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Cost-Effectiveness of Autologous Hematopoietic Stem Cell Transplantation for Elderly Patients with Multiple Myeloma using the Surveillance, Epidemiology, and End Results–Medicare Database

Gunjan L. Shah[1,*], **Aaron N. Winn**[2,3], **Pei-Jung Lin**[2], **Andreas Klein**[4], **Kellie A. Sprague**[4], **Hedy P. Smith**[4], **Rachel Buchsbaum**[4], **Joshua T. Cohen**[2], **Kenneth B. Miller**[4], **Raymond Comenzo**[4], and **Susan K. Parsons**[4,5]

[1]Adult Bone Marrow Transplantation Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York

[2]Center for the Evaluation of Value and Risk in Health, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, Massachusetts

[3]Department of Health Policy and Management, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

[4]Division of Hematology/Oncology, Tufts Medical Center, Boston, Massachusetts

[5]Center for Health Solutions, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, Massachusetts

Abstract

In the past decade, the number of autologous hematopoietic stem cell transplants (Auto HSCT) for older patients with multiple myeloma (MM) has increased dramatically, as has the cost of transplantation. The cost-effectiveness of this modality in patients over age 65 is unclear. Using the Surveillance, Epidemiology, and End ResultseMedicare database to create a propensity-score matched sample of patients over age 65 between 2000 and 2007, we compared the survival and cost for those who received Auto HSCT to those who did not undergo transplantation but survived at least 6 months after diagnosis, and we calculated an incremental cost-effectiveness ratio (ICER). Two hundred seventy patients underwent transplantation. Median overall survival from diagnosis in those who underwent transplantation was significantly longer than in patients who did not (58 months versus 37 months, $P < .001$). For patients living longer than 2 years, the median monthly

*Correspondence and reprint requests: Gunjan L. Shah, 1275 York Avenue, Box 298 Avenue, New York, NY 10065. shahg@mskcc.org (G.L. Shah).

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SUPPLEMENTARY DATA

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cost during the first year was significantly different, but the middle and last year of life costs were similar. The median cost of the first 100 days after transplantation was $60,000 (range, $37,000 to $85,000). The resultant ICER was $72,852 per life-year gained. Survival after transplantation was comparable to that in those who underwent transplantation patients under 65 years and significantly longer than older patients who did not undergo transplantation. With an ICER less than $100,000/life-year gained, Auto HSCT is cost-effective when compared with nontransplantation care in the era of novel agents and should be considered, where clinically indicated, for patients over the age of 65.

Keywords

Cost-effectiveness; Autologous stem cell; transplantation; Multiple myeloma; Geriatric oncology

INTRODUCTION

Multiple myeloma (MM) is defined by an increased clonal plasma cell population and the presence of hypercalcemia, renal dysfunction, anemia, or bone disease attributable to the plasma cells [1]. Incidence increases with age; in the United States, the median age at diagnosis is 69 years. In 2014, approximately 24,050 new cases were diagnosed with 11,090 deaths, making it the second most common hematologic malignancy [2]. Over the past 2 decades, survival for patients with MM has increased as the result of several factors: the use of novel agents, autologous stem cell transplantation (Auto HSCT), and improved supportive care [3,4].

Induction chemotherapy followed by high-dose melphalan with Auto HSCT is standard of care for the treatment of MM in younger patients, with median overall survival (OS) prolonged by at least 12 months with the use of Auto HSCT [5,6]. On the strength of these results, Auto HSCT has been increasingly used in patients over the age of 65. For older patients with MM, Medicare coverage of Auto HSCT for patients up to age 78 began in 2000. Since that time, there has been a dramatic rise in the utilization of Auto HSCT; between 2005 and 2011, almost 40% of Auto HSCT in the United States were performed on patients over age 60, with the leading indication being MM [7–9].

In the 2009 report from the Agency for Healthcare Research and Quality, the most rapid increase in total hospital costs between 2004 and 2007 was in HSCT (both autologous and allogeneic) with $1.3 billion spent in 2007, an increase of about 85% since 2004 [10]. This increase was attributed not only to the increased cost of the procedure, but also to an increase in the number of patients receiving the modality. Although most published reports of cost have been from single institutions with varied populations, treatment regimens, and diseases [11], recent papers reporting large claims data [12] and a decision analysis finding early Auto HSCT cost-effective compared with late Auto HSCT [13] were published. Studies focusing on the economics of transplantation for MM are otherwise few, focus on younger patients, and mostly not from US centers [12–20]. In general, these studies have concluded that although Auto HSCT has a higher incremental cost than therapy without

transplantation, there is also greater incremental life-year (LY) or quality-adjusted life year (QALY) benefit [21].

As the survival and cost implications of the rise in Auto HSCT are not well described in the elderly MM population and are only likely to increase as the US population ages, we used the Surveillance, Epidemiology, and End Results (SEER)-Medicare database to examine the cost-effectiveness of undergoing an Auto HSCT compared with conventional chemotherapy alone for patients over the age of 65.

METHODS

Data Source

This study used data from the merged SEER-Medicare database. Patients in the SEER registries (Appendix 1) were linked to their fee-for-service (FFS) Medicare claims successfully in 93% of cases over age 65, representing approximately 26% of the United States. SEER completeness of case ascertainment is 98% with incident cases through December 31, 2007 and Medicare claims through December 31, 2009 included in the most recent linkage completed in 2012 [22,23]. The Patient Entitlement and Diagnosis Summary (Medicare enrollment information), the Medicare Provider Analysis and Review (inpatient Medicare Part A claims), the National Claims History file (provider Medicare Part B claims), Outpatient (institutional Medicare Part B claims) files, Durable Medical Equipment files, Hospice files, and Home Health files were used in this analysis. Patients were eligible for our sample if they were enrolled in Parts A and B FFS Medicare for at least 1 year before diagnosis and for at least 1 year after diagnosis or until death.

Transplanted Patient Sample

Patients with MM as their first cancer diagnosis were identified through the SEER diagnosis code. As Medicare coverage of Auto HSCT for MM began on October 1, 2000, we restricted our study to cases diagnosed after this date. We used International Classification of Disease 9 codes (41.00, 41.01, 41.04, 41.07, 41.09) or Healthcare Common Procedure Coding System (38241) codes to identify patients who had an Auto HSCT after MM diagnosis. Cases were required to be greater than or equal to 66 years old at diagnosis to allow for calculation of the comorbidity index, based on the Charlson comorbidity index (CCI) [24] in the year before diagnosis. Patients were designated as CCI 0 if they had no comorbidities and CCI 1+ if they have a score of 1 or more. Comorbidity information was available for all patients.

Nontransplanted Patient Sample

For the primary analysis, a matched cohort of MM patients not undergoing Auto HSCT was created from patients living at least 180 days from diagnosis and not having any Auto HSCT–specific code after their diagnosis to ensure that they would have lived long enough to complete a course of induction therapy and to have been offered a transplantation. Using age, gender, race, comorbidity, year of diagnosis, and SEER location, a propensity score of the likelihood to undergo Auto HSCT was created and greedy matching [25] was used to determine a 1:1 sample. A second model using instrumental variables, which are selected to

take into account both observed and unobserved patient characteristics in both groups, as done by Potosky et al. [26], served as a sensitivity analysis for our matched sample and is reported elsewhere. A second sensitivity analysis was done, conditioned on patients living to 12 months, to explore if the incremental cost-effectiveness ration (ICER) changed with longer survival required for inclusion.

Survival Outcomes

Date of death was determined from the SEER Patient Entitlement and Diagnosis Summary File. We estimated survival for the first 100 days, 1 year, 3 years, and 5 years after diagnosis using the Kaplan-Meier method [27], stratified by whether a patient received a transplant. Patients were followed for up to 9 years and the log-rank test was used to test for significance in median survival.

Cost

Costs were based on the services paid by Medicare, including claims for inpatient and outpatient services, radiographic imaging, laboratory testing, physician services, and pharmaceuticals delivered in the hospital or clinic. Medicare Part D data was not available during our time frame and, thus, the costs of outpatient prescriptions are not included in this analysis. In addition, nonmedical costs, such as loss of income, transportation, and caregiver costs, are not included as they are not billed to Medicare, making our analysis from the payer perspective.

We inflation adjusted cost data to 2010 US dollars using the medical care component of the Consumer Price Index and then calculated lifetime costs using a phase-of-care approach [28]. Monthly median costs were calculated for the first year after diagnosis, the middle years (year 2 after diagnosis until the year before death), and the last year before death. For patients living less than 2 years, the median monthly costs were calculated from diagnosis to death.

Cost-Effectiveness

Both survival and cost were discounted 3% annually, as recommended by the panel on cost-effectiveness analysis [29]. For patients who died within the follow-up period, actual costs and survival were used. For patients who lived beyond the follow-up period, survival was forecasted after the patients were censored at last follow-up by a Weibull survival model fitted to the available data and projected for full life expectancy to incorporate costs until death for all patients. Actual costs were used until the time of censoring and projected from then until death using regression models. Forecasted costs and survival were probabilistic using distributions around the parameters in the survival model and a gamma distribution for cost. The population was then bootstrapped 1000 times and the results averaged to calculate ICER in cost per LY. LYs were selected rather than QALYs because requisite utility weights for quality adjustment are not available across phases of treatment. A cost-effectiveness acceptability curve was created to demonstrate the probability of an Auto HSCT being cost-effective at various willingness-to-pay thresholds.

Statistical Analysis

All statistical analyses were performed using SAS (version 9.3, SAS, Cary, NC), Stata (version 12, StataCorp, College Station, TX) and Excel (Microsoft, Redmond, WA).

RESULTS

Patient Demographics

Between 2000 and 2007, there were 10,832 people over age 65 with Medicare Part A and B FFS identified as having MM in SEER (Figure 1). From that group, the final sample consisted of 270 patients who underwent Auto HSCT and 270 matched patients who did not undergo transplantation. Table 1 describes the demographic characteristics of the 2 cohorts, which did not differ significantly as a result of our matching (C statistic = .87). The median age at diagnosis was 68 (range, 66 to 92 years), with less than 10% of patients over age 75. About two thirds of the sample had no comorbidities by the CCI. Geographic variability was evident in our population. The majority of transplantations were performed in New Jersey, California, and Louisiana, with the rest of the registries contributing smaller portions.

Survival

With a median follow-up of 3.5 years, the median OS from diagnosis in the patients who underwent transplantation was significantly longer than in patients who did not (58 months versus 37 months, log rank $P < .001$, Figure 2). Survival at 1 year was 95% versus 86% ($P < .001$); at 3 years, 73% versus 50% ($P < .001$); and at 5 years, 47% versus 32% ($P < .001$).

The median time to transplantation was 250 days, with 73% of transplantations occurring within the first year after diagnosis. Median post-transplantation survival was 47 months. Survival at 100 days was 94%; at 1 year, 87%; at 3 years, 60%; and at 5 years, 36%. As shown in Figure 2, the Weibull survival estimates are consistent with the empirical survival.

Cost

Lifetime medical costs are displayed in Table 2. For patients living less than 2 years, the median monthly cost was almost double that in patients who underwent transplantation patients than in those who did not. However, only about 13% of the patients who underwent transplantation lived less than 2 years, compared with 33% of the nontransplantation sample. For patients living longer than 2 years, the median monthly cost was similar between the first and last years of life in the transplantation population. In contrast, in the nontransplantation population, almost 3 times as much was spent on last year of life costs compared to immediately after diagnosis. The ongoing care or middle year costs were comparable between both groups. The median cost of the first 100 days after transplantation was $60,000 (range, $37,000 to $85,000).

Cost-Effectiveness

The ICER is calculated using the mean discounted costs and LYs, as summarized in Figure 3A. The mean overall cost of care of a patient who underwent transplantation was $299,554 versus $199,973 for a patient who did not, which is an increase of $99,581. Similarly, the mean survival was 4.94 years with transplantation compared to 3.57 years without

transplantation, which was a gain of 1.37 years with Auto HSCT. The resultant ICER is the difference in cost divided by the difference in LY ($99,581/1.37 years gained) or $72,852 per LY gained.

The cost-effectiveness acceptability curve (Figure 3B) plots a society's willingness to pay for an intervention versus the probability the intervention will be cost-effective below that threshold. When using the commonly accepted threshold of $100,000 per LY gained [30], Auto HSCT for MM patients over age 65 is cost-effective over 90% of the time. The instrumental variables analysis was consistent with these results. However, varying the time the nontransplantation sample lived to at least 12 months increased the ICER to $125,745 (nondiscounted) and $140,855 (discounted) (Appendix 2).

DISCUSSION

To our knowledge, this is the first study evaluating the cost-effectiveness of Auto HSCT using "real world" national claims data for MM patients over age 65 in the era of novel agents. The ICER compares the differences in costs and benefits between 2 strategies, with the benefit in this case being LY gained by undergoing an Auto HSCT. When conditioned on survival of at least 6 months after diagnosis, we found that elderly patients undergoing transplantation survived an average of 1.37 years longer than those patient not undergoing Auto HSCT, which translated to a median survival of 58 months from diagnosis and a 3-year OS from transplantation of 60%. This is similar to the 3-year OS of younger patients of approximately 65% [5,31], although these studies were conducted before the use of novel agents. Most recently and using a modern induction regimen, Palumbo et al. confirmed the survival benefit with Auto HSCT compared with chemotherapy in patients < 65 years with 4-year OS from the start of consolidation of 81.6% versus 65.3% [32]. These results likely differ from ours not only because of the patient age, but also because of the use of tandem Auto HSCT and maintenance lenalidomide, which would have been unlikely to be utilized during our time frame. A recent Japanese retrospective analysis of patients ages 65 to 70 showed a 5-year OS of conventional chemotherapy and Auto HSCT of 63%. Further, for patients treated with novel agents and Auto HSCT, OS was 87% [33]. Although our 5-year survival is lower, we suspect this is related to short follow-up time for the more recent patients who were more likely to have received novel agents and to a greater diversity in patients.

In terms of cost, reviews of cost for Auto HSCT by Khera et al. [11] and Moeremans et al. [19] have estimated that the cost of the transplantation to be between $20,000 and $90,000. Comparisons between studies are difficult as the time frames, countries, costs included, and available treatment options vary greatly. In an analysis using a large claims database of younger patients (<66 years) with private health insurance, Majhail et al. reported on 791 MM patients with a median transplantation hospitalization cost of $78,000 [12]. We found the median cost of the first 100 days after transplantation to be $60,000, which is within the same range.

Few studies have put these 2 componentsdoverall cost and survivaldtogether to evaluate the cost-effectiveness of Auto HSCT for MM. Previous studies have compared Auto HSCT to

conventional chemotherapy of melphalan and prednisone in younger patients [18,20,34–36], and reported ICERs of $20,000 to $50,000 per QALY gained. Although our ICER is higher, the difference may be attributed to increased cost of the induction regimens and supportive care, as the LY gained with transplantation in all of these studies are similar to the 1.37 LY gained in our analysis.

Van Agthoven et al. described the only cost-effectiveness analysis alongside a phase III trial of vincristine, doxorubicin, and dexamethasone with or without transplantation in patients younger than 65. In this study, Auto HSCT for younger MM patients was not cost-effective, although this was thought to be due to short follow-up at the time the analysis was done [19,37]. Issues with these studies include the comparison to out-of-date therapy and the lack of sensitivity analyses to determine how likely it would be for the ICER to be within the willingness-to-pay threshold.

More recently, Pandya et al. has published a decision analysis evaluating the cost-effectiveness of early versus late Auto HSCT for MM [13]. Importantly, this study used single-institution survival data from a clinical trial on which patients had median ages of 58 (early) and 61 (delayed) and received thalidomide- or lenalidomide-based therapy between 2000 and 2008; cost data were obtained from previous studies by Khera et al. [11] and Fullerton et al. [38]. Interestingly, our mean overall cost of care for patients who underwent transplantation of $299,554 is similar to the costs presented by Pandya for both the patients who underwent early ($249,236) and delayed ($262,610) Auto HSCT.

We performed 2 sensitivity analyses to examine our key assumptions in choosing the nontransplantation sample. First, we used instrumental variables, which is a methodology that controls for both observable and unobservable characteristics. We describe our findings fully elsewhere, but the results were consistent with our findings here [39]. To supplement this analysis, we also explored the impact of varying the criteria for the nontransplantation sample to be eligible for matching. Instead of conditioning on survival to 6 months, which was our primary analysis, we separately conditioned on survival to least 12 months to approximate this alternative clinical scenario. Interestingly, although overall costs were not very different, survival difference between the transplantation and nontransplantation groups population decreased by about 6 months (See Appendix 2). With this change in survival benefit, the ICER doubles, although it remains within the range of many other cancer therapies [40]. It suggests that the patients who survive for at least 12 months without transplantation may be clinically distinct from those who underwent transplantation earlier and, as such, may not derive the same benefit from transplantation as those who survive at least 6 months. Clinical factors at presentation, as well as response to therapy, may permit clinicians to predict which patients should undergo transplantation earlier in their disease course to derive the benefits of this modality.

We acknowledge our study’s limitations. First, given the nature of the data we used, disease characteristics or responsiveness to treatment could not be used in our propensity score to create the matched cohort or address our secondary question about the timing of transplantation in the disease course. Specifically, SEER does not collect factors, such as the plasma cell burden, cytogenetics, international staging system stage, or response to induction

therapy [41–43]. Further, it is possible that some patients with smoldering myeloma were included in the nontransplantation population, as the diagnosis code is the same for them. However, this would bias towards longer survival in the nontransplantation group and would make transplantation even more cost-effective, if it were possible to remove them.

Second, because Medicare Part D prescription coverage did not begin until after our time frame, oral medication costs (primarily lenalidomide and thalidomide after Food and Drug Administration approval in 2006) are not included in this analysis. However, we do include the cost of bortezomib, which was available for the majority of our time frame. In addition, as described above, our overall cost of care was similar to patients treated with immunomodulatory agents. Analysis of the novel agents has shown that costs vary based on the drugs chosen [44–46]. As available data accumulate on the costs and benefits of novel therapeutics, analyses, such as ours, will need to be updated.

We also acknowledge that our cost analysis may not be translatable outside the United States, given variability in pharmaceutical costs worldwide. Finally, we identified 270 (4.4%) Auto HSCT during the time frame of our study, based on available billing codes. This figure is lower than would be expected from transplantation registry data, which show that about 1 of 10 patients over the age of 65 undergoes an Auto HSCT [7,47]. One possibility is that the International Classification of Disease 9 or Healthcare Common Procedure Coding System code was never present in some transplantation patients' claims. However, we think that a more likely explanation is the representativeness of transplantation centers located in SEER reporting areas. Although New Jersey and California patients make up a good portion of our sample, large transplantation centers in New York, Massachusetts, Texas, and Arkansas are not included as these states are not included in the SEER registries.

Regardless of this, the propensity score matching allows us to make accurate comparisons to a matched sample of nontransplantation patients. As there are only a few transplantation centers in each region (Appendix 1), we attempt to account for interinstitution variability by including SEER region in the matching criteria. In addition, using SEER-Medicare strengthens our analysis by capturing all of the treatment and complications over time, which allows not only for inclusion of all costs incurred at any location, but also a true determination of the overall survival benefit of Auto HSCT. Furthermore, by using a national database, we can generalize our findings to the broader elderly US population [48].

In conclusion, for elderly patients with MM, the use of Auto HSCT leads to survival comparable with patients under 65 years. With an incremental cost-effectiveness ratio of $72,850/LY, which is less than the commonly accepted willingness-to-pay threshold of $100,000, Auto HSCT is cost-effective when compared with nontransplantation care in the era of novel agents and should be considered for patients over the age of 65, particularly for those identified early in their disease course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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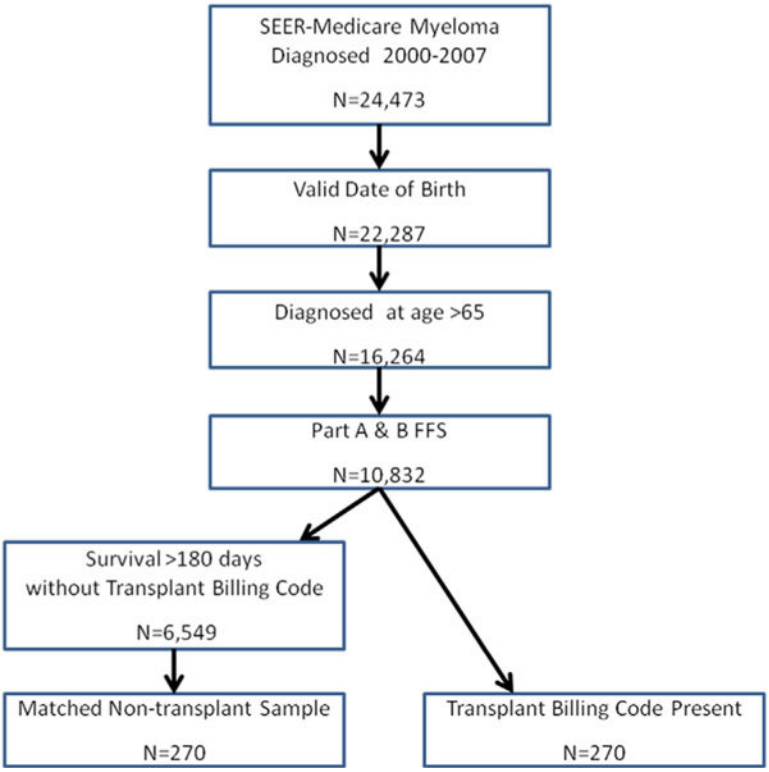

Figure 1.
Patient selection.

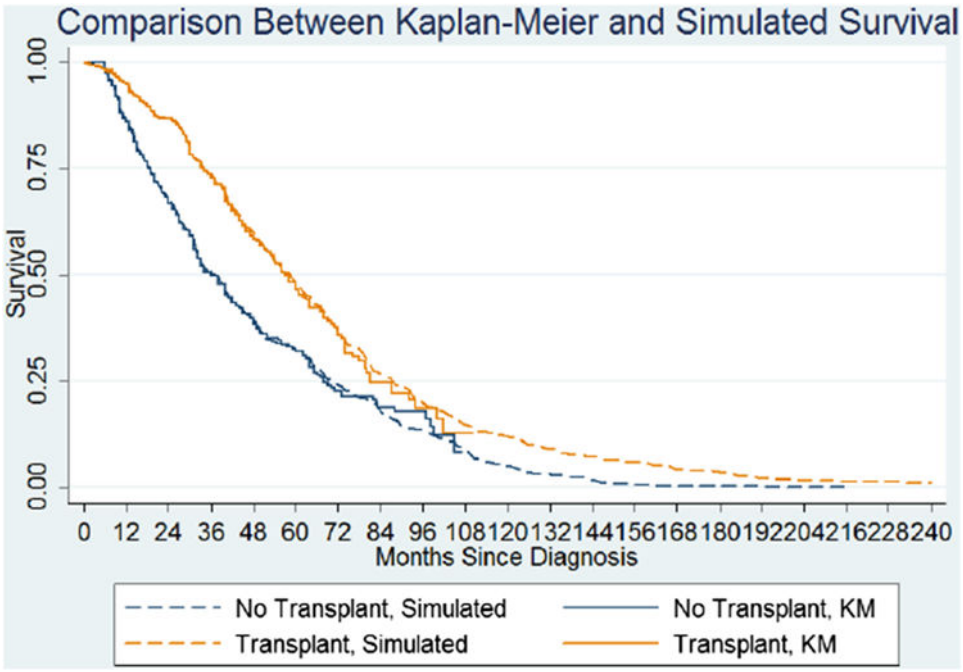

Figure 2.

Overall survival. Kaplan-Meier and Weibull model simulated survival curves until death of all patients. With a transplantation, the median survival was 58 months. Without, median survival was 37 months (log-rank $P < .001$).

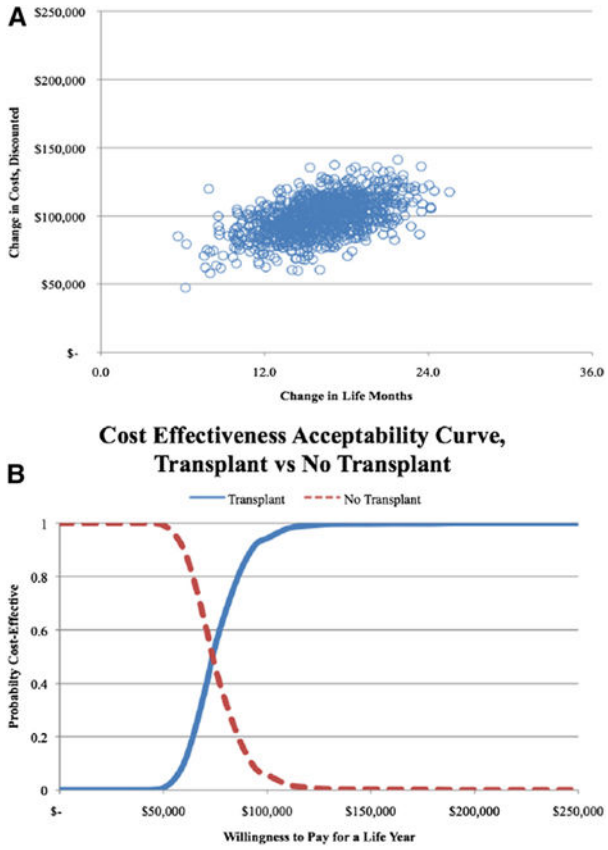

Figure 3.

(A) Discounted ICER calculation. Scatterplot of projected incremental costs and life year gains for transplantation versus no transplantation with 1000 bootstrapped simulations. Each circle represents 1 running of the model. The average discounted total cost of care for transplantation patients was $299,600 and, for nontransplantation patients, was $200,000. With the transplantation, patients lived an average of 4.94 years versus 3.97 years without the transplantation. The average ICER is the difference of cost divided by the difference in life-years gained. In this case, $99,600/1.37 LY = $72,700/LY. (B) Incremental cost-effectiveness acceptability curve. The ICER would be less than $100,000/life year gained more than 90% of the time.

Table 1

Patient Characteristics

Characteristic	Transplantation n = 270	Nontransplantation n = 270
Female	108 (40)	103 (38)
Race		
White	238 (88)	235 (87)
Black	22 (8)	24 (9)
Age, median (range), yr	68.6 (66–92)	68.7 (66–92)
66–69	176 (65)	170 (63)
70–75	73 (27)	84 (31)
76–92	21 (8)	16 (6)
CCI *		
CCI 0	170 (63)	173 (64)
CCI 1+	100 (37)	97 (36)
SEER registry †		
Connecticut	19 (7)	19 (7)
Kentucky	16 (6)	19 (7)
Louisiana	38 (14)	35 (13)
New Jersey	84 (31)	78 (29)
California	68 (25)	78 (29)

Data presented are n (%), unless otherwise indicated.

* Patients were designated as CCI 0 if they had no comorbidities and CCI 1+ if they have a score of 1 or more.

† Registries with less than 11 patients each include: Detroit, Iowa, New Mexico, Seattle, Utah, and Georgia.

Table 2

Median Monthly Cost

	Transplantation	Nontransplantation
Living more than 2 years	n = 234	n = 180
First year after diagnosis *	$8337	$2607
Middle years	$2435	$2088
Last year	$8114	$6809
Living less than 2 years	n = 36	n = 90
Monthly †	$13,106	$6756

Total cost of care per month during each time frame. Significant differences were seen only in the first year after diagnosis for patients living longer than 2 years and monthly for those living less than 2 years.

* $P < .001$.

† $P = .013$.