost of IST was reduced to 0, HSCT still had an advantage. However, when the transplant failure rate was as high as 18.6% or the mortality rate reached 41.2% within half a year after the successful transplant or the IST no-responserate decreased to 1.36%, the ideal decision becameIST. For the 35–50 age group, the cost of transplantation, failure rate of transplantation, and change in mortality during the half-year after transplantation did notchange IST as the preferred treatment, but when the cost of IST raised to $89,147, the IST no-response rate reached 57.37% or the relapse rate within half a year reached 46.84%, the ideal decision changed to HSCT. This model is not sensitive to variations in utility values and discount rates.

Table 4
Sensitivity analyses for age-stratified groups

	18–35 age group		35–50 age group	
	Base case	threshold	Base case	threshold
Cost of HSCT	57,142	129,714	57,142	/
Cost of IST	17,142	/	17,142	89,147
The failure rate of transplantation	1.5%	18.6%	3.91%	/
The mortality rate within half a year after successful transplant	8.86%	41.2%	14.63%	/
No-response rate of IST	33.2%	1.36%	25.2%	57.37%
Relapse rate within half a year after IST	15.19%	/	11.57%	46.84%
Discount rate	3%	/	/	/
Abbreviations: HSCT: hematopoietic stem cell transplantation; IST: immunosuppressive therapy.				

4. Discussion

Immunosuppressive therapy (IST) and hematopoietic stem cell transplantation (HSCT) have been extensively approved in the treatment of severe aplastic anemia (SAA) [7–8]. The long-term survival rate of SAA patients has been significantly improved in recent years, but the 2 treatment methods have diverse limitations[9]. IST does not cure SAA, it only allows patients to achieve complete or partial remission and it may have 3major adverse consequences: no response, relapse, and clonal evolution. HSCT costs more and is limited by the source of donors and acute and chronic GVHD [10]. The current guidelines recommend that sibling HSCT is the treatment of choice for adolescent and young adult SAA patients, but the choice of treatment options for SAA patients aged 35–50 years is clinically controversial and there are no concise recommendations [4].

From the perspective of clinical economics, this study took main factors, such as age, cost, and effect into account to create a Markov model for comprehensive analysis and drawsuggestions for the choice of treatment options. For patients aged 18-35-years-old with SAA, it is recommended to use HSCT at the current GDP level in China. The cost of obtainingquality-adjusted life years (QALY) is $14,054.19, which is less than the WTP value of $25,397.57, indicatingthat patients obtain more QALYs under an acceptable direct cost input. For patients aged 35-50-years-old with SAA, the recommended option is IST, with more QALYs and less direct cost input. This conclusion was corroborated in the sensitivity analysis and the same conclusion was attained using a Monte Carlo simulation to simulate 1000 samples. We found that when the treatment cost doubles or the transplant failure rate, mortality, or IST relapse rate changes more than 5 times, it possibly change the conclusion by adjusting different variables, which once again proves the conclusion of this study. If we can decrease the total cost of a particular treatment, we will achieve a better incremental cost-effectiveness ratio (ICER) and improve the efficiency of health care. Similarly, increasing the success rate of a particular treatment and reducing the relapse rate are also key methodsin increased cost-effectiveness.

Previous comparisons of treatments for severe aplastic anemia (SAA) have focused on outcomes such as the success/remission rate, overall survival rate, relapse rate, and event-free-survival rate [11]. There are numerous studies comparing the outcomes of diverse treatments for different age groups, but there is no comparison of the cost-effectiveness of the treatments for SAA and the economic factor has not been included in these considerations [12–15]. This study is the first cost-effectiveness analysis of SAA treatments. For patients with SAA that find it difficult to choose between the two main treatment methods, a cost-effectiveness analysis was performed in a younger patient group and an older patient group. It is concluded that HSCT is the first choice for younger patients and IST is preferred for older patients, which has great guiding value for clinical practice.

It is also important to evaluate the treatment effect when assessing the effectiveness of a treatment regimen, as well as evaluating the cost of treatment and the cost of adverse events. For patients and the government, economic factors are very important and cannot be ignored. Often, clinicians pay more attention to the assessment of clinical effects and it is easy to overlook the evaluation of adverse events or costs [16–17]. A clinical decision made this way may have certain biases but adverse events and costs are also significant factors to consider in clinical decision-making [18]. For example, a cost-effectiveness evaluation of primary central nervous system lymphoma (PCNSL) treatment in 2012 [19] concluded that young patients that select high-dose Methotrexate (MTX) chemotherapy combined with radiation therapy can reduce costs and improve quality-adjusted life years (QALYs) and that patients over the age of 60 are more suitable for chemotherapy because the cost of chemotherapy alone for the elderly is lower while the QALYs acquired by the 2 treatment options are almost the same. This study provides suggestions with comprehensive considerations for PCNSL patients to choose a treatment option. In patients with SAA, the incidence and severity of adverse events associated with IST compared with those of HSCT greatly differ and the resulting costs are also very different. Consequently, this study takes both the effect of treatment and the direct costs of treatment into consideration.

There are some limitations to this study. First, the model assumes that the transition probabilities are equal in each cycle, but the transition probability may change over time. Also, HSCT requires informed consent from donors and recipients prior to treatment. Therefore, no randomized controlled trials have been completed to investigate this problem, so we selected high-quality studies with other designs that met the inclusion criteria as sources of data. We performed a sensitivity analysis to recognize sources of reliability. The health utility value parameters used in the models were also derived from expert advice and may not accurately reflect the patient's quality of life because health utility values have not received sufficient attention and lack accurate and credible data sources.

Despite these limitations, this study investigated the cost-effectiveness of the 2 main treatments for severe aplastic anemia (SAA) for the first time, which can address a controversial area in SAA treatment and explore differences in treatment options across diverse age ranges. This study also confirmed that SAA patients aged 18-35-years-old have the most cost-effective choice of HSCT and that IST is preferable for patients aged 35-50-years-old to maximize the quality-adjusted life years (QALYs) while minimizing costs. The results of this study can provide significant reference information for clinicians and SAA patients.

Abbreviations

severe aplastic anemia (SAA)

immunosuppressive therapy (IST)

hematopoietic stem cell transplantation (HSCT)

quality-adjusted life years (QALYs)

willingness to pay (WTP)

aplastic anemia (AA)

graft-versus-host disease (GVHD)

Antithymocyte globulin (ATG)

Cyclosporine (CSA)

incremental cost-effectiveness ratio (ICER)

willingness to pay (WTP)

primary central nervous system lymphoma (PCNSL)

Methotrexate (MTX)

Declarations

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Authors' contributions

MXZ and XQW conceived and designed the project and prepared the manuscript. MXZ and QW collected and analyzed the data. All authors read and approved the manuscript.

Ethics approval and consent to participate

This present study was approved by the Ethics Committee of our hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

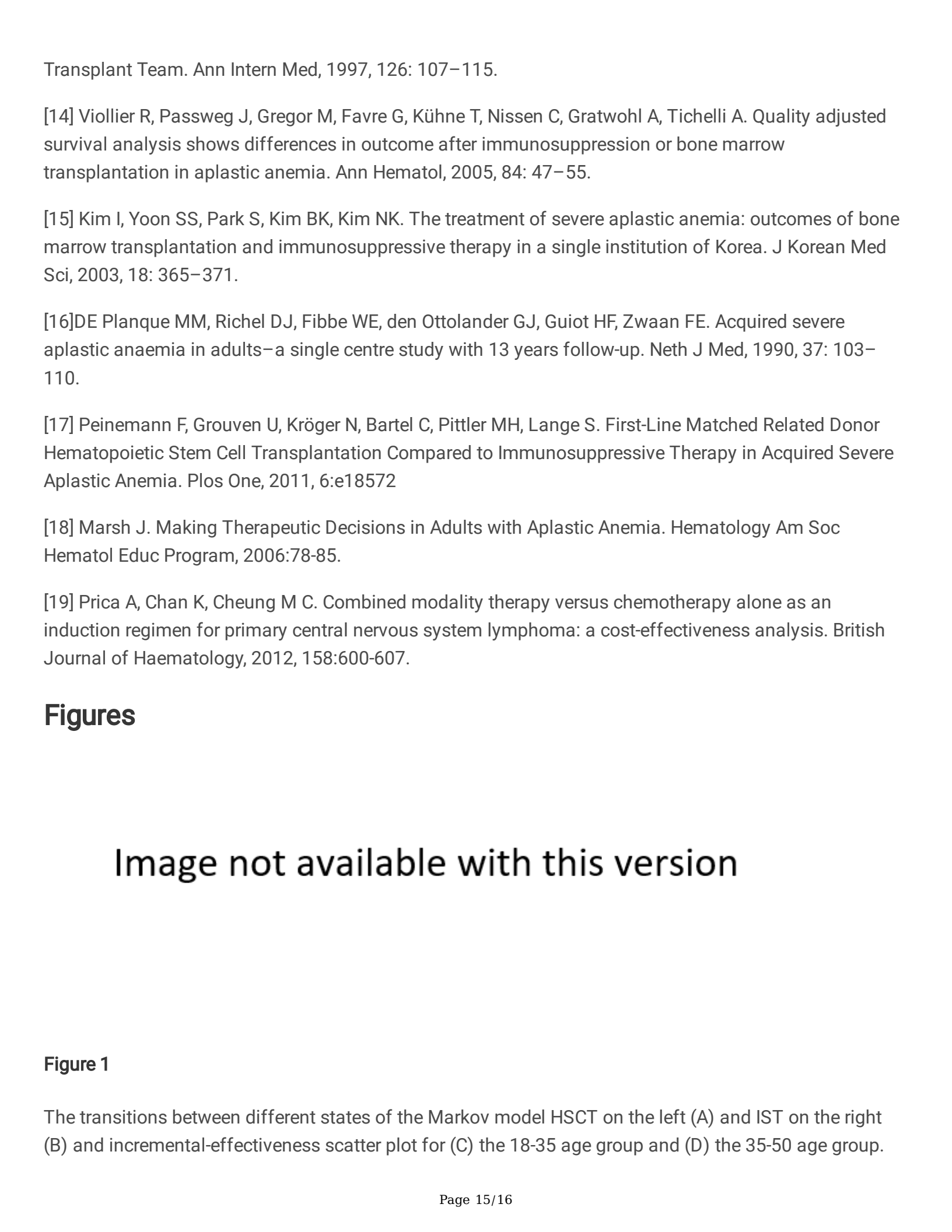

Figure 1

The transitions between different states of the Markov model HSCT on the left (A) and IST on the right (B) and incremental-effectiveness scatter plot for (C) the 18-35 age group and (D) the 35-50 age group.

Note: CR: complete remission; PR: partial remission; SAA: severe aplastic anemia