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Comparison of the Cure Rate in Blood Cancer Patients using Defective Marshall-olkin Extended Weibull Model

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Abstract

Background: Blood cancer is a type of cancer that affects the blood cells derived from the bone marrow. Leukemia, lymphoma, and myeloma are the most common subtypes. Usually, bone marrow transplantation (BMT) is performed alongside curative treatments, such as chemotherapy and radiotherapy to transfuse healthy hematopoietic stem cells into a person after their own unhealthy bone marrow has been treated to kill invasive cells.

Objectives: The aim of this study was to compare the percentage of remission (cure rate) between different types of blood cancer.

Methods: In this retrospective cohort study, 458 patients who received BMT between 2007 and 2014 were analyzed. Patients were followed up until 2017 to determine whether they were still alive or had relapsed. The defective Marshall-Olkin Extended Weibull model was used with death being the event of interest.

Results: The study included 34 cases of acute lymphoblastic leukemia, 155 cases of multiple myeloma, 59 cases of acute myeloid leukemia, 156 cases of Hodgkin's lymphoma, and 54 cases of non -Hodgkin 's lymphoma. The cure rate was highest in patients with Hodgkin 's lymphoma and multiple myeloma, while it was lowest in patients with acute lymphoblastic leukemia. in addition, age had an inverse effect on the cure rate for blood cancer (P=0.003), and relapse after BMT had a negative effect on the cure rate (P=0.003). In addition, relapse before transplantation had no effect, and body mass index was found to influence cure rate. A sensitivity analysis showed that the estimated cure rates increased slightly with decreasing cohort length.

Conclusion: Multiple myeloma and Hodgkin 's lymphoma had the highest cure rate, while acute lymphoblastic leukemia is barely curable. Obesity may increase the potential for cure and the experience of recurrence after BMT is associated with a lower cure rate.

Keywords: Cure rate, Defective models, Hematologic neoplasms, Survival analysis

1. Background

According to GLOBOCAN statistics, cancer is known to be one of the leading causes of death and a major obstacle to increasing life expectancy worldwide. In 2020, 19,300,000 new cases of cancer were detected worldwide, and it is estimated that the number of cancer cases will increase by 47 % by 2040, corresponding to 28,400,000 new cancer cases worldwide. Aging and population growth are only the main reasons for this prediction. However, this could be exacerbated by changes in the distribution and increasing prevalence of the main risk factors for cancer in many parts of the world (1).

Blood cancers originating in the bone marrow and lymphatic system can be divided into leukemias, lymphomas, and plasma cell cancers. There are four major subgroups of leukemias, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and chronic lymphocytic leukemia Chronic Lymphoblastic Leukemia (CLL), which account for 12.4%, 23.1%, 6.6% and 17.5% of leukemia incidence, respectively (2). Lymphoma is divided into two subtypes: Hodgkin 's lymphoma (HL) and non-Hodgkin s lymphoma (NHL), accounting for 15% and 85% of cases respectively. Multiple myeloma (MM) is a malignant disease of plasma cells that accounts for around 13% of all hematologic malignancies. According to recent studies, the number of new cases in 2020 is estimated at 474,500 for leukemia, 627,500 for lymphoma, and 176,400 for myeloma, while the mortality rate is estimated at 311,600 for leukemia, 283,200 for lymphoma, and 117,100 for myeloma (1).

As cancer treatment has made considerable progress, extensive statistical research has been carried out to develop cure models. The classical survival analysis assumes that all subjects will live to see the event. In contrast, cure models (known as long-term survival models)consider long-term survivors who may never experience the event of interest (3). Looking at the survival curve is a simple approach to determine whether there might be a subset of long-term survivors, called a cure fraction. A cure model might be an appropriate method to analyze survival data if the survival curve shows a plateau at the end of the study (4). In the presence of a cure fraction, standard methods of survival analysis, such as Cox's proportional hazard model might be

inappropriate and lead to completely biased results. Common usage cure models include mixture cure models and non-mixture cure models. The survival function for the standard mixture model is defined as $S(t) = p + (1-p)S_0(t)$, and for the non-mixture model it is defined as $S(t) = p^{(1-S_0(t))}$, where $p \in (0,1)$ is the cure rate and $S_0(t)$ is a traditional survival function. The cure rate is assumed and estimated in as parameter in both methods (5). Another recently introduced approach is the use of defective distributions. Instead of considering a separate parameter for the cure rate, its survival function eventually reaches a plateau that tends to the value of the cure rate due to the possible existence of a cure fraction. In other words, due to the unusual definition of its parameters, the survival function does not necessarily have to reach zero in the end. New studies have been carried out in this field (6,7).

2. Objectives

The aim of this study was to compare the percentage of remission (cure rate) of different blood cancers in patients who received BMT based on their clinical data.

3. Methods

In this historical cohort study, we analyzed patients with hematologic malignancies who received a bone marrow transplant (BMT). The data set was collected over a nine -month period from patients with hematologic malignancies, including non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL), multiple myeloma (MM), acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL). The candidates for BMT were registered between 2007 and 2014 in the BMT department of Taleghani Hospital, affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran, and continued to be followed until 2016. In order to determine whether patients were still alive or had already died, recorded information was mainly used, and occasionally telephone calls had to be made. Death from cancer was the event of interest, and the time between BMT and cancer-related death was considered the survival time. Risk factors used were type of diagnosis, age, gender, body mass index (BMI), pre-transplant hemoglobin (Hb) level, pre-BMT recurrence, and post- BMT recurrence. Some data sets were excluded due to incomplete information. Ultimately, 458 patients were selected. We considered a BMI of less than 18.5 kg/m^2 as underweight, from 18.5 to 24.9 kg/m^2 as normal weight, from 25 to 29.9 kg/m^2 as overweight and from 30 kg/m^2 as obese (8).

Kaplan-Meier (K-M) charts were created to assess survival differences and determine whether a cure fraction is presented. Based on the above factors, the cure rate was modeled using the Defective Marshall-Olkin Extended Weibull (MOeW) distribution family (9), and the best performance in terms of the lower Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) was chosen. The survival function for the MOeW distribution family is defined as

$$S(t|\boldsymbol{x}) = \frac{exp\{\boldsymbol{\beta}'\boldsymbol{x}\}S_0(t)}{(1+exp\{\boldsymbol{\beta}'\boldsymbol{x}\})S_0(t)-1} \quad (1)$$

Where β is the coefficient vector, $\boldsymbol{x}$ is the covariate vector and $S_0(t)$ is one of the following distributions: Exponential, Rayleigh, Lomax, Weibull, Gompertz, BurXII, Chen, Modified Weibull, Weibull Extension, Traditional Weibull and Log-Logistic. In addition, the independent variables were selected using the stepwise backward selection approach (10). All analyses and figures were created using R version 4.1.1.

To perform a sensitivity analysis, we compared the estimated cure rates after shortening the cohort to eight, seven, six, and five years.

4. Results

Of the total of 458 cases, 96(21%) died of blood cancer. The mean survival time, restricted to the maximum value, was 78.47 months [95% CI: 73.45, 83.48]. Age was used as a continuous variable, with a mean and standard deviation of 38.9 and 13.7, respectively. In addition, 53.9% of patients were under 40 years of age at diagnosis and 46.1% were older than 40 years. Table 1 summarizes the information about the patients by diagnosis type [Table 1].

Table 1. Patient characteristics stratified by the type of hematologic malignancy

Variables	Type of Hematologic Malignancy (Diagnosis)						P-Value
	HL	NHL	MM	AML	ALL	Total	
Categorical	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
Survival Status							
Died	25 (16.0)	16 (29.6)	29 (18.7)	14 (23.7)	12 (35.3)	96 (21.0)	0.045
Censored	131 (84.0)	38 (70.4)	126 (81.3)	45 (76.3)	22 (64.7)	362 (79.0)	
Sex							
Male	77 (49.4)	35 (64.8)	91 (58.7)	29 (49.2)	18 (52.9)	250 (54.6)	0.214
Female	79 (50.6)	19 (35.2)	64 (41.3)	30 (50.8)	16 (47.1)	208 (45.4)	
Transplantation Type							
Autologous	144 (92.3)	51 (94.4)	151 (97.4)	14 (23.7)	7 (20.6)	367 (80.1)	<0.001
Allogeneic	12 (7.7)	3 (5.6)	4 (2.6)	45 (76.3)	27 (79.4)	91 (19.9)	
Body Mass Index							

Obese	35 (22.4)	12 (22.2)	28 (18.1)	5 (8.5)	3 (8.8)	83 (18.1)	0.004
Overweight	49 (31.4)	18 (33.3)	70 (45.2)	15 (25.4)	11 (32.4)	163 (35.6)	
Normal	61 (39.1)	21 (38.9)	56 (36.1)	33 (55.9)	17 (50.0)	188 (41.0)	
Underweight	11 (7.1)	3 (5.6)	1 (0.6)	6 (10.2)	3 (8.8)	24 (5.3)	
Relapse Before Transplantation							
Relapse +	103 (66.0)	31 (57.4)	19 (12.3)	9 (15.3)	7 (20.6)	169 (36.9)	<0.001
Relapse -	53 (34.0)	23 (42.6)	136 (87.7)	50 (84.7)	27 (79.4)	289 (63.1)	
Relapse After Transplantation							
Relapse +	21 (13.5)	11 (20.4)	32 (20.6)	6 (10.2)	9 (26.5)	79 (17.2)	0.121
Relapse -	135 (86.5)	43 (79.6)	123 (79.4)	53 (89.8)	25 (73.5)	379 (82.8)	
Continuous	**Mean (Sd)**	**Mean (Sd)**	**Mean (Sd)**	**Mean (Sd)**	**Mean (Sd)**	**Mean (Sd)**	
Age	29.9 (8.8)	39 (13.7)	52 (8.23)	32.1 (9.68)	32.2 (11.4)	38.9 (13.7)	<0.001
Hb	9.46 (1.24)	9.41 (1.19)	9.7 (1.32)	9.45 (1.23)	9.46 (1.40)	9.53 (1.28)	0.295

HL: Hodgkin Lymphoma, NHL: Non-Hodgkin Lymphoma, MM: Multiple Myeloma, AML: Acute Myeloid Leukemia, ALL: Acute Lymphoblastic Leukemia, BMI: Body Mass Index, Hb: Hemoglobin Before Transplantation, N: Number, Sd: Standard Deviation
The P-Values For Categorical Variables Reflect Pearson's Chi-Squared Test And One-Way ANOVA (Analysis Of Variance) For Continuous Variables

According to Figure 1, which depicts the overall survival probability, the K-M curve reached a plateau approximately six years after transplantation and estimated the cure rate at just under 60% [figure 1].

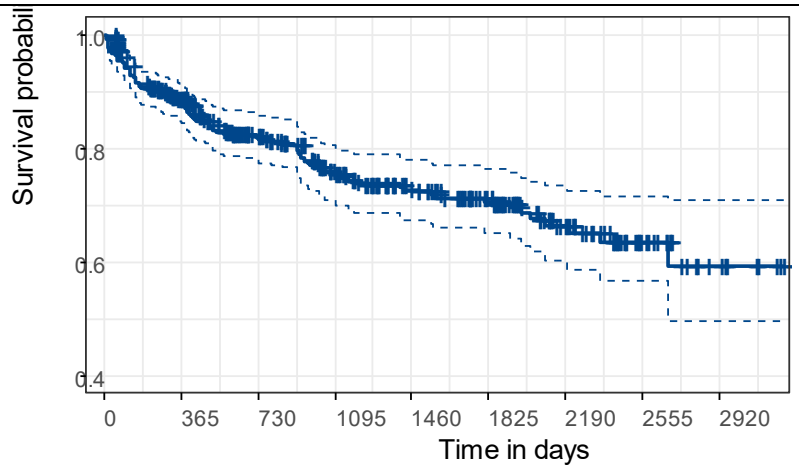

Figure 1. Overall survival probability of blood cancer for all patients in the study with 95% confidence interval

Figure 2 shows the survival fit using the parametric model (MOeW) together with the K-M estimates. As shown in Figure 2.A, survival and cure fraction rates were highest for HL and lowest for ALL. The estimated overall cure rates using the defective MOeW model were 0.21 [95% CI: -0.039, 0.459] for ALL, 0.32 [95% CI: 0.009, 0.630] for NHL, 0.34 [95% CI: 0.013, 0.666] for AML, 0.53 [95% CI: 0.118, 0.941] for MM and 0.56 [95% CI: 0.140, 0.979] for HL. There is no significant effect for gender (P=0.42) and relapse before BMT (P=0.26), which is visually confirmed in Figure 2.B and Figure 2.C. By the way, those effects lacked significance in any of the diseases (Figure 3). Ass shown in Figure2.D, there was a significant difference in cure rate between patients who experienced at least one relapse after BMT and those who did not (P<0.001). This difference was significant for HL, and NHL, whereas it was less clear for other malignancies, primarily due to the lack of information (Figure 4). Figure 2. E illustrates the survival estimate for different BMI categories. Patients with normal and overweight BMI had approximately the same survival time, although the survival time of patients with obesity was significantly increased. Again, despite sparse information, a higher survival rate was observed for obese patients, at least for MM, HL and NHL (Figure 5). In addition, more information would have been needed for the underweight category, as there were only a few cases, as can be seen in Table 1. Furthermore, when adjusting with covariate" type of transplantation alone, there is evidence of a higher cure rate with autologous transplantation; however, in the presence of other variables, this was not a significant variable. Figure 6 provides an excellent overview of this factor when stratified by each disease. Finally, there was no significant indication of the influence of pre-transplant Hb level (P=0.09). The results of the adjusted multiple cure model are also shown in Table 2 [figure 2-6].

After the modeling and variable selection procedure, a defective Marshall-Olkin-Lomax model for survival time was fitted with the following variables: Diagnosis, BMI, recurrence after transplantation and age. AIC and BIC for this model were the lowest possible among all models in the MOeW family, as their values were 211.29 and 256.68, respectively [table 2].

Table 2 summarizes the meaningful factors for cure rate obtained by fitting a Defective MOeW Lomax model. After adjusting for other variables, patients in the MM and HL groups were 6.64 and 2.7 times more likely to be cured, respectively, than patients in the ALL group. The estimated odds ratio

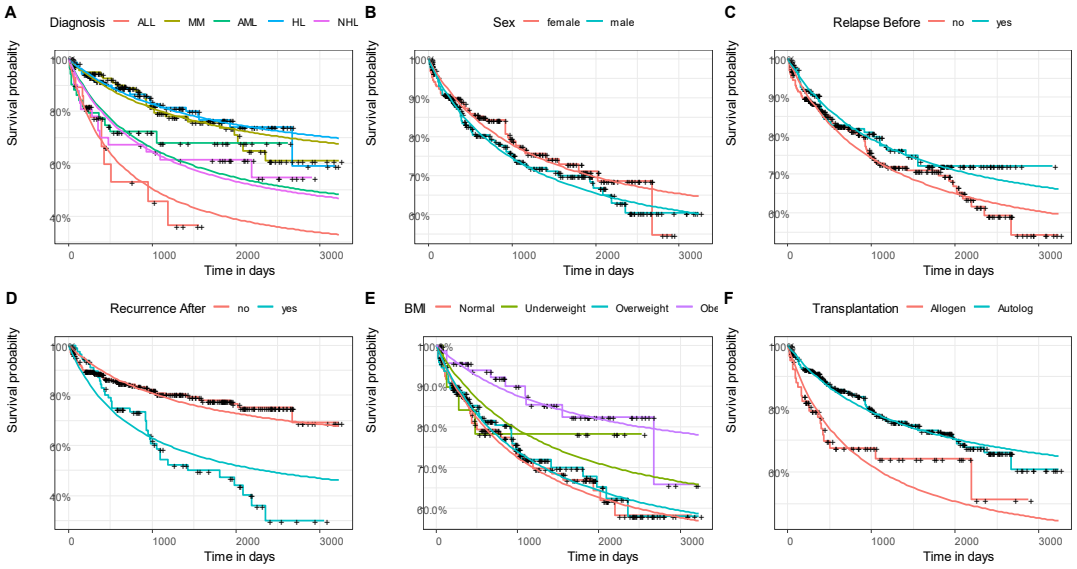

Figure 2. Univariate Kaplan-Meier estimation plus Defective Marshall-Olkin Lomax based on: (A) Type of blood cancer, (B) Sex, (C) Experience of relapse before bone marrow transplantation, (D) Having at least one recurrence of the disease after bone marrow transplantation. Note that the vertical axis has been trimmed to compact the figure

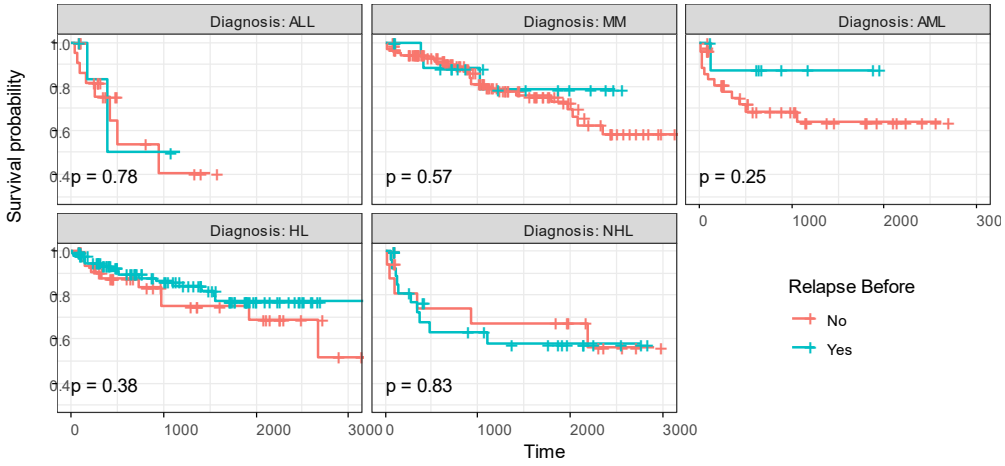

Figure 3. Survival comparison between patients with and without relapse before transplantation in each hematological malignancy using Kaplan-Meier curve and Log-Rank test

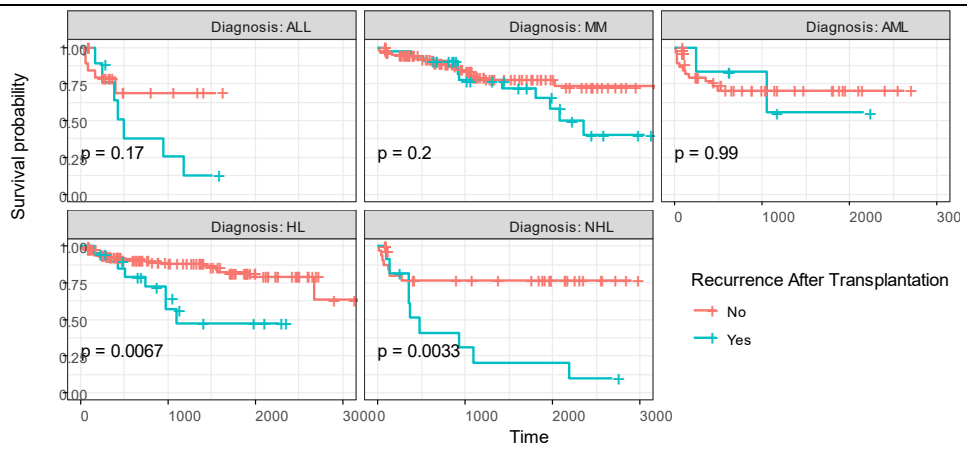

Figure 4. Survival comparison between patients with and without recurrence after transplantation in each hematological malignancy using Kaplan-Meier curve and Log-Rank test

for cure of AML and NHL compared to ALL was greater than one. However, due to the remarkable variability, these effects were not significant. Patients with obesity were 2.58 times more likely to be cured

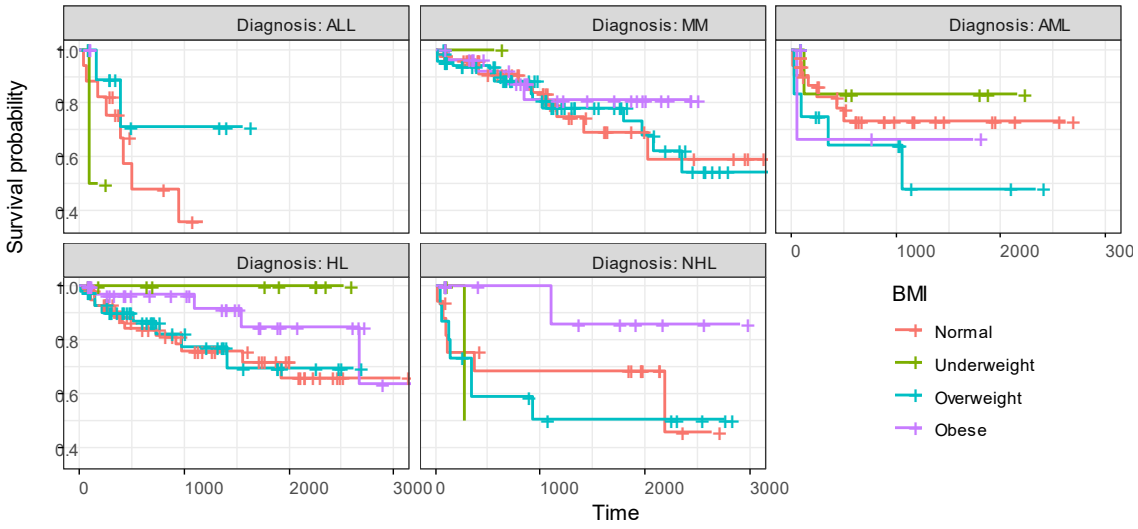

Figure 5. Survival comparison of four groups of body mass index in each hematological malignancy using Kaplan-Meier curve and Log-Rank test

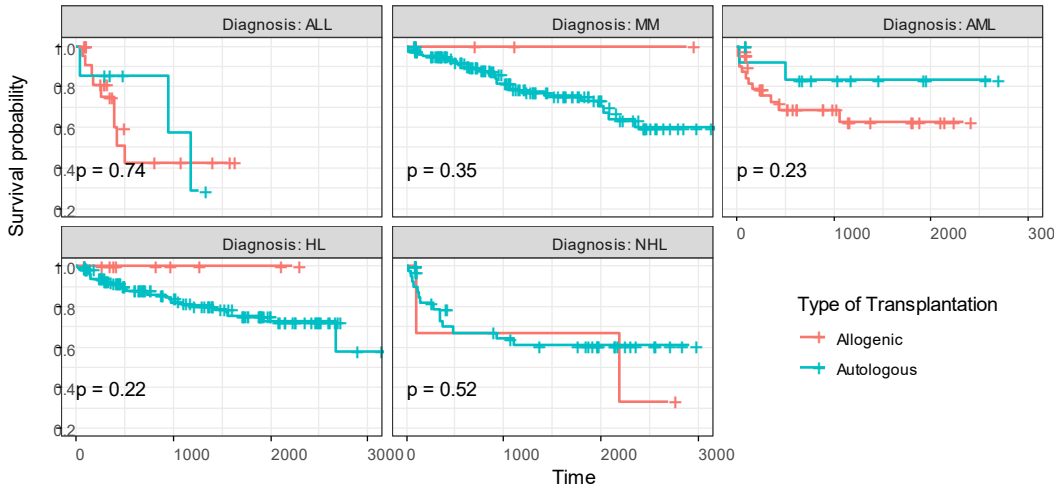

Figure 6. Survival comparison between patients received autologous and allogenic transplantation in each hematological malignancy using Kaplan-Meier curve and Log-Rank test

Table 2. Results of Defective Marshall-Olkin Lomax Model

Factor	Coefficient	Standard Error	Odds Ratio	95% Confidence Interval	P-value
Diagnosis					
MM	1.89	0.521	6.64	(2.39, 18.42)	<0.001
AML	0.21	0.524	1.24	(0.44, 3.44)	0.677
HL	0.99	0.466	2.70	(1.08, 6.71)	0.033
NHL	0.41	0.515	1.51	(0.55, 4.15)	0.424
ALL	0	-	1	-	-
BMI					
Underweight	0.22	0.629	1.25	(0.36, 4.24)	0.725
Overweight	0.10	0.280	1.10	(0.63, 1.89)	0.734
Obese	0.95	0.415	2.58	(1.14, 5.82)	0.022
Normal	0	-	1	-	-
Relapse after transplantation					
Relapse +	-0.77	0.264	0.46	(0.27, 0.76)	0.003
Relapse -	0	-	1	-	-
Age	-0.04	0.010	0.96	(0.94, 0.98)	0.003

HL: Hodgkin Lymphoma, NHL: Non-Hodgkin Lymphoma, MM: Multiple Myeloma, AML: Acute Myeloid Leukemia, ALL: Acute Lymphoblastic Leukemia, BMI: Body Mass Index

Table 3. Results of the sensitivity analysis. Estimated cure rates (95% confidence intervals)

Diagnosis	Length of follow-up				
	Full cohort	8 years	7 years	6 years	5 years
MM	0.53 (0.118, 0.941)	0.480 (0.094, 0.866)	0.488 (0.097, 0.879)	0.510 (0.107, 0.904)	0.579 (0.211, 0.967)
AML	0.34 (0.013, 0.666)	0.317 (0.083, 0.651)	0.327 (0.090, 0.664)	0.341 (0.100, 0.683)	0.388 (0.152, 0.725)
HL	0.56 (0.140, 0.979)	0.542 (0.083, 0.902)	0.559 (0.095, 0.923)	0.578 (0.120, 0.936)	0.650 (0.150, 0.971)
NHL	0.32 (0.009, 0.630)	0.317 (0.052, 0.582)	0.323 (0.054, 0.592)	0.345 (0.060, 0.629)	0.389 (0.115, 0.663)
ALL	0.21 (-0.039, 0.459)	0.224 (0.009, 0.439)	0.233 (0.015, 0.451)	0.246 (0.019, 0.473)	0.286 (0.052, 0.521)

HL: Hodgkin lymphoma, NHL: Non-Hodgkin lymphoma, MM: Multiple myeloma, AML: Acute myeloid leukemia, ALL: Acute lymphoblastic leukemia, BMI: Body mass index

than patients with normal body types. There was no significant difference in patients who were overweight or underweight compared to the normal category. In addition, patients who had a recurrence after transplantation had a 0.54 lower chance of being cured than patients who had no recurrence after transplantation. In addition, age had a negative effect on the cure rate, so that the probability of cure decreased by an estimated 0.04 for each additional year of life, assuming all other variables at a fixed value.

A sensitivity analysis is shown in Table 3. With the reduction in cohort length, the defective MOeW model showed a slight upward trend in the estimated cure rates [Table 2].

5. Discussion

To evaluate the progress in cancer therapy, it is a valuable approach to monitor the survival trend of patients over time. Survival monitoring in various cancer types has been reported in numerous studies (11–13).

Defective models estimate the treatment rate without additional parameters, which is an advantage over previous methods. In the current study, the relationship between the cure rate of blood cancer patients who received BMT and demographic variables was investigated using a new flexible and exacting model.

On the whole, obesity had a positive effect on the cure rate, mainly due to the fact that most obese cases in our study belonged to the lymphoma (HL and NHL) diagnosis group. These results are thus consistent with other studies (14); nevertheless, it is suggested that higher BMI is associated with increased leukaemia -related mortality in adult patients (15). It is also noteworthy that there were more underweight cases in the study, resulting in a higher estimated variance value (Table 1).

We were able to show that disease recurrence after BMT had a significant impact on cure rate, which is consistent with previous studies (16,17).

Age had a negative effect on cure rate in the present study, confirming previous reports (18,19). Interestingly, gender was not statistically significant Other studies confirmed this lack of importance (20), while others did not (21).

Despite the observation of a significant univariate effect on the type of transplantation, we did not use this variable in our model because in the MM, HLand NHL diagnosis group, almost all patients underwent autologous transplantation. On the other hand, patients with AML and ALL had mainly received allogeneic transplantation therapy. Since the transplantation strategy is different for the various malignant blood malignancies, it was not a good choice to include this variable in the adjusted cure model, even though it may have a significant effect.

The effect of pre-transplant hemoglobin was not well established in this study, which is in contrast to previous studies (22,23).

The results of the sensitivity analysis suggest that a shorter overall follow-up period leads to a slight inflation of the estimated cure rates based on the defective MOeW model. These results are in tandem with previous studies on flexible cure models. Models with greater flexibility have a greater potential for variation in estimates. Nevertheless, the model used in this study did not show great sensitivity to cohort length (24).

The current study had several limitations. First, data extraction was performed by a statistical group and not by medical experts. Second, it took nine months to collect the data because the data was not uniformly integrated. Third, as mentioned earlier, the number of BMT operations was insufficient in some groups. Collecting more cases will improve the results. In addition, the data were from a single medical center, so the results obtained with this dataset cannot be generalized to all patients with the same malignant blood disorders. We also needed more information about the patients, such as socioeconomic situation and family history.

In this study, we used the type of diagnosis as a prognostic factor. However, this is not common in medical cancer studies, as risk factors vary among patients depending on age group, diagnosis and numerous biological, clinical and pathological factors. We only wanted to present a report here.

Further research on the effect of BMI on cure rate would be a good idea.

6. Conclusion

Multiple myeloma and Hodgkin's lymphoma have the best chances of being cured, while acute lymphoblastic leukemia is virtually incurable. The results also indicate that patients with obesity can be better cured by BMT and that the chances of cure worsen with the occurrence of a relapse after BMT.

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Footnotes

Conflicts of Interest: There is nothing to declare.
Author's contributions: Data collection was done under the supervision of Dr. H. Bonakchi. The manuscript was reviewed and statistically analyzed by Dr. AR. Baghestani. The medical concept was approved by Dr. S. Parkhide. The data were analyzed, interpreted and drafted by D. Kadkhoda. Final review and approval was by Dr. Maboudi, corresponding author.
Funding/Support: None.
Ethical statements: This research was an observational study and as all information was extracted from the BMT ward record archive, no ethical concerns arose.

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