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Multistate Markov Modelling for Disease Progression of Breast Cancer Patients Based on CA15-3 Marker

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Abstract

Multi-state models are a flexible tool for analyzing complex time-to-event problems with multiple endpoints, especially in chronic diseases where the patients move through different states. It provides a more detailed insight into the disease process as compared to other statistical models. The primary objective of this paper is to study the significance of CA15-3 as a disease marker in monitoring and evaluating the diseases progression of breast cancer patients using a multistate Markov model. Based on ranges of CA15-3 marker (< 25 U/ml and ≥ 25 U/ml) states have been defined and transition intensities, transition probabilities and expected state specific survival time have been estimated. Also, the effect of prognostic factors viz. age, tumor size, tumor grade, involve lymph nodes, ER status, PR status etc., on transition intensities have been explored.

Keywords: Multistate model, breast cancer, CA15-3 marker, prognostic factors, Cox PH model.

1. Introduction

Cancer is one of the leading causes of adult deaths worldwide. According to IARC (International Agency for Research on Cancer) about 635,000 (indirect estimate) people died from cancer in 2008 in India. This is approximately 8% of all estimated global cancer deaths and about 6% of all deaths in India (Ferlay et al. 2010). Breast cancer is the most commonly diagnosed malignancy among women and has become a big threat to human beings globally. As per Indian population census data, the rate of mortality due to cancer in India is high and alarming with about 806,000 existing cases by the end of the last century (Ali et al. 2011). The rising graph of breast cancer both in developed and developing countries is a great challenge for biomedical researchers, especially in India it is the first common cancer of urban women and second of rural women.

The global breast cancer incidence has significantly increased from 641,000 (95% confidence intervals 610,000-750,000) cases in 1980 to 1,643,000 (1,421,000-1,782,000) cases in 2010, an annual rate of increase of 3.1% (Foreman et al. 2011). It has been suggested that both earlier diagnosis and treatment change contributes to improve breast cancer survival (Webb et al. 2004). Over the past few decades, there has been appreciable progress in therapeutic strategies for early stage (i.e., localized and operable, as opposed to metastatic) breast cancer, with a well-developed array of

treatment options. Due to increased screening vigilance and disease awareness, currently over 75% of women diagnosed have early stage tumors. Despite this progress, the clinical course of breast cancer after diagnosis remains heterogeneous from patient to patient and thus highly unpredictable for individuals (Dukic and Dignam 2007).

Traditional prognostic markers such as auxiliary lymph node status, tumor size, histological grade, hormone receptor expression are helpful to stage the disease, predict overall survival of patient and response to hormonal therapy. However, all these factors need tissue sampling, which is costly and results also depend on the expertise of histopathologist. None of these factors can single handedly predict risk of development of distant metastasis in individual patient, overall survival of patient and patients needing close surveillance and follow-up. So in this scenario soluble circulating tumor marker if found to be accurate prognostic factors, would be ideal candidates for predicting outcome and monitoring treatment response (Colomer et al. 1989). Serum CA15-3 has been the most frequently investigated tumor marker in breast cancer. Although it has low sensitivity and specificity and has no value for primary diagnosis (Tondini et al. 1988), but it can, however be useful in predicting prognosis, measuring treatment response in advanced breast cancer patients.

Tumor markers are a potentially powerful means of obtaining information about cancers whilst causing minimal morbidity, inconvenience and cost. CA15-3 has been suggested as a marker of distant metastasis in breast cancer. In general, the higher the CA15-3 level, the more advanced the breast cancer and heavier the tumor burden. CA15-3 concentrations tend to increase as the cancer grows. In metastatic breast cancer, the highest levels of CA15-3 often are seen when the cancer has spread to the bones and/or the liver. Elevated pre-operative CA15-3 level is directly related to tumor burden and independent prognostic factors for breast cancer. A highly significant correlation exist between elevated CA15-3 levels (> or = 30 U/ml) and metastasis disease (Tomlinson et al. 1995). Currently, it has been used for the surveillance and monitoring the treatment of patients with advanced disease (Duffy et al. 1997). It could be considered for clinical use such as predicting patient outcome and determining adjuvant treatment for better outcome (Berruti et al. 1994).

To the best of our knowledge, no study has been conducted for evaluating the disease progression of breast cancer patients using CA15-3 as a disease marker in multistate Markov model. We have developed a three state Markov model based on ranges of CA15-3 values to evaluate the progression of breast cancer patients. Multistate models have extensively been used to evaluate disease progression. It enables us to estimate transition intensities and transition probabilities between states of the disease.

Multistate models are particularly used in biomedical applications in which stages or levels of a disease are represented by the states in the model. A wide range of situations viz., in HIV/AIDS (Longini et al. 1989, Aalen et al. 1997, Hendriks et al. 1998, Grover et al. 2013), breast cancer (Duffy et al. 1997, Putter et al. 2006), psoriatic arthritis (Cook et al. 2004, O'Keeffe et al. 2011), dementia (Joly et al. 2002), diabetic retinopathy (Marshall and Jones 1995), and liver cirrhosis (Andersen et al. 1991, Grover et al. 2014).

Putter et al. (2006) developed a multistate model for breast cancer patients to estimate transition rates between the states in the model and later used these estimates to predict the future progression of disease for patients with a given history. Taghipour et al. (2013) used a multistate model to describe invasive breast cancer progression in the Canadian National Breast Screening Study and constructed progression models with and without covariates. They suggested that the modeling and estimating the parameters of cancer progression are essential steps towards evaluating the effectiveness of screening policies. Broet et al. (1999) used a multistate model to study prognostic factors associated with each transitions in breast cancer disease. Ventura et al. (2014) provided an illustration of the

application of multi-state Markov models for breast cancer progression to data from the first two rounds of the Florentine screening programme (1991-1993). Authors extensively discussed the pros and cons of three different estimation procedures (non-linear least squares, maximum likelihood, Bayesian approach) widely used in multistate model.

In this paper we have developed a three state Markov model based on the ranges of CA15-3 marker for disease progression of breast cancer patients. Moreover, we have tried to estimate the transition intensities and probabilities between various states and also estimated the effect of prognostic factors on transitions using Cox proportional hazards model.

The remaining parts of the paper have been divided into the following sections, in Section 2 the material and methods used are discussed, Section 3 deals with results and the discussion, and conclusion is given in Section 4.

2. Materials and Methods

The study population includes all female primary breast cancer patients treated at breast clinic. (Dept of General Surgery, IPGMER, SSKM Hospital, Kolkata) from January 2009 to December 2010, and had their pre-op serum CA15-3 measured and it was repeated on 7^{th}, 30^{th} post-op day and every 6 months for 2 years. Patients were excluded if any other malignancy was known from their previous history or if staging investigations at the time of diagnosis revealed evidence of instant metastasis. A total of 85 patients fulfilled the criteria for this analysis. Patients were treated with either modified radical mastectomy (MRM) or quandrantectomy and auxiliary lymph node dissection with local radiotherapy (RT). After completion of surgery, RT and appropriate adjuvant chemotherapy or hormone therapy was not altered according to marker levels but was administered as indicated based on international guidelines. All the statistical analysis has been performed using *msm* package in R software (Jackson 2011). In all case p-value < 0.05 has been considered as statistical significant.

2.1. Multi state Markov model

Multi-state model (MSM) is a model for a continuous time stochastic process allowing individuals to move among a finite number of states. In this analysis the three states of disease progression of breast cancer patients are defined based on the established cut-off value of CA15-3 tumor marker (Ebeling et al. 2002). The two reversible transient states are defined as follows; State 1; CA15-3 < 25 U/ml, state 2; CA15-3 > 25 U/ml; and one absorbing death state. The death state is an absorbing state i.e a patient is in the death state she/he will remain in that state forever. The elapse time between state transitions are calculated using the difference (in months) between the dates of CA15-3 measurements. The schematic representation of the proposed model is shown in Figure 1. The possible transitions along with intensities have been illustrated in the diagram.

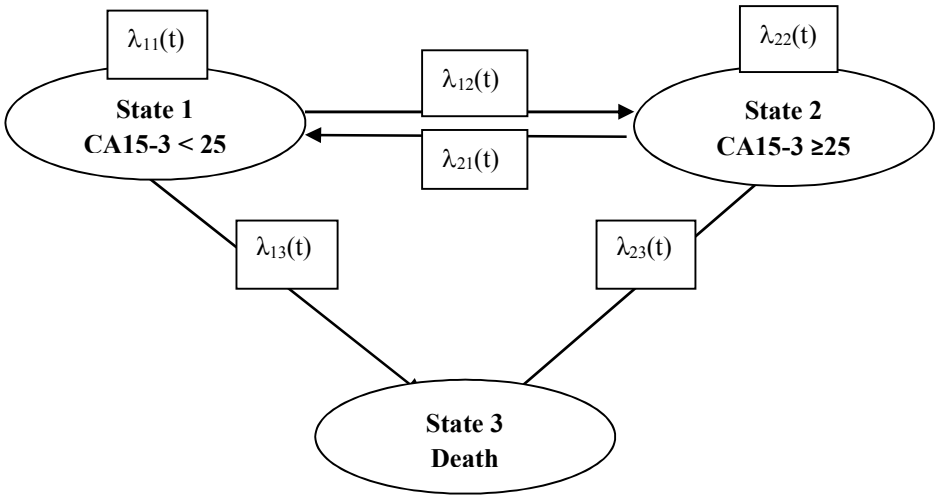

Figure 1 Schematic representation of three states Markov model

More formally, let us suppose that there are n breast cancer patients under study, and a patient may move in the three state Markov model with discrete state space $S = \{1, 2, 3\}$, where 1 and 2 are transient states, and 3 is absorbing state. If $X(t) = r$ be the state of a patient at any time t, then the intensity with which the patient moves to state s during the interval $(t, t + \Delta t)$ is defined as

$$\lambda_{rs}(t) = \lim_{\Delta t \to 0} \frac{P(X(t + \Delta t) = s / X(t) = r)}{\Delta t}, \quad \text{for } r, s = 1, 2, 3. \tag{1}$$

The transition intensity matrix, defined as $P = \left[\lambda_{rs}\right]_{3\times 3}$ has the following properties:

(i) $\sum_{s \in S} \lambda_{rs} = 0$ for all $r \in S$,

(ii) $\lambda_{rr} = -\sum_{r \notin S} \lambda_{rs}$,

where λ_{ij} 's are the transition intensities, and the corresponding 3-states transition probability matrix can be defined as:

$$P = \begin{pmatrix} P_{11} & P_{12} & Q_{13} \\ P_{21} & P_{22} & Q_{23} \\ 0 & 0 & 0 \end{pmatrix},$$

where P_{11}, P_{12}, P_{21} and P_{22} are the illness transition probabilities and Q_{13} and Q_{23} are the death absorbing probabilities. The transition probability $P_{rs}(t)$ is defined as of a patient being in state s at time $(t, t + \Delta t)$ given that the patient was at state r at time t. More specifically, that can be calculated as:

$$P_{11}(0,t) = \Pr\left[\text{that an individual in State 1 at time 0 will be in same state at time } t\right]$$

$$= \exp[\int_0^t \lambda_{11} du]$$

$$= \exp[\lambda_{11} t]$$

$$P_{12}(0,t) = \Pr\left[\text{that an individual in State 1 at time 0 will be in State 2 at time } t\right]$$

$$= \int_0^t \exp[\int_0^{t_1} \lambda_{11} du]\lambda_{12} \exp[\int_{t_1}^t \lambda_{22} dv] dt_1$$

$$= \int_0^t \exp(\lambda_{11} t_1)\lambda_{12} \exp[\lambda_{22}(t - t_1)] dt_1$$

$$= \lambda_{12} e^{\lambda_{22} t} \int_0^t \exp[(\lambda_{11} - \lambda_{22}) t_1] dt_1$$

$$= \frac{\lambda_{12}}{\lambda_{11} - \lambda_{22}} [\exp(\lambda_{11} t) - \exp(\lambda_{22} t)]$$

$$P_{21}(0,t) = \Pr\left[\text{that an individual in State 2 at time 0 will be in State 1 at time } t\right]$$

$$= \int_0^t \exp[\int_0^{t_1} \lambda_{22} du]\lambda_{21} \exp[\int_{t_1}^t \lambda_{11} dv] dt_1$$

$$= \int_0^t \exp(\lambda_{22} t_1)\lambda_{21} \exp[\lambda_{11}(t - t_1)] dt_1$$

$$= \lambda_{21} e^{\lambda_{11} t} \int_0^{t_1} \exp[(\lambda_{22} - \lambda_{11}) t_1] dt_1$$

$$= \frac{\lambda_{21}}{\lambda_{22} - \lambda_{11}} [\exp(\lambda_{22} t) - \exp(\lambda_{11} t)]$$

$$P_{22}(0,t) = \Pr\left[\text{that an individual in State 2 at time 0 will be in same state at time } t\right]$$

$$= \exp[\int_0^t \lambda_{22} du]$$

$$= \exp[\lambda_{22} t]$$

$$Q_{13}(0,t) = \Pr\left[\text{that an individual in State 1 at time 0 will be in absorbing state at time } t\right]$$

$$= \int_0^t \exp[\int_0^{t_1} \lambda_{11} du]\lambda_{13} dt_1$$

$$= \int_0^t \exp(\lambda_{11} t_1)\lambda_{13} dt_1$$

$$= \lambda_{13} \int_0^t \exp(\lambda_{11} t_1) dt_1$$

$$= \lambda_{13} [\exp(\lambda_{11} t) - 1]$$

$$
\begin{aligned}
Q_{23}(0,t) &= \Pr\left[\text{that an individual in state 2 at time 0 will be in absorbing state at time } t\ \right] \\
&= \int_0^t \exp[\int_0^{t_1} \lambda_{22} du]\lambda_{23} dt_1 \\
&= \int_0^t \exp(\lambda_{22} t_1)\lambda_{23} dt_1 \\
&= \lambda_{23} \int_0^t \exp(\lambda_{22} t_1) dt_1 \\
&= \lambda_{23}[\exp(\lambda_{22} t) - 1].
\end{aligned}
$$

The detailed mathematical derivation and also maximum likelihood estimation procedure has been given (Chiang 1968, Kalbfleish and Lawless 1985).

The Incorporation of Covariates: The effect of covariate vector **z** on transition $i \to j$ for a breast cancer patient is modeled by $\lambda_{ij}(t),$ using Cox proportional regression model the transition hazard is given by

$$\lambda_{ij}[t \mid z] \quad = \quad \lambda_{ij,0}(t) \exp\left\{\beta_{ij}^T z\right\}, \tag{2}$$

where $\lambda_{ij,0}(t)$ is the baseline hazard of transition $i \to j,$ and β_{ij} is the vector of regression coefficients that describe the effect of **z** on transition $i \to j.$ An alternative way of writing this model (Andersen et al. 1991) is as

$$\lambda_{ij}(t \mid z) \quad = \quad \lambda_{ij,0}(t) \exp\left\{\beta_{ij}^T z_{ij}\right\}, \tag{3}$$

where z_{ij} is a vector of covariates specific to transition $i \to j,$ defined for the patients based on his/her covariates $z.$ The estimates $\hat{\beta}$ can be obtained by maximizing the partial likelihood function as given by

$$L(\beta) = \prod_{k=1}^{n} \frac{\exp(\beta_{ij}^T Z_{ij})}{\sum_{l \in R(t_{ij,k})} \exp(\beta_{ij}^T Z_{ij,l})}, \tag{4}$$

where $z_{ij,k}$ is the covariate vector for patient $k,$ and $R(t_{ij,k})$ is the risk set at time t for making transition from $i \to j.$ The detailed estimation procedure is stated in (Kalfleisch and Lawless 1985, Kay 1986).

3. Results

The study population includes 85 breast cancer patients, who were diagnosed during January, 2009 to December, 2010. Out of total 69 (81.2%) were alive at the end of the study and being considered as censored for the analysis. The mean age of patients at diagnosis was 50.09 years (SD=12.82), ranging from 25 to 85 years. The descriptive characteristics of important prognostic factors are summarized in Table 1.

Table 1 Descriptive characteristics of breast cancer patients (N=85)

Factors	Categories(Code)	Frequency	Percentage
Age (in years)	<50 (0)	46	54.1
	≥50 (1)	39	45.9
Tumor size (cm)	<2 (0)	24	27.9
	2-5 (1)	48	55.8
	≥5 (2)	13	15.1
Lymph nodes	0-3 (0)	50	58.8
	4-9 (1)	19	22.4
	≥9 (2)	16	18.8
Tumor Grade	I (1)	23	27.1
	II (2)	42	49.4
	III (3)	20	23.5
ER Status	Negative (0)	40	47.1
	Positive (1)	45	52.9
PR Status	Negative (0)	48	56.5
	Positive (1)	37	43.5
HN2 Status	Negative (0)	53	62.4
	Positive (1)	32	37.6

Table 2 Number of observed transitions between states (rows to columns)

States	State 1	State 2	Death	Censored
State 1	238	14	9	44
State 2	74	56	7	7

Table 3 Estimate of transitions Intensities with 95% CI using multistate Markov models

States	State 1	State 2	State3
State 1	-0.116 (-0.802, -0.014)	0.104 (0.013, 0.810)	0.012 (0.001, 1.210)
State 2	0.461 (0.073, 3.150)	-0.493 (-3.174, -0.072)	0.032 (0.001, 3.336)

Table 4 Estimated one year transition probabilities

States	State 1	State 2	State 3
State 1	0.91934	0.06043	0.02236
State 2	0.34437	0.63528	0.03532

Table 5 Estimates of hazard ratio with 95% CI for breast cancer patients

	State 1-State 2	State 1-State 3	State 2-State 1	State 2-State 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age (≥50 years)	2.71 (0.12 - 59.67)	1.08 (0.03 - 33.78)	1.61 (0.08 - 30.94)	4.64 (1.01 - 121.60)*
Tumor size	2.09 (0.58 - 7.54)	1.02 (0.56 - 1.84)	1.60 (0.45 -5.62)	1.41 (0.24 - 8.21)
Lymph nodes	1.51 (0.87 - 2.61)	1.40 (1.13 - 1.74)*	1.42 (0.82 - 2.45)	1.42 (0.81 - 2.48)
Tumor grade				
II	5.77 (0.81 - 40.16)	0.07 (0.01 -1.15)	2.75 (0.49 - 9.54)	3.33 (1.01 - 66.20)*
III	13.87 (0.01 - 184.0)	1.08 (0.11 - 9.18)	14.32 (0.12 - 171.0)	0.31 (0.01 - 49.10)
ER Status	13.97 (0.54 - 361.4)	0.12 (0.01 - 1.62)	20.70 (9.96 - 443.0)	0.81 (0.01 - 17.35)
PR Status	0.04 (0.00 - 1.25)	2.19 (0.27 - 17.92)	0.07 (0.01 - 0.12)*	1.34 (0.04 - 44.37)
HN2 Status	3.14 (0.38 - 25.83)	0.34 (0.02 - 4.66)	0.88 (0.12 - 6.55)	2.87 (0.05 - 15.30)

The Table 2 shows that the observed transitions between states (rows to column) during the follow up visits. There are 14 transitions from State 1 (CA 15-3 < 25) to State 2 (CA 15-3 > 25) and 9 deaths occurred from the same state during the study. A total of 74 transitions occurred from higher to lower i.e back transition from State 2 to State 1, which shows a decline in CA 15-3 values post-operatively. At the end of the study period 44 and 7 transitions were censored from State 1 and State 2, respectively, i.e, their exact states were not known.

Initially, the Markov model without covariate has been used to study the overall disease progression. The estimates of transition intensities (λ_{ij}) with 95% confidence intervals (CI) are presented in Table 3. It reveals that a patient in State 1 is 8.66 (0.104/0.012) times more likely to move to State 2 than dying in State 1. Similarly, a patient in State 2 is 14.40 (0.461/0.032) times more likely to move to State1 than of dying in State 2.

The estimated transitions probabilities are presented in Table 4. It can be seen from the Table 4 that there are 91% chances of remaining in State1 as compared to 6% and 2% of moving to State 2 and of dying respectively. Similarly a patient has 63% chances of remaining in State 2 than 34% and 3% of moving to State 1 and of dying respectively at end of one year. The estimated total length of estimated survival time for patients in State 1 is found to be 8.8 years and for patients in State 2 is 2.1 years, respectively.

Table 5 summarizes the hazard ratios (HR) for each covariate (i.e age, tumor grade, tumor size, lymph nodes, ER Status, PR Status and HN2 status) on each transition along with their 95% confidence interval (CI). Covariates viz., age, lymph nodes, tumor grade and ER status are found to be significantly associated with hazard of death of breast cancer patients. The higher age group (> 50 years) is significantly associated with transition 2 → 3. More precisely, patients (> 50 years age) in State 2 have 4.64 times more likely to move to State 3 as compared to patients of aged below 50 years. Patients with tumor grade II are 3.33 times more likely to leave State 2 than patients having tumor grade I, given that they move to State 3 (death). Patients having Progesterone Receptor (PR) status positive have 97% less chances of transition from State 2 to State 1. The numbers of involved axilary lymph nodes are significantly associated with the transition 2 → 3. However, the factors like tumor size, ER status and HN2 status are not found to be significant in our analysis. Also we have made an attempt to assess the goodness of fit of our multistate Markov model by comparing the observed prevalence of states with expected prevalence under the model at a series of times. The

model was found to be fitting well (confirmed by prevalence.msm plot, not shown here) to this breast cancer data set.

4. Discussion

CA15-3 is most useful tumor marker for monitoring patients post–operatively for recurrence in metastatic carcinoma. Serum CA15-3 has been the most frequently investigated marker in breast cancer. However, it can be useful in predicting prognosis, measuring treatment response in advanced breast cancer patients and for early detection of metastasis (Dnistrian et al. 1991, Lamerz et al. 1991, Robertson et al. 1991, Safi et al. 1991, and Vizcarra et al. 1994). In order to understand the role of pre-operative CA15-3 in identifying patients with low and high risk with respect to their overall prognosis and time to occurrences of distant metastasis relapse or death from the disease. We have developed a multistate Markov model for breast cancer patients using the value of CA15-3 marker. Since the multistate model is the natural choice for the study of disease progression and also it enable us to estimate transition intensities and transition probabilities between the states. To the best of our knowledge this is the very first attempt to model CA15-3 marker in disease progression of breast cancer patients using a multistate Markov model. Although some previous studies viz. Broet et al. (1999), Putter et al. (2006), Ventura et al. (2014), have used multistate model in the applications of breast cancer disease but in different scenario. By exploiting the properties of Markov models, we have illustrated the usefulness of multi stage illness death model in the analysis of follow-up study of breast cancer diseases.

As discussed in the results section the significant findings of our analysis is the estimated survival time for patients in State 1 (CA15-3 < 25) is found to be 8.8 years and for State 2 (CA15-3 > 25) is 2.1 years respectively. Hence the elevated CA15-3 values highly associated with lower survival of the patient. Covariates viz., age, lymph nodes, tumor grade and ER status are found to be significantly associated with hazard of death of breast cancer patients. All the results are in agreement with the medical literature, except for the effect of tumor size which is not found to be significant predictor in our analysis.

Despite some controversies, CA15-3 level could provide independent prognostic information to be taken together with conventional markers measured in tumor tissues (Gasparini 1998). Furthermore, Duffy (2006) reported that pre-op concentration could be combined with existing early treatment based exclusively on increasing marker concentration showed improved prognosis compared with controls.

There are some limitations in our study, the sample size of the study population is small so the strict generalization of our findings needs to be substantiated by from other large scale study. Many ways this study could be extended to a hidden or semi-Markov model to obtain more detail and flexible results.

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