

Marital Status and Survival in Patients with Multiple Myeloma: The Role of Marriage in the Management of Multiple Myeloma

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1. Abstract

Despite better understanding of Multiple Myeloma (MM) and the development of novel therapeutic strategies which improved overall survival, MM still remain largely incurable. This warrants a better understanding of socio-demographic factors that may influence disease course and outcomes across MM patient. Positive influence of marital status is well established for many solid and liquid cancers. However, limited literature is available showing its influence on MM patients. Surveillance, Epidemiology and End Results programme (SEER) data was used to identify total 29,507 MM patients diagnosed in 2011 through 2015 and 16,519 patients who had symptomatic MM and their clinical and follow-up information available were analysed. The outcome variable was the survival time from diagnosis to death due to myeloma. On mixed effects Cox regression for myeloma-specific mortality, there was a significant interaction between marital status and sex at the nominal significance level (α) of 0.01. Holding demographic covariates age, income, education, race, and residence at a fixed value, the hazard ratio (HR) of myeloma-specific mortality for married male patients over the HR for married female patients was about 18% lower. In addition, younger age, high income, African-American patients were less likely to die of myeloma. Further analysis indicated that patients who were unmarried, widowed or divorced, were at significantly greater risk of myeloma-specific mortality after being adjusted for the demographic covariates ($p < 0.01$). Our analysis supports the positive effect of marriage on the outcome of MM patients. The effect of strengthening psychosocial support should be investigated as supplementary treatment for MM patients.

3. Introduction

Multiple myeloma (MM) accounts for 1% and 10% of all cancers and of all hematologic malignancies respectively [1]. Each year over 30,000 new MM cases are diagnosed in the United States, and over 12,000 patient's die of the disease [2]. The median age of diagnosis is about 65 years [3]. MM is currently an incurable condition. Introduction of several novel anti-myeloma drugs over the last decade has improved the survival of MM patients; however,

MM still remains largely incurable. Survival estimates in MM vary based on the source of the data. Data from trials using novel therapies show that the median survival in MM is approximately 6years [4]. In the subset of patients eligible for autologous stem cell transplant (ASCT), the median overall survival (OS) is approximately 8 years [5]. Among elderly patients (age >75years), median OS is lower, and is approximately 5 years [6]. Evidence also suggests greater improvements in OS among white individuals

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compared with patients of ethnic minorities [7].

Many factors affect the OS of patients newly diagnosed with MM, for example, disease stage, chromosome abnormalities [8], gene expression patterns in clonal myeloma plasma cells [9], the presence of elevated lactic dehydrogenase [10] and host factors including age, race, comorbidities, performance status, and ultimately response to treatment [11]. However, not all the MM patients with same or similar risk factors attain similar treatment outcome with same regimen. Hence, we hypothesised that socio-dynamic factors, particularly marital status may have influence on the treatment outcome for myeloma patients.

Marriage is the most important type of social support which could be linked to a variety of physiological mechanisms. There is an increasing interest in associations of marital status and survival in many cancers such as prostate and breast [12,13]. These literatures indicate that a positive correlation between marriage and longer survival can be attributed to the fact that a spouse can provide emotional support and can play a crucial role in monitoring and shaping health-related behaviour [14]. Effects of marital status on cancer have been extensively evaluated in many solid tumors [15]. However, the effect of marriage on survival of MM patients has not been addressed adequately and warrants further research. Hence, we evaluated a large SEER data on MM patients to test our hypothesis.

4. Materials and Methods

Using the Surveillance, Epidemiology, and End Results (SEER) program [16], we examined the impact of marital status on survival of patients with Myeloma. There were 29,507 patients diagnosed with Myeloma in 2011 through 2015. Patients were excluded if age at diagnosis was less than 18 years, a diagnosis of cancer was made at autopsy, a prior malignancy had been diagnosed, the cause of death was unknown, the descriptors for multiple myeloma (collaborative stage site-specific factor 3) was unknown or asymptomatic, clinical information was incomplete, marital status at diagnosis was unmarried or domestic partner, and selected variable values were unknown, leaving 16,519 patients available for the analysis.

The outcome variable for the survival analysis was the survival months from diagnosis to the occurrence of death (mortality) due to myeloma. The variable of mortality was a binary variable having value zero for right-censored patients and one for dead patients with myeloma. The outcome variable was modelled as

a linear combination of seven predictor variables, also called covariates. The covariates included marital status, age at diagnosis, sex, race, median household income, percentage of adults with a high school education, and residence. Marital status was married or unmarried which consisted of four subgroups, including never married, separated, divorced, and widowed. Race was classified as white, African American, Native American, American Asian, and Hispanic by SEER. Residence type was classified as rural and urban for this research. The income, education, and residence type were county level covariates by linkage to American Community Survey (ACS) for 2011-15, ACS for 2011-15, and the 2013 Rural-Urban Continuum Codes from the United States Department of Agriculture, respectively. Year of diagnosis was also used when the relationship between the marital status and year of diagnosis was examined using Chi-squared (χ^2) test, which will be discussed next.

5. Statistical Analysis

Patient characteristics divided by two groups, married and unmarried patients, were compared using the independent samples t-test for continuous variables (age at diagnosis, median household income, percentage of adults with a high school education, and survival months) and χ^2 test for categorical variables (sex, race, residence, year of diagnosis, and myeloma mortality). In order to control the familywise error rate, the Bonferroni correction was used: The nominal significance level (α) for an individual test was $0.05/9 = 0.006$. In other words, the p value less than 0.006 were considered to be significant in the individual test. The tests were conducted in JASP software [17].

For the outcome measure of symptomatic myeloma mortality and the county level covariates, mixed effects Cox proportional hazards multiple regression was used to examine the impact of marital status on myeloma mortality after adjustment for demographic covariates. The mixed effects Cox regression accounts for the baseline hazard as well as within-cluster homogeneity in outcomes by incorporating cluster-specific random effects. For the analysis, the R package of 'coxme' ver. 2.2-10 [18] was employed in R software [19]. The reference group for the regression was the married white male patients living in urban area.

6. Results

(Table 1) presents demographic statistics of myeloma patients diagnosed in 2011 through 2015 selected for the analysis. Married patients were, on average, 1.3 years younger, but had higher

income, education, and survival months, than unmarried patients. As shown in (Table 2), all the mean differences of age, income, education, and survival months between married and unmarried patients were statistically significant. However, their effect sizes were small according to the criteria suggested by Cohen [20]. For the marital status, a plot of survival curves using Kaplan-Meier method [21] is in (Figure 1a). The dark grey curve is for married patients and the light grey curve is for unmarried patients. The dotted line represents the median survival probability (0.5). The survival curves indicated that the married patients had higher survival probability than the unmarried patients. The survival probability of 0.5 for the unmarried patients reached at about 53rd month. Married patients were more likely to be male or white. Most of patients in the data were urban situated. During five years from 2011 to 2015, the percentages of patients diagnosed with myeloma between married and unmarried patients were quite similar one another. Married patients were more likely to be alive than unmarried patients. The χ^2 test showed that sex, race, and mortality had a strong relationship with marital status while residence and year of diagnosis did not (Table 2).

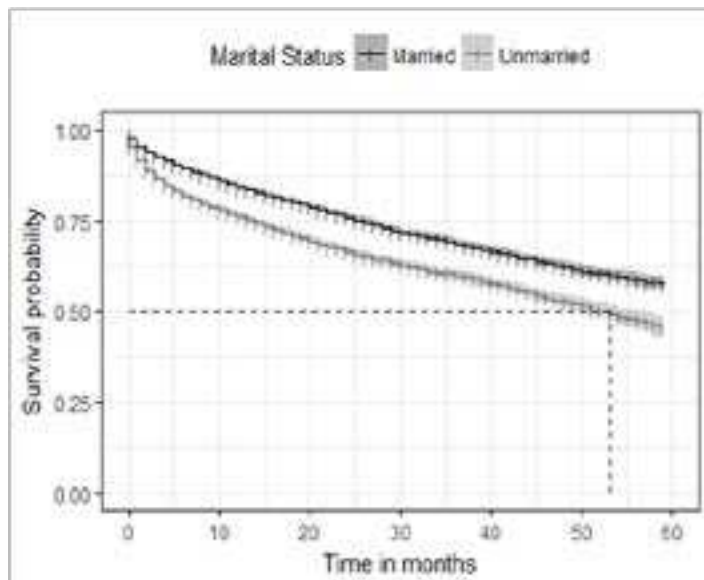


Figure 1a: Survival curves (Kaplan-Meier curves) for Marital Status

On mixed effects Cox regression for MM mortality, there was a significant interaction between marital status and sex at the nominal significance level (α) of 0.01. Holding the other covariates, such as age, income, education, race, and residence at a fixed value, the hazard ratio of MM mortality for married female patients over the hazard ratio for married male was about 18% higher. In other

words, male patients benefitted more from marriage than did female patients. In contrast, female patients who were not married benefitted more than male patients who were not married. In addition to the male married patients, younger patients, or patients who had a higher income or were African American were less likely to die of MM. The output of the mixed effects Cox regression is described in (Table 3a).

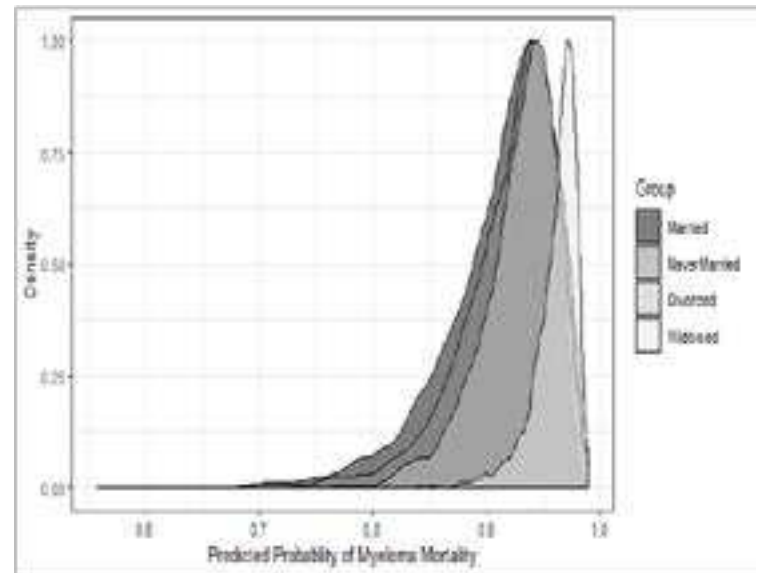


Figure 1b: Density plots of Predicted Probability of Myeloma Mortality

The associations between subgroups of unmarried patients and the myeloma mortality were also investigated. (Table 3b) summarizes the adjusted hazard ratio, the 95% confidence interval (CI), and the p value, for each subgroup of unmarried patients after adjusting for demographics. All the subgroups of unmarried patients, except separated patients, were at significantly greater risk of MM mortality. For example, patients who were never married showed the highest hazard ratio, about 52% higher, than patients who were married, followed by patients who were widowed and divorced, with 46% and 39% higher, respectively. (Figure 1b) depicted the density of married patients and three subgroup unmarried patients over predicted probability of myeloma mortality. The distribution of married patients lied in the lowest probability while the widowed patients lied in the highest probability.

7. Discussion

Adhering to the vow, “Til death do us part,” may be health promoting. Among individuals who are well and among patients who are suffering a wide array of illnesses, marriage is often

Table 1: Demographic Statistics

Characteristic	Unmarried		Married	
	(n = 6,443)		(n = 10,076)	
	No.	%	No.	%
Age, years				
Mean	67.1		65.8	
SD	13.1		11.3	
Income, USD*				
Mean	58,519.8		60,227.7	
SD	15,185.2		15,439.8	
Percent that completed high school*				
Mean	85.0		85.4	
SD	6.0		6.1	
Survival months				
Mean	19.2		21.7	
SD	16.6		16.7	
Sex				
Male	2,694	41.8	6,375	63.3
Female	3,749	58.2	3,701	36.7
Race				
White	3,357	52.1	6,545	65
African American	1,921	29.8	1,451	14.4
Native American	40	0.6	48	0.5
Asian	285	4.4	738	7.3
Hispanic	840	13.1	1,294	12.8
Residence*				
Rural	72	1.1	138	1.4
Urban	6,371	98.9	9,938	98.6
Year diagnosis				
2011	1,147	17.8	1,732	17.2
2012	1,241	19.3	1,935	19.2
2013	1,295	20.1	2,021	20.1
2014	1,310	20.3	2,121	21.1
2015	1,450	22.5	2,267	22.5
Mortality				
Alive (Censored)	4,316	67.0	7,585	75.3
Dead (Myeloma)	2,127	33.0	2,491	24.7

* County-level data

associated with longer life and better quality of life [22]. The aim of this study was to investigate the impact of marital status on the survival of MM patients. Our results demonstrated that married patients had better survival compared with unmarried

patients. These findings remained significant after controlling for demographic variables.

Studies assessing the impact of marital status on disease specific survival among cancer patients showed conflicting results, with protective [23,24], mixed, [25] and non-significant, [26] effects. Very little literature is available about the effect on marriage on the survival of MM. None of these above studies has examined the effect of marriage on the outcome of MM treatment and its survival. National Institutes of Health/National Cancer Institute spends approximately \$5 billion per annum [27] on cancer research focused mainly on biologic investigations. However, our study suggests that targeted psychosocial support interventions could prove to be a cost-effective method of improving survival among patients with myeloma.

Table 2: Comparison between the married and unmarried patients

t-test	Mean Difference	95% CI of the Difference	Pr (2-tailed)	Effect Size*
Age, years	1.371	0.981 to 1.760	< 0.001	0.114
Income, USD	-1,707.83	-2,185.751 to -1,229.911	< 0.001	0.112
Percent that completed high school	-0.460	-0.650 to -0.270	< 0.001	0.076
Survival months	-2.451	-2.972 to -1.930	< 0.001	0.147
Chi-squared (χ ²) test	χ ² Statistics	df	Pr	
Sex	729.900	1	< 0.001	
Race	620.800	4	< 0.001	
Residence	1.794	1	0.180	
Year diagnosis	1.832	4	0.767	
Mortality	133.700	1	< 0.001	

Previous studies among cancer patients showed associations between marital status and improved outcomes [15,28] An explanation for the relationship is that marriage is a source of social support. Spouses may encourage their partners to take cancer screening, support to complete recommended treatment, and receive more intensive therapy. Numerous published studies have observed that unmarried patients are at significantly higher risk of late stage diagnosis, suboptimal treatment, and cancer death [15]. We found that unmarried patients, including those who are never married, are at significantly greater risk of death resulting from MM than patients who are married. It may be because married people seek medical attention earlier due the possible

encouragement by their spouses and have an early diagnosis and early appropriate treatment. Spouses also may encourage patients to undergo definitive versus expectant management [29], potentially accounting for the discrepancies in the survival. There are many explanations for the vital question of why marriage is associated with improved cancer-specific survival after adjustment for demographics, stage, and treatment, but the most likely reason is that married patients have better adherence with prescribed treatments than unmarried patients [30].

Table 3a: Estimate and Hazard Ratio from the Mixed Effects Cox Regression

Random effects						
Group	Variable	Std Dev	Variance			
County Intercept 0.055126838 0.003038968						
	Estimate	HR	Std. Error	z value	Pr (> z)	
Married	-0.448	0.639	0.042	-10.690	0.00E+00	***
Age	0.047	1.048	0.001	34.290	0.00E+00	***
Income	0.000	1.000	0.000	-5.640	1.70E-08	***
Education	-0.002	0.998	0.003	-0.530	0.590000	
Female	-0.225	0.798	0.044	-5.070	4.10E-07	***
African American	-0.138	0.871	0.041	-3.390	0.000710	***
Native American	-0.106	0.899	0.202	-0.530	0.600000	
Asian	0.010	1.01	0.067	0.150	0.880000	
Hispanic	0.048	1.049	0.049	0.980	0.330000	
Rural	-0.071	0.931	0.125	-0.570	0.570000	
Married x Female	0.163	1.177	0.061	2.650	0.008000	**
Signif. Codes: 0 '***' 0.001 '**' 0.01						

Note. HR refers to Hazard Ratio.

Psychologically, cancer diagnosis usually results in more distress than other diagnoses [31]. Married patients display less distress, depression, and anxiety than their unmarried counterparts after cancer diagnosis, this may be because a partner shares the emotional burden and provide appropriate psychological support [32]. Labile psychological state can lead to poor adherence to treatment and as a consequence poor outcome. A study showed

that women with depression who are diagnosed with breast cancer undergo definitive treatment less often, hence poorer survival [33]. Treating healthcare professionals should consider screening for psychological health among unmarried patients with MM and refer patients to mental health specialists if symptoms are identified. In addition, physicians should consider closer observation of unmarried patients with MM to maximize adherence.

Table 3b: Association between subgroups of unmarried patients and the myeloma mortality

	HR	95% CI	Pr (> z)	
Married	Reference Group		-	
Never Married	1.517	1.392 to 1.654	0.00E++	***
Separated	1.071	0.791 to 1.450	0.66	
Divorced	1.386	1.250 to 1.537	5.30E-10	***
Widowed	1.464	1.346 to 1.592	0.00E++	***

One study has shown that cortisol levels to be lower in patients with cancer who have adequate support networks. A diurnal cortisol patterns have been linked with natural-killer cell count and survival in cancer patients [34], providing a physiological basis for the psychologically data. Hence the married MM patient may have shown survival advantage in our study. If the benefits of marriage on MM survival are mediated through spousal psychosocial support, then the most effective way to combat the increased risks associated with unmarried MM patients would be to aggressively promote support mechanisms. A randomized controlled trial revealed that a psychosocial support-based intervention was associated with a near doubling of overall survival among advanced metastatic breast cancer patients [35]. Similar effect was shown among metastatic non-small-cell lung cancer that early implementation of supportive measures/palliative care along with standard oncologic care improved the median survival of patients relative to standard oncologic care alone [36]. This may again explain why married MM patient has better survival in our study in compare to their unmarried counterpart as the married patients had better support system.

Our study shows a clear protective effect of marriage among myeloma patients. Interestingly, the impact of marriage specific mortality seemed to be greater in men than in women in our study. The exact reasons for this will need to be explored further, but it could, for example, reflect that unmarried women receive greater psychosocial support from their relatives (e.g. their own children),

friends, or the community than unmarried men.

Potential limitations of our study should be considered. Firstly, due to the nature of these data, we did not have information regarding disease and treatment factors (such as chromosome abnormalities, treatment regimens, disease staging, or other clinic-pathologic features) that are known to influence survival. Secondly, data related to chemotherapy and other active drug treatment was not accessible in SEER that clearly will have significant impact on survival as we know different treatment regimen produce differing survival. Thirdly, data patient related risk factors such as renal function, ECOG performance status etc. were not available. Fourthly, it is possible that some patients were cohabitated with a partner but not married [37]. However, such patients would be categorized as unmarried by SEER and expected to display better outcomes than the unmarried population, hence biasing our results toward the null.

It is inevitable that more disadvantaged patients have inadequate or poorer access to health care and may present with advanced disease or with complications. This possibility is supported further by the finding that marital status, insurance status, and county-level education also affected early mortality in this study. It is possible that unmarried patients are innately different from married patients in ways that cannot be accounted for by our multivariable analysis and that the associations between marital status and outcome identified in this study reflect the influence of an unmeasured confounder. This possibility is mitigated, however, by the fact that widowed MM patients also displayed poorer outcomes than patients who were married, suggesting that the lack of social support, and not the presence of an unmeasured confounder, is the driver of the findings in this study.

Marital status is an important support strategy for MM patients for improved survival as shown in our study and we recommend additional social support for unmarried MM patients to improve outcomes. Targeting single MM patients with regular monitoring, disease awareness programs and offering psychological counselling are possible interventions that may be beneficial [38]. Despite the stated limitations, our study has yielded conclusive results regarding the association between marital status and outcome of MM. Marriage is an independent predictor of improved survival in patients with MM due to increased social and psychological support. Interventions such as social and psychiatric referral

should be considered for better outcomes for unmarried MM patients, who are at greater risk. Some roles of marriage in the management of multiple myeloma are not included in statistics like the story of a lawyer who was the wife and caregiver of her husband a consultant cardiologist who was a patient with myeloma. She convinced scientists in Harvard University and the clinician in UAMS hospital to use Thalidomide in treatment of myeloma [39]. In her desperate effort she inspired an international research on immunomodulatory drugs in myeloma, nowadays a back bone of any treatment regimes.

8. Conclusion

Findings from our analysis support the positive effect of marriage on the survival of multiple myeloma patients. Psychological distress among cancer patients is enormous. Unmarried MM patients (i.e. divorced, widowed and never married) often lack adequate support network to cope with such distress. Given the potential benefits of psychological and social support via marriage linked to the greater survival of MM patients, the effects of adding empirically supported interventions such as Forgiveness Therapy [40] to the regular treatment regimen should be further investigated.

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