MODELLING THE EFFECTS OF MINDFULNESS BASED STRESS ON BREAST CANCER SURVIVAL RATE AMONG WOMEN IN MERU AND NYERI COUNTIES, KENYA, USING COX PROPORTIONAL HAZARD MODEL

ABSTRACT

Breast cancer remains the most commonly diagnosed cancer among women, affecting 34 women per every 100,000. This has led to high number of fatalities annually, which need to be mitigated. Establishing alternative conventional therapies such as working on mindfulness-based stress (MBS) may be a good alternative to improve prognosis and survival rate of breast cancer patients. However, there is little information on the effects of MBS factors on breast cancer survival. The objective of this study is to predict the effect of MBS factors on breast cancer survival rate among women in Meru and Nyeri Counties using Cox Proportional Hazard Model. Both primary data and secondary data were used. Primary data was obtained using a structured questionnaire from the breast cancer survivors and the medical practioners, while secondary data was obtained from records at Meru teaching and referral hospital and Nyeri level five hospital for the period 2012 to 2017. The MBS variables included cost burden of treatment, stress on diagnosis, prolonged time taken to access treatment, poor diet, alcohol use, physical activity and lack of awareness. . This study used mixed method research design. Data obtained were analysed using R software. Kaplain-Meier estimators were used to estimate the varying effects of MBS factors on survival rate. Log-rank test was used to perform comparisons of survival curves on the patients' survival rate considering age. The likelihood ratio test showed that MBS factors are significant in predicting hazard rates (χ^2 = 66.7, p = 0.0000119). Treatment period, lack of awareness, ease of coping with stress and observing the right diet were also found to significantly ($p < 0.05$) affect breast cancer survival rate. Access of treatment immediately after diagnosis, availing the right information to the patients, helping patients to cope easily with stress and observing the right diet were found to be the best estimators in increasing breast cancer survival rate. The study showed the importance of using model in predicting breast cancer survival rates, which can greatly improve breast cancer prognosis.

Keywords: Mindfulness-Based Stress, Breast cancer, Survival rate, Cox proportional Hazard Model, Predictive Modelling.

Introduction

Cancer remains the primary cause of mortality worldwide in countries of all income levels and is expected to continue growing precipitously due to changes in demographics and lifestyles (Lindsey *et al.,* 2016). Breast Cancer is a major health burden in the society and the prominent source of cancer-related deaths among females worldwide (Lindsey *et al.,* 2016; Bozorgi et al., 2016). Breast cancer remains the most common form of cancer among women worldwide and the second main cause of death in women, after lung cancer (Nordqvist, 2018). Cancer pose a great health care burden in the world with 60% of the world's new cases being diagnosed in developing countries (Ruff, 2016).

In Kenya, cancer ranks third among the main causes of mortality and morbidity (Kenya Cancer Statistics and National Strategies [(KCSNS), 2016]. The annual estimate of new cancer cases in Kenya is 39,000 and more than 27,000 deaths, with 60% comprising individuals who are younger than 70 years old (KCSNS, 2016). Female breast cancer is the most widespread among women in Meru County at 26% (Muchui, 2019). Therefore, interventions for its prevention and control are urgently required.

Mindfulness-Based Stress (MBS) is a condition experienced by person going through a difficult time, for example, through pain, illness and stress (WebMD, 2005-2017). Every breast cancer survivor battle with the disquiet of a cancer recurrence or developing a new cancer. This may cause anxiousness, lack of sleep and depression that may lead to high blood pressure or high blood sugar levels (Musiala *et al.,* 2011). Diagnosis of breast cancer is normally experienced as one of the difficulty situations which may result to a high level of emotional strain (Musiala *et al.,* 2011). To work on the 'existential plight' brought about by a cancer diagnosis therapeutic interventions should be employed including use of mind-body medicine (Musiala *et al.*, 2011).

The purpose of many medical studies is prognostic factors of patients' survival time based on clinical classification (Lo *et al*., 2017). Regression models have been widely used in clinical studies and prognosis. Peretti *et al*., (2016) used logistic regression in breast cancer prediction. They showed promising results with the optimised model giving prediction accuracy of 91%. Parametric statistical methods can be considered in survival data analysis if distribution is known, or semi parametric methods, if distribution is unknown.

The Cox proportional hazard regression model is the most widely used semi parametric survival model in health sciences, since it relies on fewer assumptions compared to parametric models (Georgousopoulou *et al*., 2015). The model can be used to eliminate non-significant variables ending up with a model containing variables with significant effect on breast cancer survival rate (Smith, 2011). The model is popular in survival analysis because it can be estimated semi-parametrically (Bradburn *et al*., 2003). It is also flexible in that it allows assumption of the baseline hazard function, and the coefficient estimates can be obtained through the partial likelihood function (Bradburn *et al*., 2003). This study aimed to develop a statistical model that would help in analysing the impact of MBS on breast cancer survival rate. The MBS variables considered were: costly burden of treatment, stress on diagnosis, prolonged time taken to access treatment, poor diet, poor lifestyles, alcohol use, physical activity, other diseases such as diabetes and lack of awareness. The cox proportional hazard model was used to determine the variables that have significant effect on breast cancer survival rate.

Methodology

This study was conducted in Meru and Nyeri counties, Kenya, which were selected purposively due to high number of breast cancer reported in this counties. The target population for the study consisted of the breast cancer patients who had attended Meru level five hospital and Nyeri referral hospital between the periods 2012 to 2017 and the medical practitioners who attended to the breast cancer patients in the two health facilities. Mixed method research design was used for this study. This research design is appropriate when both quantitative and quality data sets are used in handling a research problem (Creswell & Clark, 2017). The population estimates as obtained from the two hospital records were; 1350 breast cancer patients, 415 care providers and 200 breast cancer survivors for the period 2012 – 2017. The sample sizes of the three groups of subjects were determined using the formula by Kathuri and Pals (1993). The resulting sample sizes obtained for this study are shown in table 1.

Table 1: sample random sampling sizes

Group	Population	Sample Size
Patients from hospital records	1350	300
Medical practitioners	415	200

Breast cancer survivors	200	120
Total	1965	620

The study targeted the female breast cancer patients and survivors who we are younger than 80 years. These were the ones who had attended the two medical facilities considered in this study in either of the cancer stages. Exclusion criteria were: other types of cancer different from breast cancer; those with abnormal renal function tests, those who had developed other types of cancers, and them that were not willing to work on MBS factors.

Validity of the instruments in this study was done by incorporating experts' opinion. The experts in the field of breast cancer treatment scrutinized the instruments for face validity, construct validity and content validity. The experts also evaluated the appropriateness of the issues that were to be investigated. Their input was put into consideration and necessary adjustments were made before the instrument was used. Reliability of the research instruments was tested by administering the same instrument twice to the same group of subjects at two separate times with a time lapse between the first and second test. This helped establish the extent in which an instrument yields consistent results or information after repeated trials (Henn & Foard, 2006). The study used Pearson's product moment correlation coefficient formula to determine the correlation between the two set scores. A coefficient of 0.70 or more showed that there was high reliability of data (Ratner, 2009).

R software which was used for analysis of data in this study. Data analysis involved generation of descriptive statistics and inferential statistics. Descriptive statistics generated were inform of tables and graphs. The inferential statistics generated included the Kaplan Meir curves and the log rank tests. Kaplan –Meier curves were used to represent the differences in survival among different covariates and their outcomes. Log rank tests were used to determine significance of different covariates by determining the p values of different covariates. The study utilized the cox proportional hazard model. In a proportional hazards model, the unique effect of a unit increase in a covariate is multiplicative with respect to the hazard rate.

The model is given as follows

$\log_{hi}(t)=\alpha+\beta_1 X_{i1}+\beta_2 X_{i2}+\ldots\ldots\ldots\ldots\ldots+\beta_k X_{ik}$

or equivalently

$$hi(t) = \exp\,(\alpha+\ \beta_1 X_{i1}+\beta_2 X_{i2}+\ldots\ldots\ldots\ldots\ldots+\beta_k X_{ik})$$

where, i is a subscript for the observations, while the x's are the co-variates (costly burden of treatment -X_1, stress on diagnosis -X_2, poor diet-X_3.........X_k) βi their respective coefficients and baseline hazard function $h_0(t)$. The constant n this model represents a kind of log-baseline hazard, since$\log_{hi}(t)=\alpha$ when all of the x's are equal to zero. The goal was to test whether or not the model h (t | x) is improved with the inclusion of the different MBS covariates. Beginning with the null hypothesis$H_0: \ \beta_1=0$

With composite Hypothesis $H_1: \beta_1=0$. This is essentially testing whether a proposed covariate has significant effect on the model;

$$h\,(t\mid x_1) = h_0(t)e^{\beta_1 x_1}$$

is significantly (α = 0.05) at least as accurate at predicting survival as the null model.

Reject H_0 if D > χ^2 at α = 0.05. Since comparing the difference of one parameter in the model, there is 1 degree of freedom for the $\chi^2 >$ statistic, which is equal to 3.84 with 95% confidence. Where D > 3.84, H_0 was rejected concluding that a certain covariate was an important factor in determining survival rate. D is the test statistic. The Log-Rank test was used to perform comparisons of survival curves using hypothesis tests on the patients' survival rate considering age.

Kaplan-Meier estimators played a crucial role in determining the varying effects which the MBS variables have on survival rate. The Kaplan-Meier curves helped in showing a plot of percentage survival (y-axis) against time (x-axis). They are often used in survival analysis to provide a very digestible graphical output, which can be easily interpreted by those less familiar with the statistical concepts at work. The Kaplan-Meier method is based on individual survival times and assumes that censoring is independent of survival time (that is, the reason an observation is censored is unrelated to the cause of failure).

Kaplan-Meier estimator of survival at time t is shown below;

$$S\ (t_i) = \prod_{0 \le j \le n} \Pr(T > t_i \mid T \ge t_i)$$

$$= S\ (t_{j-1})t\ \Pr(T > t_j \mid T \ge t_j)$$

$$= \frac{S\ (t_{j-1})(n_j - m_j)}{n_j} \text{for } 0 \le t \le T$$

Here $t_{i,j}$ = 1,2,....n is the total set of failure times recorded, T is the failure time with distribution F and density f, m_j is the number of failures at time t_j, and n_j is the number of individuals at risk at time t_j.

The goodness of fit of the log rank tests was done using the probability values. If the probability value was less than the level of significance, the test was adequate. The adequacy of the cox proportional hazard model was determined using the likelihood ratio value and the probability value. Model validation was done by dividing the collected data into two sets. One set was used in fitting the model and the other set was used to test if the model fitted produced similar results with a different data set.

Results and Discussion

The average age of the respondents was 52.23 years (Table 2). The skewness and the kurtosis values showed that the data satisfied the normality assumptions. The average number of fatalities from breast cancer reported by medical practitioners was on average 42.19 per year (Table 2). The average time of survival for the breast cancer patients was 3.77 years (Table 2). The percentage of censored patients was 66.7% with the remaining 33.33% having succumbed to breast cancer. This implied that there is high mortality rate from breast cancer.

Table 2: Summary statistics for data on the breast cancer patients and the medical practitioners

Statistic	Number of fatalities	years worked	Time	Patient Age
Mean	42.19	6.44	3.77	52.23
Standard Deviation	16.41	5.56	2.03	10.74

Median	39	5	4	53
Skewness	0.42	2.2	0.36	-1.3
Kurtosis	-0.17	5.7	0.04	4.19
Maximum	90	31	10	75
Minimum	1	1	1	3

The mindfulness based stress that seemed to affect the breast cancer patients in the areas of study were alcohol use, stress after diagnosis, adherence to prescribed diet, access to treatment, burden of treatment, engaging in regular exercises after diagnosis and awareness of how to handle the disease after diagnosis (Table 3; Table 4; Figure 1). These findings concurred with (Shennan *et al.*, 2010, Frauke *et al.*, 2011 & Sahar *et al.*, 2014) who found out that the mindfulness based stress factors that affected the cancer patients were anxiety, depression, stress, sexual problems, and psychological arousal and immunity problems. Shennan *et al.* (2010) found out that the mindfulness based stress factors that affected the cancer patients were anxiety, depression, stress, sexual problems, and psychological arousal and immunity problems.

Table 3: Mindfulness-based stress following breast cancer diagnosis as analysed from practitioners' perspective

Variable	S. D		D.		U.		A.		S. A		M	M.d
	N	%	N	%	N	%	N	%	N	%		
Stress	44	14.67	33	11	36	12	91	30.33	96	32	4	5
Diet	31	10.4	40	13.42	75	25.17	79	26.51	73	24.5	4	4
Regular-exercise	30	10.07	52	17.45	81	27.18	67	22.48	68	22.82	3	3
Treatment-period	27	9.09	36	12.12	78	26.26	73	24.58	83	27.95	4	5
Awareness	28	9.33	45	15	81	27	65	21.67	81	27	3	3
Cost-burden	18	6	15	5	21	7	10.0	33.33	14.6	48.67	4	5
Drug use	46	15.38	69	23.08	82	27.42	55	18.39	47	15.72	3	3

S.D. Strongly Disagree, D. Disagree, U= Undecided A=Agree S.A = Strongly Agree, M= Median and M.d = Mode

Table 4: Mindfulness-based stress following breast cancer diagnosis as analysed from patients' perspective

Variable	Strongly Disagree		Disagree		Undecided		Agree		Strongly Agree		Median	Mode
	N	%	N	%	N	%	N	%	N	%		
Stress	44	14.67	33	11	36	12	91	30.33	96	32	4	5
Diet	31	10.4	40	13.42	75	25.17	79	26.51	73	24.5	4	4
Regular exercise	30	10.07	52	17.45	81	27.18	67	22.48	68	22.82	3	3
Treatment period	27	9.09	36	12.12	78	26.26	73	24.58	83	27.95	4	5
Awareness	28	9.33	45	15	81	27	65	21.67	81	27	3	3

Cost burden	18	6	15	5	21	7	100	33.33	146	48.67	4	5
Drug use	46	15.38	69	23.08	82	27.42	55	18.39	47	15.72	3	3

Patients who showed lack of awareness portrayed less survival than those who had awareness of breast cancer (Figure 1). This result was confirmed inferentially using the log rank test. The log rank test results were; chi-square value of 18.439521 at 4 degrees of freedom and a p -value (P = 0.0010124.) This showed that there were significant different survival proportions for the different awareness groups. This agreed with findings of Mahony et al. (2013), Akram *et al*. (2017) and Niksic *et al*. (2016). who found out that awareness of breast cancer was found to have a positive impact on recognition and screening of breast cancer which in return was observed to lead to increased survival rates.

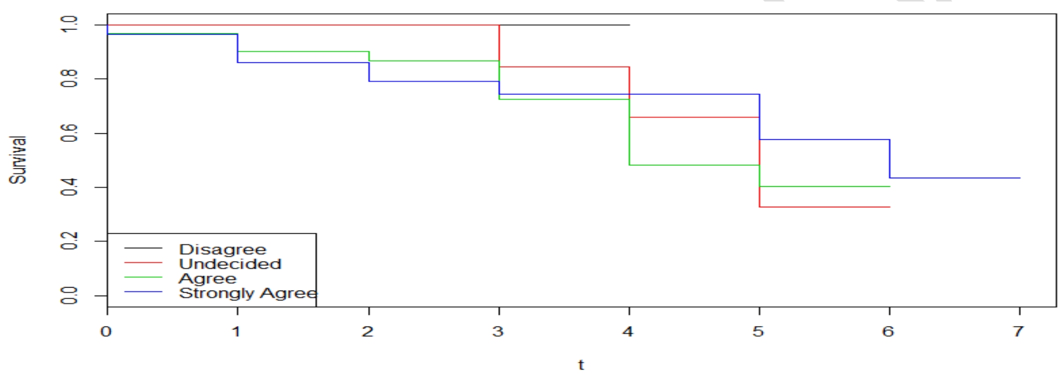

Figure 1: Kaplan-Meier curve for lack of awareness and its effect on survival of breast cancer patients.

The interpretation of the mindfulness based stress factors and their effects on the hazards of succumbing to breast cancer was done using the odds ratios (Table 5). For instance, a patient who got stressed after diagnosis of breast cancer increased their hazards of succumbing to breast cancer with a factor of 1.1336900 on average which is 13.4 % as compared to a patient who did not get stressed after diagnosis (Table 5). In this case, failing to get stressed was used as the reference level with all the other covariates being held constant. Further, adhering to the prescribed diet reduced the hazards of succumbing to breast cancer by a factor 0.0537464 on average or a percent of 93.64 % as compared to not adhering to the prescribed diet. Failing to adhere to the prescribed diet was used as a reference level with all the other covariates being held constant (Table 5). The findings of this study are in agreement with what was found by Niksic *et* *al*., 2016 who found out that a combination of regular exercise and a healthy diet was found to reduce rate of mortality among the breast cancer patients.

Table 5: Cox Proportional Hazard Model Summary

Variables	Coef	exp(coef)	se(coef)	Z	P
stress2	0.3054337	0.7368038	0.4260715	0.7168602	0.0636625
stress3	0.5865294	0.5562545	0.4686214	1.2516063	0.3098143
stress4	0.1254778	1.1336900	0.3572049	0.3512768	0.0000266
stress5	0.0781929	0.9247860	0.3515676	0.2224122	0.0095962
diet2	0.7228825	2.0603637	0.4023171	1.7967978	0.0723677
diet3	0.1906592	0.8264142	0.3987844	0.4781011	0.6325783
diet4	0.0523518	0.0537464	0.3844883	0.1361596	0.8916951
diet5	0.1280030	0.8798507	0.3944284	0.3245280	0.7455384
regular_excercise2	0.3336016	0.7163391	0.4092474	0.8151588	0.4149814
regular_excercise3	0.3918727	0.6757901	0.4070606	0.9626890	0.3357036
regular_excercise4	0.0328456	0.9676879	0.3677216	0.0893220	0.9288260
regular_excercise5	0.7066343	0.4933017	0.4015523	1.7597564	0.0784491
awereness2	1.1643320	0.3121311	0.4760576	2.4457798	0.0144539
awereness3	1.1813812	0.3068546	0.4176557	2.8286005	0.0046752
awereness4	0.0780022	0.9249624	0.3767364	0.2070471	0.8359731
awereness5	0.5754583	0.5624470	0.3773989	1.5248012	0.1273087
cost_burden2	0.2314046	1.2603691	0.6430587	0.3598499	0.7189594
cost_burden3	0.7506953	0.4720382	0.7251326	1.0352524	0.3005511
cost_burden4	0.0873911	1.9163186	0.4513698	0.1936131	0.8464789
cost_burden5	0.0547216	0.9467487	0.4364036	0.1253922	0.9002131
alcohol_use2	0.7794422	2.1802559	0.4202895	1.8545364	0.4734604
alcohol_use3	0.4176308	1.5183599	0.4112110	1.0156118	0.2107134
alcohol_use4	1.6932928	5.4373551	0.4030935	4.2007440	0.7253807
alcohol_use5	1.1439328	3.1390896	0.4416647	2.5900483	0.8239930
treatment_period	0.1845982	1.2027351	0.0941169	1.9613708	0.0498358

Model selection

Model selection was done by the help of Akaike information criterion (AIC). On fitting all the estimators the AIC was 1001.47. The burden of treatment was dropped to achieve an AIC value of 994.55. The stress was further dropped to achieve an AIC of 991.55. The next covariate to be dropped was regular exercise and awareness level, alcohol use and treatment period were found to be the best estimators since they gave the least AIC (989.30). The summary statistics of the fitted model is presented on Table 6.

Table 6: Summary Statistics of the fitted Model

	Statistics	χ^2	df	p-value
Fitted Model	Loglk	55.24	12	0.0000002
	Waldtest	53.32	12	0.0000004
	Logrank test	56.33	12	0.0000001

The fitted cox proportional hazard model is summarized as:

ln (odds of hazard rate/ succumbing to breast cancer)= 0.4315 Awareness_2 + 0.4215 + 1.2784 Awareness_3+ 0.7267 + 1.9974 Alcohol use_ 2 + 1.4306 Alcohol use_ 3+ 0.3628 Alcohol use_ 4+ 0.9365 Alcohol use_ 5 + 0.7358 Treatment period_ 2+ 0.4919 Treatment period_ 3 + 1.2942 Treatment period_ 4 + 1.3858 Treatment period_ 5

Conclusion

Most MBS factors were found to significantly affect survival. Stress, being able to access treatment as soon as diagnosis has been made, observing the right diet and being aware of how to handle the disease were significant. Treatment period (p = 0.000143) was found to significantly affect survival rate compared to other covariates; lack of awareness (p = 0.0010124), ease of coping with stress (p = 0.000514) and observing the right diet (p = 0.04092). The likelihood ratio test showed that MBS factors are significant in predicting hazard rates with a chi-square value of 66.7 and a p-value (p = 0.0000119).

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