THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 14 Issue 5

RESEARCH ARTICLE

Trends and Cost Effectiveness of Allogeneic Stem Cell Transplant in Chronic Myelogenous Leukemia in the Era of Tyrosine Kinase Inhibitor Therapy

Indumathy Varadarajan[1], MD, Maneesh Jain[2], MD, Bharadhwaj Kolipakkam[3], MD, Parshva Patel[4], MD, Kristine Ward[5], MD, Michael Styler[6], MD

[1]University of Virginia, VA ,USA
[2]George Washington School of Medicine and Health Sciences, VA
Maneesh.Jain@va.gov
[3]Virginia Commonwealth University, VA
Bharadhwaj.Kolipakkam@vcuhealth.org
[4]Drexel University College of Medicine, PA Parshvapatel@gmail.com
[5]University of Pennsylvania, PA
Kristine.Ward@pennmedicine.upenn.edu
[6]Fox Chase Cancer Center, Temple Health, PA
Michael.Styler@fccc.edu

OPEN ACCESS

PUBLISHED
31 May 2026

CITATION
Varadarajan I., et al., 2026. Trends and Cost Effectiveness of Allogeneic Stem Cell Transplant in Chronic Myelogenous Leukemia in the Era of Tyrosine Kinase Inhibitor Therapy. Medical Research Archives, [online] 14(5).

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ISSN
2375-1924

ABSTRACT

Introduction: The FDA approval of tyrosine kinase inhibitor (TKI) therapy in May 2001 dramatically affected the treatment and clinical course of patients with chronic myelogenous leukemia (CML). In this study, we examined the long-term trends in the rates of stem cell transplants (SCTs) and the mortality and clinical complications of CML following the FDA approval of Imatinib. We also compared the cost of inpatient health care, mortality, length of stay (LOS), and complications among patients who have had stem cell transplantation to those on TKI therapy.

Methods: We queried the Healthcare Cost and Utilization Project's (HCUP) Nationwide Inpatient Sample (NIS) between 1998 and 2011 using the ICD-9 code for CML (205.1) in both the primary and secondary diagnosis fields. We monitored the trends in allogenic SCT, mortality, and clinical complications related to CML. We used the information from the database between 2002 and 2011 to compare trends in hospitalizations, cost, and mortality between patients who had an allogenic transplant and those who were treated with TKI therapy.

Results: A total of 53,254 (weighted n=262,964) hospitalizations for CML (Male 54.6% and average age 65.9+/-0.8 years) occurred from 1998-2011. There has been a 408% decrease in the rate of transplants and a 79.9% ($p<0.0001$) decrease in in-hospital mortality since the introduction of TKIs. There has been an almost 200% reduction in blast crises, and a nearly 100% reduction in both bleeding and thrombotic complications (p-value < 0.0001). For comparing the length of stay, mortality, and cost of hospitalization, a total of 39,850 hospitalizations (weighted n = 191,285) were analyzed (male, 54.6%; age, 65.9 ± 0.08) from 2002 to 2011. The average length of stay was 7.05 days in the TKI group and 18.4 days in the transplant group. The average length of stay for the transplant procedure was 33.85 days ($p<0.0001$). The inpatient mortality for the transplant procedure itself was 8.9%, but was 6.3% in the group that was readmitted after having a successful transplant, and it was 7.9 % in the TKI group ($p=0.032$). The odds of inpatient mortality are in favor of TKI therapy with an OR of 1.9 against the transplant procedure. The average cost of hospitalization in the transplant group was $173,780, compared to $46,955 in the TKI group. The transplant procedure cost $ 338,229 ($p < 0.0001$).

Conclusion: The Introduction of TKIs has not only reduced the reliance on allogeneic transplants but has also led to remarkable improvement in mortality and CML-related complications. Patients on TKI therapy have a lower mortality rate, shorter length of stay, and lower hospitalization costs compared to the transplant group. The main reason for in-hospital admission for patients on TKI therapy was typically due to comorbidities of the elderly, not complications of CML. Therefore, TKI therapy is associated with improved mortality, a shorter length of hospital stay, and better cost-effectiveness.

Introduction

The introduction of tyrosine kinase inhibitors has brought about unprecedented changes in the outcomes for patients with chronic myelogenous leukemia. Hematopoietic stem cell transplant was considered the "only standard of cure for CML" before the introduction of TKI therapy[1-5]. Feifer et al in 1974 reported the first syngeneic transplant from a healthy twin for two patients who were in blast crises of CML, enabling a short but effective eradication of the malignant BCR-Abl clone and introducing a new perspective to the treatment of CML[6]. This extended to HLA matched allogeneic transplants, which proved to be an effective option for the disease that otherwise harbored a fatal outcome. The first allogeneic transplant was reported to the European Bone Marrow transplant (EBMT) in 1975 in France[7]. Outcomes of transplant were dismal until patients with CML were transplanted in the chronic phase. Data of 138 patients with CML who underwent transplantation between 1978 and 1982 and reported to the International Bone Marrow Transplant Registry showed 3-year survivals of 63%, 56%, and 16% for patients who underwent transplantation in the chronic, accelerated, and blast phase, respectively. Only 2 of 29 patients (7%) who underwent transplantation in the chronic phase relapsed[8]. Transplant continued to be only therapy to eradicate the BCR-ABL clone till the late 90s and CML was the most common cause for allogeneic stem cell transplant in 1990s.CML was one the first diseases on which the EBMT score for transplant risk assessment was created.[9-11] Studies of transplant in CML also played a pivotal role in understanding the graft versus disease effect. Increased numbers of relapses were noted with T cell depleted transplants, indicating that the donor T lymphocytes that caused graft versus host disease were also effective in preventing relapses. Donor lymphocyte infusions proved to be one of the most powerful tools for disease control[12-14]

Data from 138 patients with CML who underwent transplantation between 1978 and 1982 and were reported to the International Bone Marrow Transplant Registry showed 3-year survivals of 63%, 56%, and 16% for patients who underwent transplantation in the chronic, accelerated, and blast phases, respectively. Only 2 of 29 patients (7%) who underwent transplantation in the chronic phase relapsed[14]. Transplant continued to be the only therapy to eradicate the BCR-ABL clone until the late 1990s, and CML was the most common indication for allogeneic HSCT[15].

Stem cell transplantation was associated with significant toxicity. In a retrospective analysis of 373 patients, transplanted in chronic phase CML with HLA-matched siblings, had an 8-year overall survival of 54%. This study also revealed a transplant-related mortality of 41%, and 52% of patients had chronic GVHD 4 years after transplantation[16]. Even with an EMBT risk score of 0, the treatment-related mortality is around 15%, and it increases considerably to 47% for an aEBMT risk score of 6-7[17].

The introduction of Imatinib brought a paradigm shift in the management of CML. Imatinib was approved by the FDA in December 2002 as a first-line treatment for CML in the chronic phase based on the results of the IRIS trial. The International Randomized Study of Interferon and STI571 (IRIS) was a phase III trial that compared 400 mg of daily Imatinib to Interferon alpha and cytarabine in newly diagnosed CML patients who were in chronic phase. At 18 months, the rate of complete cytogenetic remission (CcyR) in patients treated with imatinib was 76% versus 15% for patients treated with IFN alpha plus Cytarabine[18].

The 5-year follow-up of this study showed an overall survival of 89% in the Imatinib arm, and 87% of the patients achieved a complete cytogenetic response.[19] The durable responses and minimal toxicities have currently placed TKIs as the first-line therapy for adults who present with CML in the chronic phase. Allogeneic transplant is currently restricted to providing curative therapy in patients who are resistant to multiple TKIs and in those presenting with accelerated phase or blast crises[20]. This study aimed to determine the rate of reduction

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in transplant and CML-related complications after the introduction of TKI therapy.

Methods

DATA SOURCE

The Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality, was queried to identify trends of CML-related hospitalizations. This nationally representative discharge dataset contains information, including but not limited to patient characteristics (age, sex, race, payer information); hospital information (hospital bed size, location, teaching status); admission information (length of stay [LOS] and total charges). Diagnoses are coded according to the International Classification of Diseases, Ninth Revision (ICD-9).

STUDY SAMPLE

Using ICD-9 code, all CML hospitalizations from 1998 to 2011 were identified.ICD-9 codes 205.1 and 205.11 were used for CML. Admissions for individuals under 18 years of age were excluded from the study as the National Inpatient Sample did not include this cohort. These hospitalizations were divided into 1. Admission for transplant procedure, 2. Hospitalization in patients with a history of transplant and 3. The remaining CML-related admissions. Patients were analyzed from 2002 to 2011 for odds ratios according to their classification into the above three groups. Reasons for hospitalizations were further delineated as CML-related complications and non-CML-related complications. CML-related complications included splenic infarct, blast crises, disseminated intravascular coagulation, splenomegaly, septic shock, anemia, thrombocytopenia, hyperviscosity, tumor lysis syndrome, and complications from bone marrow transplant, including GVHD and graft rejection. The non-CML-related complications included atrial fibrillation, congestive heart failure, acute renal failure, chronic renal failure, and pneumonia.

OUTCOME VARIABLES

The primary outcome variables analyzed were mortality and complications in the above-defined groups. The secondary outcomes analyzed were length of stay (LOS) and hospitalization costs. The NIS includes information about inpatient hospitalization only. We assumed that most CML patients without a history of transplant had been getting TKI as an outpatient. We analyzed trends of CML-related complications, LOS, and total charges for hospitalization for the above-defined groups. The cost of hospitalization was adjusted for inflation in reference to the year 2011.

BASELINE STATISTICAL ANALYSIS

We analyzed the baseline characteristics of CML admissions over a 14-year period. The NIS is a complex survey design that includes weights, stratification, and clusters. Categorical variables are given in percentage, and continuous variables are shown in mean +/- standard error. Differences in groups of categorical variables were assessed by chi-square analysis. T-test and/or ANOVA were used to assess differences between groups of continuous variables. A survey logistic multivariate model was used to analyze odds ratios, maximum likelihood and variance of regression. Different multivariate models were used to analyze independent predictors of cost, LOS, mortality and major CML-related complications. Statistical analysis was performed in SAS for windows. P-values of <0.05 were considered statistically significant.

Results

PATIENT CHARACTERISTICS

A total of 53,254 (weighted n=262,964) CML admissions were analyzed from 1998 to 2011. The overall age for all CML hospitalizations from 1998-2011 was 65.93+/- 0.8 (Mean +/- SE). For patients with history of CML and transplant, the average age was 52.73 in 2011 compared to 40.18 in1998. 54.6% of total CML hospitalizations were for male patients. The ratio between female and male hospitalization did not change during the time period analyzed. Trends from 1998 to 20101 also indicate that there has been 15.2 % increase in tranplants amongst the Caucasians while there was only a 4.43 % increase

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amongst the African -Americans.(p<0.0001). Please refer to supplemental table 1 for further details.

		1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Relative Chan	P-value for Trend
Age																	
	All CML Hospitalization																
	Mean±SE	62.65±	63.18±	64.01±	64.24±	64.39±	65.19±	65.85±	66.15±	66.30±	65.09±	66.71±	66.53±	65.88±	66.66±0.23		<0.0001
	18-34	8.63	8.21	6.36	6.15	7.03	6.39	6.31	6.35	5.99	6.65	5.09	5.5	6.252	5.6123	-53.84	
	35-49	16.9	16.5	16	17	15.6	15	13.3	12.4	12.6	12.8	12.7	11.9	12.48	10.953	-53.87	
	50-64	21.4	20.5	22.3	19.5	20.6	19.6	19.6	19.6	20.4	24.5	21.3	22.1	22.1	22.4399	4.47	
	65-79	33.6	34.8	35.7	37.3	35.6	36.4	37.1	35.9	35.5	31.8	34.5	33.8	33.57	35.2977	4.86	
	>=80	19.5	20	19.7	20.1	21.2	22.7	23.7	25.8	25.4	24.3	26.4	26.7	25.59	25.6971	24.15	
	CML + History of Transplant																
	Mean±SE	40.18±	42.12±	42.12±	42.31±	41.96±	43.77±	45.06±	45.15±	44.24±	48.64±	47.97±	50.46±	45.67±	52.73±1.31		
	18-34	32	26	20.4	25.3	29.3	20.2	24.1	22.1	27.7	15.8	18	7.47	20.43	9.7379	-228.16	
	35-49	49.9	47.3	57	52.9	43.4	46	34.9	36.6	40	36.5	30	41.2	36.96	22.0386	-126.44	
	50-64	18.1	26.6	21.3	21	26.3	32.5	37.7	36.2	30.1	38.4	43.1	41.4	33.3	45.4232	60.07	
	65-79	.	.	1.34	0.74	.	1.35	3.37	5.06	2.24	9.26	8.88	9.86	9.322	22.8003		
	>=80	.	.	.	.	1.03	.	.	.	.	.	.	.	.	.		
Sex																	0.16
	Male (%)	55.01	57.03	56.45	55.83	55.98	51.81	54.68	53.23	54.34	54.47	56.71	53.33	55.32	55.5382	0.96	
	Female (%)	44.99	42.97	43.55	44.17	44.02	48.19	45.32	46.77	45.66	45.53	43.29	46.67	44.68	44.4618	-1.20	
Race																	<0.0001
	White	58.59	62.34	56.59	57.2	56.18	55.91	57.4	57.4	56.03	54.75	60.96	66.28	66.09	69.0903	15.21	
	Black or African American	9.981	7.733	6.918	8.542	9.395	9.648	10.2	6.161	6.459	7.432	7.973	7.573	11.94	10.4433	4.43	
	Hispanic or Latino	6.276	4.594	5.303	5.816	5.85	7.251	5.153	5.876	5.779	6.259	6.199	6.86	6.669	6.9576	9.79	
	Other	2.253	3.252	3.465	3.074	3.191	3.623	3.287	3.254	3.58	4.219	4.511	4.821	4.342	4.0059	43.75	
	Missing	22.9	22.08	27.72	25.37	25.38	23.57	23.96	27.31	28.15	27.34	20.35	14.46	10.96	9.5028	-141.03	
Primary Payer Type																	<0.0001
	Medicare	53.8	54.9	56.8	57.5	60.4	64.3	63.1	65.8	65.7	60.6	62.2	62.6	63.6	64.8534	17.11	
	Medicaid	8.77	8.92	8.65	9.76	7.68	7.97	9.01	7.21	7.85	7.34	7.66	7.31	9.189	7.5896	-15.55	
	Private	34.4	31.4	30.3	29	27	24	24	22.1	21.5	26.8	25	24.5	21.96	21.8791	-57.24	
	Uninsured	3.07	4.78	4.24	3.69	4.92	3.74	3.97	4.83	4.94	5.3	5.11	5.52	5.248	5.6779	45.97	
Hospital Size																	0.586
	Small	14.6	9.05	7.87	13.1	10.7	16.2	10.7	11.6	12.8	10.9	10.9	12.7	13.14	10.7666	-35.70	
	Medium	21.6	24.6	23.9	23.5	20	20.5	22.9	20.8	23.8	20	19.1	21.6	19.55	22.1768	2.70	
	Large	63.8	66.4	68.3	63.3	69.3	63.3	66.5	67.6	63.4	69.1	70.1	65.7	67.31	67.0566	4.84	
Hospital Teaching Status																	0.92
	Non-Teaching	43.9	43.3	45.8	48	45.9	47	48.6	53.3	46.9	48.4	46.9	49.4	46.88	47.3998	7.43	
	Teaching	56.1	56.7	54.2	52	54.1	53	51.4	46.7	53.1	51.6	53.1	50.6	53.12	52.6002	-6.70	
Hospital Setting/Location																	0.556
	Rural	12.4	11.5	12.5	11.6	12.6	12.5	11.8	11.2	10.4	13	10.6	10.7	9.169	9.433	-31.24	
	Urban	87.6	88.5	87.5	88.4	87.4	87.5	88.2	88.8	89.6	87	89.4	89.3	90.83	90.567	3.25	
Hospital Region																	0.974
	Northeast	21.9	19.7	21.3	21.5	20.9	18.5	20.1	19.6	20.4	18.4	18.6	21.1	20.66	20.2617	-8.30	
	Midwest	24.5	29.6	27.1	25.2	21	25.9	25.5	27.1	21.6	24.3	23.1	27.7	25.42	25.5535	4.29	
	South	29.9	32.1	33.6	32.8	40.3	34.6	39	36	41	39.8	39.6	34	36.83	36.8626	18.98	
	West	23.7	18.6	17.9	20.5	17.7	21	15.4	17.3	17	17.4	18.7	17.2	17.09	17.3222	-37.00	

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Table 2 - Trends in Mortality and Transplant

Trends table	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Relative Change	P-value
Tot. No of CML admissions	18446 ±1525	17559± 1274	18311 ±1300	17362 ±1281	16829 ±1642	16473 ±1296	16384 ±1075	17405 ±1116	17519 ±1112	18665 ±1407	19779± 1366	21474 ±1324	22520 ±1389	24237 ±1552		<0.0001
Number of hospitalization for transplant procedure	991 ±362	753 ±204	614 ±167	518 ±213	399 ±133	500 ±247	312 ±102	347 ±110	150 ±45	353 ±140	263 ±86	379 ±114	356 ±100	256 ±80		<0.0001
Percentage of hospitalization for transplant procedure	5.3729	4.2895	3.3552	2.9868	2.3742	3.0399	1.9072	1.9962	0.8611	1.894	1.3306	1.7689	1.583	1.0575	-408.08	<0.0001
Mean Age±SE	62.65 ±0.3	63.18 ±0.3	64.01 ±0.28	64.24 ±0.29	64.39 ±0.29	65.19 ±0.3	65.85 ±0.3	66.15 ±0.29	66.30 ±0.28	65.09 ±0.28	66.71 ±0.26	66.53 ±0.26	65.88 ±0.26	66.66 ±0.23		<0.0001
Length of Stay (Mean ± SE)	9.72± 0.21	8.55± 0.18	8.58±0 .18	8.64±0 .19	8.11± 0.18	8.20± 0.18	7.66±0 .17	7.98±0 .16	7.41± 0.16	7.38±0 .15	7.42± 0.16	7.40±0 .15	7.39± 0.14	6.55± 0.12	-48.3969	<0.0001
Total Charges ($)(Mean ± SE)	44892± 1488	40585 ±1451	41561 ±1426	45931 ±1601	45207 ±1459	50711 ±1659	44858 ±1404	47899 ±1310	43884 ±1135	54880 ±1681	54756 ±1622	57687 ±1724	58975 ±1521	54675 ±1292	17.8934	<0.0001
Mortality	10.7498	11.013	11.641	10.299	10.868	9.7806	9.4591	8.7522	8.4048	7.0799	7.8554	6.7327	5.8432	5.9727	-79.98225258	<0.0001

There has been a 408% decrease in the rate of transplants and a 79.9% ($p<0.0001$) decrease in in-hospital mortality since the introduction of TKIs as shown in Table 2. There was a 24.15% increase in hospitalizations above the age of 80 and a decrease of 53.84% for patients 18-34 years old from 1998 to 2011 ($p<0.0001$). There has also been a 48.3% reduction in the average length of hospital stay.

Table 3 - Trends in Complication

Symptoms	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Relative Change	P-value
Splenic Infarct/Splenic Vein Thrombosis	1.0419	0.6574	1.086	0.2624	0.3591	0.5721	0.5049	0.3658	0.5098	0.6601	0.5294	0.4584	0.6902	0.4718	-120.84	0.0001
Epistaxis	1.5211	1.401	1.804	1.622	1.316	1.278	1.123	1.057	1.034	0.733	0.814	0.95	0.843	0.974	-56.11	0.0004
Hemoptysism, Unspecified	1.0384	1.031	0.613	1.272	1.092	0.935	1.103	1.266	0.854	0.781	1.515	0.907	0.82	0.406	-155.51	<0.0001
Blastic Crisis	1.0203	0.999	1.214	1.145	1.538	1.391	1.395	1.013	1.12	0.51	0.464	0.402	0.431	0.339	-200.62	<0.0001
Complications of transplanted bone marrow	7.5325	7.289	6.171	6.632	4.378	6.622	3.618	3.963	2.519	3.785	2.711	3.469	3.015	2.638	-185.58	<0.001
Infection and inflammatory reaction due to other vascular device, implant, and graft	2.6434	2.52	1.997	2.532	1.723	2.217	1.824	1.755	1.783	1.863	0.539	0.463	0.571	0.174	-1420.07	<0.001
Aplastic anemia and other bone marrow failure syndromes	13.678	11.66	9.958	10.25	9.324	10.39	8.729	8.524	7.463	7.436	7.863	9.125	9.482	8.004	-70.89	<0.001

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There have been marked reductions in the complications related to CML since the advent of TKI therapy. There has been almost a 200% reduction in blast crises, a 120.8% decrease in splenic infarct/ splenic vein thrombosis ($p < 0.0001$), and a 56.1% reduction in epistaxis ($p < 0.0004$). As evidenced by trends in Table 3, complications of bone marrow transplants have decreased substantially by 185.5%. Graft failure, rejection has reduced 70.8%.There has been an impressive 14 fold decrease in in the rate of infection related complications after introduction of TKI therapy. (all $p<0.001$). Figure 1 depicts a spider plot of the trend in complications. The relative change in percentage is marked on the Y axis and the time span from 2002 to 2011 has been sequentially plotted in the X axis. The different colors as labeled represent the above mentioned complications.

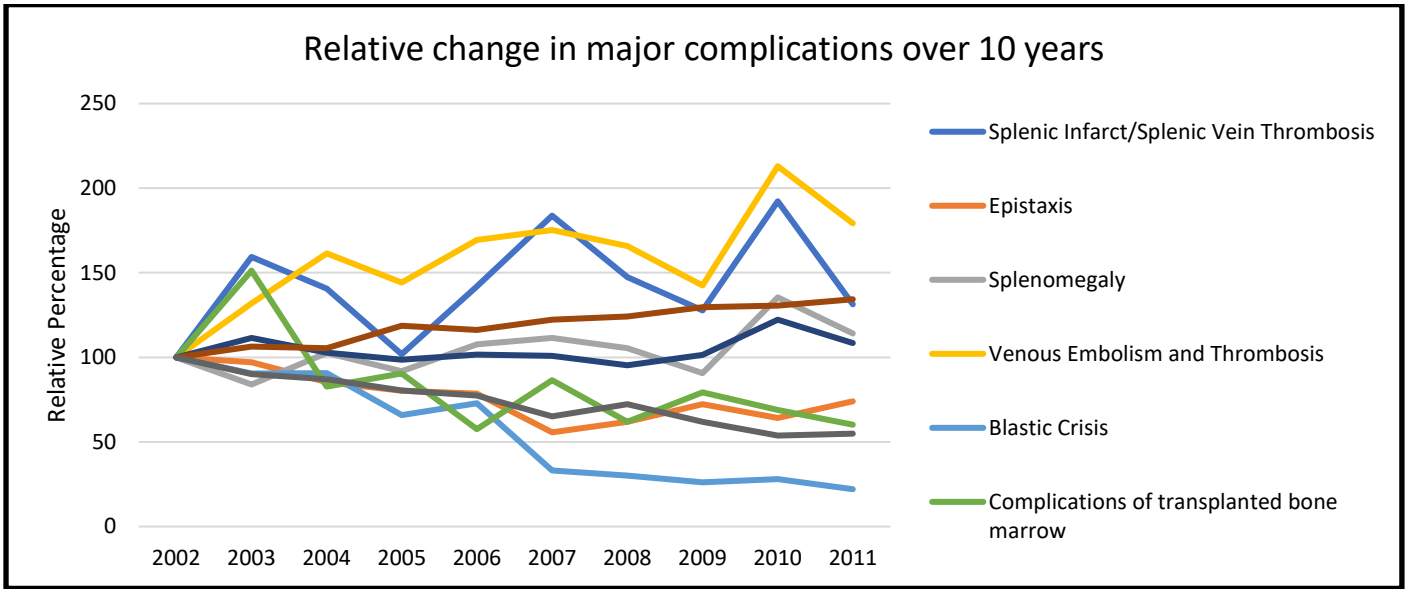

Figure 1 – Spider plot of the trends in complications, X axis showing number of years and Y axis relative percentage.

Table 4 - Multi-variate Analysis and Odds Ratio for Cost, Length of Stay, Mortality and Complications Related to CML

	Transplant Group	Readmission Group	Non transplant group
No of Admissions	3,320	4,289	183,706
Cost of Admission	338,229.02±9944	46,955.83±415	47,301.48
Age (years)	44.3.	46.7	66.8.
Mortality (%)	7.93	8.94	4.44
Length of stay (days)	33.85	6.64	7.05
CML related complications	36%	14%	14%
Non CML related complications	19%	36%	51%

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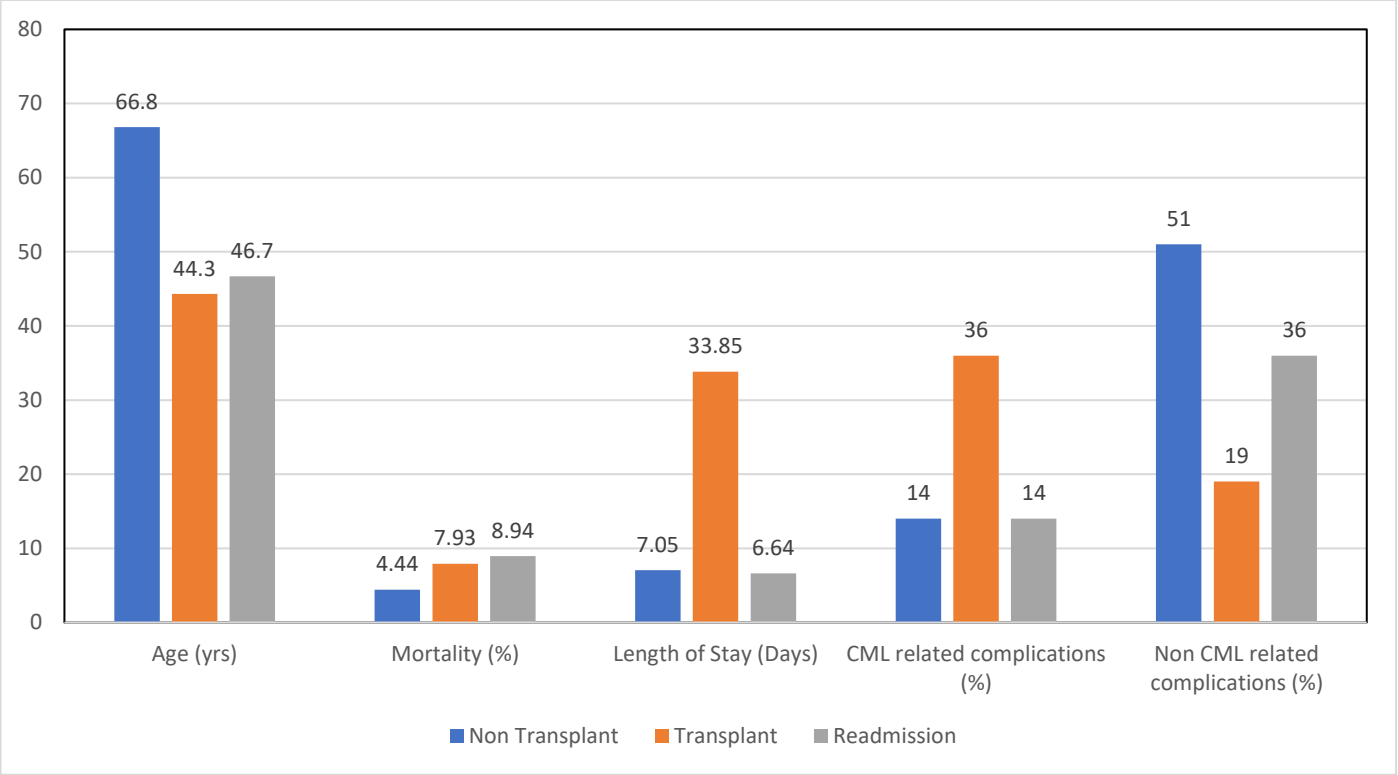

Figure 2 - Multi bar graph comparing key charecteristics in the three groups – Non-transplant , Transplant and Readmission Characteristics – Age, Length of Hospitalization, Mortality, CML related co-morbidities and non CML related Comorbidities.

Table- 5 Odds estimates for cost and length of Stay

	Inclusion Criteria	Cost /LOS estimate compared to Non transplant group	Lower Limit	Upper Limit	P- Value
	Readmission	-8490.97	-13,738.4	-3,243.5	0.0015
Cost	Readmission +BMT procedure	92,281	87,651.83	96,910.7	<0.0001
	BMT procedure	243,633.8	236,822.6	250,445.1	<0.0001
	Readmission	-1.4061	-2.0353	-0.7769	<0.0001
Length of stay (days)	Readmission +BMT procedure	8.7547	8.2274	9.282	<0.0001
	BMT procedure	23.7476	22.9652	24.53	<0.0001

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COSTS

The overall hospitalization cost for a non-transplant patient was $46,955.83 +/- $415 and the overall length of stay was 7.05 days compared to a patient with transplant history when the cost was $47,301.48 and the length of stay was 6.64 days. transplant procedure, the overall hospitalization expenditure was $338,229.02 and the overall length of stay was 33.85 days.

Discussion

Imatinib Mesylate has undoubtedly changed the natural course of CML, providing a normal functional lifespan in most patients who are found to be in complete cytogenetic remission at two years after starting therapy[18-21]. The study reports the drastic reduction in mortality and the need for stem cell transplant over the last ten years. It has also led to a substantial reduction in CML-associated complications. This study has used one of the largest available national inpatient databases to report the trend of reductions in complications and mortality since the introduction of Imatinib.

Not only has Imatinib led to an overall decrease in in-hospital mortality and length of stay, but it has also dramatically reduced the incidence of blast crises and complications related to transplant.

Carlo et al performed a prospective analysis on 832 patients to monitor the adverse effects of Imatinib[21]. Imatinib had minimal long-term side effects, based on a median time of analysis of 5.8 years. Reasons for discontinuing treatment due to side effects included muscle cramps, edema, skin toxicity, diarrhea, arthritis and cardiovascular events (2.3%). Only 5% of patients discontinued therapy due to relapse or insufficient response. The IRIS study revealed the overall survival data in patients who were treated with Imatinib versus interferon alfa plus Cytarabine, and recently a 10.9 year follow-up was reported[22]. Both arms had an overall survival of 83.3%, with minimal difference between the two arms due to crossover after a median of 0.8 years. Given the remarkable clinical outcomes and decreased morbidity and mortality with the use of tyrosine kinase inhibitors, the role of allogenic stem cell transplantation in the post-TKI era is primarily in accelerated phase and blast crises. It is also restricted to second line treatment after treatment failure with second generation TKIs or in patients with T315I mutations after a trial of Ponatinib therapy[23]. SCT is still the only option that offers complete cure, though the use of "treatment free remission (TFR)" as a new criterion for assessing clinical outcome has helped assess the feasibility of stopping TKIs in those with sustained deep molecular remissions[24,25].

Patients on TKI therapy have re-admissions for non-CML-related complications like congestive heart disease, chronic renal failure and falls as opposed to the post-transplant group that get admitted due to complications from CML and stem cell transplant. Imatinib was initially priced at $26,000 per year in 2001[26]. At present Imatinib is available as a generic drug and is priced from 300-3000 dollars/year by various companies. Patented TKIs are priced from 150,000 to 200,000 a year[27,28,29]. .At present it is acceptable to stop TKI therapy and closely observe patients who have achieved a MR4 (4.5 log) reduction molecular response, after 3 yrs of TKI therapy. Hence, this select population is able to stop the TKI therapy[30]. Not only does this have an incredible impact on their quality of life and overall survival it is also more cost-effective when compared to an allogeneic stem cell transplant. This study has multiple limitations. The study has used the national inpatient database and hence we are not able to include the costs that are incurred with treatment and management of complications with stem cell transplant or TKI therapy in the outpatient setting. It is a retrospective analysis, and hence, the impact of patient comorbidities leading to inpatient admissions might have had a significant effect on inpatient costs.

The current 10-year survival for patients with CML on TKI therapy is similar to the general population, with a relative survival rate of 91.4% in patients who achieve a complete cytogenetic response within 1 yr

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of TKI initiation[31].Imatinib has further encouraged discovery of second-generation TKI s such as dasatinib, Bosutinib and Nilotinib have shown to achieve deeper molecular responses in patients with all risk scores in Chronic Phase CML, facilitating potential discontinuation in the future[32,33,34]. Most recently, Asciminib has been approved in frontline therapy, with a major molecular response of 67% at 48 weeks when compared to 49.0% with other second generation TKIs[35]. Indeed Imatinib has ignited the potential of small molecule inhibitors targeting driver mutations, changing the primary therapeutic approach of Cancer therapy. It has served as the edifice for the revolution of targeted therapies for hematologic and oncologic malignancies.

Data Availability Statement:

The data that support the findings of this study are openly available in the Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality – hcup-us.ahrq.gov/databases.jsp. , for the years 1998-2011.

Funding Statement:

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest Disclosure:

Dr. Indumathy Varadarajan has received consulting fees from Omeros and Kite, unrelated to the current study. None of the other authors has any financial disclosure.

This study did not require institutional IRB or Ethics approval as it accessed a publicly available database of de-identified patients.

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