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REHOSPITALIZATION AND SURVIVAL ANALYSIS OF HEART FAILURE PATIENTS

Tanvir Ahmad[1], Sameet Baig[1], Shazia Aslam[2] and Sajjad Haider Bhatti[1]

[1]*Department of Statistics, Government College University Faisalabad, Pakistan*
[2]*Department of Pathology, University Medical and Dental College, Faisalabad, Pakistan*
Correspondence author: dr_tanvir@gcuf.edu.pk

ABSTRACT

Heart failure is a severe issue globally affecting more than 26 million people. On the average in every 40 seconds someone dies of this fatal disease. As reported by American Heart Association (AHA) 2017, the number of diagnosed heart patients is increasing drastically and figure is expected to rise 46% by 2030. Despite the significant improvements in treatment and prevention survival rates are intimidating and show geographical variations. The prevalence of disease is more alarming in developing or underdeveloped countries like Pakistan. The present study was focused on survival analysis on rehospitalization of heart failure patients who were admitted to Faisalabad Institute of Cardiology (FIC), Pakistan during July 2016 to May 2017. Latest analytical tools supported by graphical appreciation have been used to model the rehospitalization considering age, ejection fraction, serum creatinine, serum sodium, platelets, blood pressure, gender, diabetes, potassium, coronary artery disease, hemoglobin, myocardial infraction, blood urea nitrogen, smoking status and functional class as potentially contributing risk factors. Age, blood pressure, serum creatinine, coronary artery disease, myocardial infraction and functional class were found significant risk factors for rehospitalization of heart failure patients. The study is important for the patients, physicians and policy makers related to the heart failure syndrome.

Key words: Rehospitalization, Heart failure, Functional Class, Survival Analysis, Kaplan Meier plot, Cox regression, Nomogram.

INTRODUCTION

Heart failure is the condition in which muscles in the heart wall get stiff and enlarge; arteries become narrow which restricts the pumping of blood in the body. The ventricles of heart can get inflexible and do not fill properly with blood between beats and demand of blood becomes insufficient in body and as a consequence person starts feeling difficulty while breathing or performing any physical activity.

The main reasons behind heart failure include high blood pressure, diabetes, coronary artery disease and other diseases like HIV, thyroid disorders, drug addiction etc. Presently about 26 million people worldwide are suffering from heart failure as per report by AHA (2017) and Martin (2011). According to World Health Organization (WHO, 2017) about 17 million people die of heart failure every year. The situation in Pakistan is even worse as there is a rapid increase in number of heart failure patients and their hospitalization. Rehospitalization due to heart failure is time to event data thus suitable for survival analysis.

The main objective of this study was to estimate rehospitalizations due to heart failure and to investigate its link with some major risk factors by choosing Faisalabad the third most populous city of Pakistan as study area.

MATERIAL AND METHODS

Detail of data

Current study is based on 257 patients of heart failure comprising of 86 women and 171 men. All the patients were more than 40 years old. Follow up time was 15-335 days. Disease was determined by cardiac echo report of patient. Age, Serum Sodium (Na), serum creatinine, gender, smoking, Blood Pressure (BP), Ejection Fraction (EF), platelets, Potassium (K), diabetes, Hemoglobin (Hb), Coronary Artery Disease (CAD), Myocardial Infraction (MI), Blood Urea Nitrogen (BUN) and functional class were considered as potential variables explaining rehospitalization caused by Cardiovascular Heart Disease (CHD). Information about required characteristics was obtained through blood reports of patients and physician's notes in the beginning of study and then patients were followed through phone calls. Age is a continuous variable whereas Hb was divided into three levels (i.e. $Hb \leq 10$, $10 < Hb \leq 14$ and $Hb > 14$), platelets, ejection fraction and serum sodium were also divided into three level on the basis of quartiles.

Level of serum creatinine above from its normal level (1.2) is an indicator of renal dysfunction. Its effect on rehospitalization was studied as creatinine > 1.2 vs ≤ 1.2.

Statistical techniques

Survival analysis was used to estimate the survival and rehospitalization rates because data also included censored observations. Kaplan Meier product limit estimator, presented by Kaplan and Meier (1958), was used to make comparisons between rehospitalization rates at different levels of explanatory variables. A model was developed using Cox regression as presented by Collet (2003) to link the hazard of rehospitalization for an individual with one or more explanatory variables and for testing the significance of these variables for the response.

Let hazard of rehospitalization depends on p explanatory variables $X_1, X_2, \ldots, X_p$ then the hazard function for i^{th} individual at time *t* can be defined by Cox model as

$$h_i(t) = h_0(t)e^{\beta_1 x_{1i} + \beta_2 x_{2i} + \ldots + \beta_p x_{pi}}$$

We have also plotted Martingale residuals against different values (or levels) of a variable to determine the functional form of any particular independent variable as presented in studies by Tavazzi *et al.,* (2013) and Curtis *et al.,* (2008). The functional form was found linear for all variables therefore no transformation was required. For graphical appreciation of prediction function, survival probabilities were also plotted using nomogram.

RESULTS AND DISCUSSION

Follow up time of the patients under study was 15-335 days. Up to the end of follow-up period, 178 (69%) patients were rehospitalized due to CHD. Table **1**, presents different baseline characteristics of rehospitalized and censored patients at the end of follow up period.

The results of Cox regression model are presented in Table **2**. Estimate of baseline hazard (intercept) was not provided by model fitting because Cox regression is a semi parametric model. According to Cox model, serum creatinine, and MI were most significant variables for rehospitalization due to heart failure as in Dunlay *et al.,* (2009).

Hazard ratio for serum creatinine was 6.096 which means that there were 6 times more chances of rehospitalization for patient with high level serum creatinine than those who had its normal level, significance was judged by p-value 0.0013. MI was another significant factor with hazard rate 2.309, that is, patients suffering from MI were 2 times more likely to be rehospitalized than patients who did not have this disease with p-value 0.0014 which is analogous to the results by Goda *et al.,* (2010) and Lee *et al.,* (2003).

Table 1. Baseline characteristics for rehospitazed and censored patients.

Variable	Rehospitalized (178)	Censored (79)	Variable	Rehospitalized (178)	Censored (79)
Age	158	99	Potassium	13	244
Gender	118	139	EF	40	217
BP	172	85	Platelets	181	76
Smoking	50	207	CAD	176	81
Hemoglobin	150	107	BUN	168	89
Sodium	130	124	MI	154	103
Creatinine	173	84	Diabetes	117	140
Functional class	178	79			

Results in Table **2** show that gender, smoking, Hb, Na, Potassium, EF, Platelets, diabetes, and platelets are non-significant for the response.

It was identified through statistical analysis that serum creatinine and blood pressure were most significant factors having smallest p-values. Blood pressure, serum creatinine and MI had a constant effect on rehospitalization. Though age was a time dependent variable, Age, CAD and functional class effected rehospitalization rate after some time during the study period which means that with the passage of time, patients having intensity of these factors get near to be rehospitalized. Similar results were found in studies by Goda *et al.,* (2010), Lee *et al.,* (2003), Pecini *et al.* (2011) and Kaneko *et al.,* (2014). Other variables including gender, smoking, Hb, Na, K, EF, platelets, BUN and diabetes were not significant according to Cox model. Non significance of EF was also discussed in the study of Vasan *et al.,* (1999). Kaplan Meier plot was constructed to study the pattern of rehospitalization rate and survival of

patients after heart failure which showed high rehospitalization rate at initial 150 days of study. This finding is similar to studies of Tavazzi *et al.,* (2013) and Curtis *et al.,* (2008).

Table 2. Significance of variables under Cox Model.

Variable	β-coefficient	HR	Z-value	P-value
Age	0.176	1.1920	2.93	0.0034
Gender	-0.107	0.899	0.66	0.5100
BP	1.959	7.090	5.07	0.0036
Smoking	-0.181	0.835	1.08	0.2800
Hb≤10 vs 10<Hb≤14	0.482	1.619	1.30	0.1900
10<Hb≤14 vs Hb>14	0.060	1.0620	0.77	0.4400
Na≤130 vs 130<Na≤140	-0.107	0.898	0.28	0.7800
130<Na≤140 vs Na>140	-0.064	0.938	0.75	0.4500
Serum creatinine	1.808	6.096	5.27	0.0013
Potassium	0.317	1.373	1.06	0.2900
EF	-0.104	0.901	0.89	0.3800
Platelets($\leq Q_1$)	-0.167	0.846	0.83	0.4100
Platelets($\geq Q_3$)	-0.0378	0.963	0.28	0.7800
CAD	0.2596	1.297	4.03	0.0370
BUN	-0.3880	0.679	1.18	0.2400
MI	0.8370	2.309	3.19	0.0014
Diabetes	-0.2240	0.799	1.42	0.1600
Functional class	0.2893	1.336	4.29	0.0121
Gender*Smoking	-0.1340	0.874	0.78	0.4300
Na*Hb	0.0670	1.069	1.25	0.2100
Potassium*EF	0.2570	1.293	1.14	0.2500
Platelets*BUN	-0.1410	0.869	1.10	0.2700

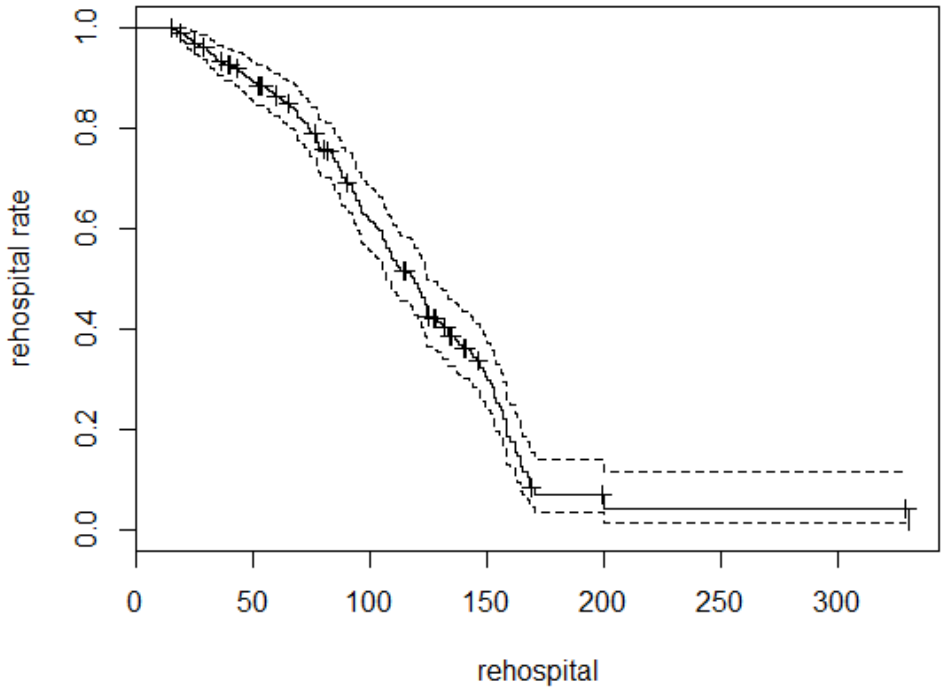

Fig 1. Plot of Kaplan Meier estimate of survivor function against time (days)

178 people were rehospitalized during the follow up time of 16-335 days in which 118 were men and 59 were women. Kaplan Meier graph was made to see the pattern of rehospitalizations and survival of patients. Fig.**1** showed that with the passage of time chances for rehospitalization increased so that survivor function had downward tendency but at the end of study it became flat which showed that with the passage of time survival of patients became stable.

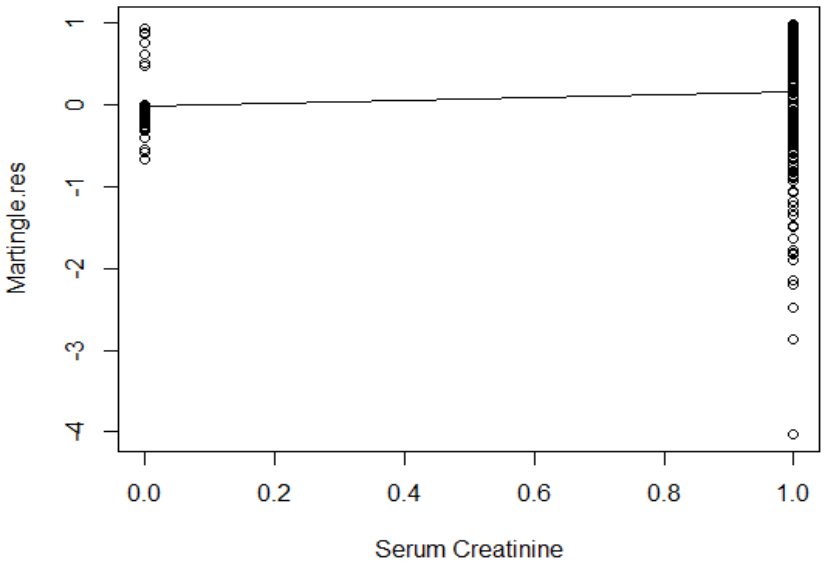

Fig 2. Graph of martingale residuals under null model versus serum creatinine with a superimposed smooth curve

To check the functional form of serum creatinine graph of creatinine versus martingale residuals of null model was made in Fig.**2** which showed a horizontal line. It indicated that serum creatinine had linear functional form.
Graph of MI was plotted against martingale residuals for null model in Fig.**3**. According the figure MI had approximately linear functional form and did not showed any curvature to disturb linearity.

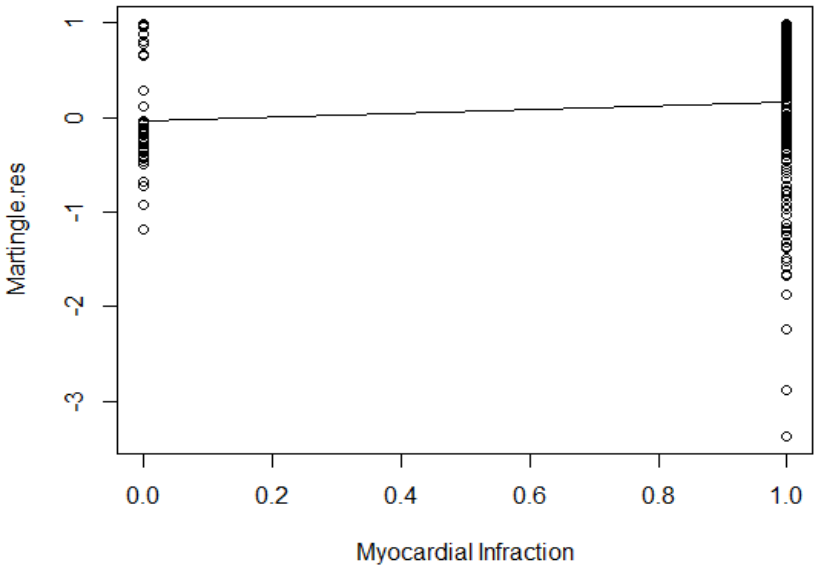

Fig 3. Graph of martingale residuals with a superimposed smooth curve under null model versus myocardial infraction

Nomogram is presented in Fig.**4** to provide the graphical predictions of probability after assigning different points to each independent variable with respect to their significance. Sum of these points provides an estimate of probability of rehospitalization of patients. The Cox model used for constructing this nomogram was fitted on original values of variables.

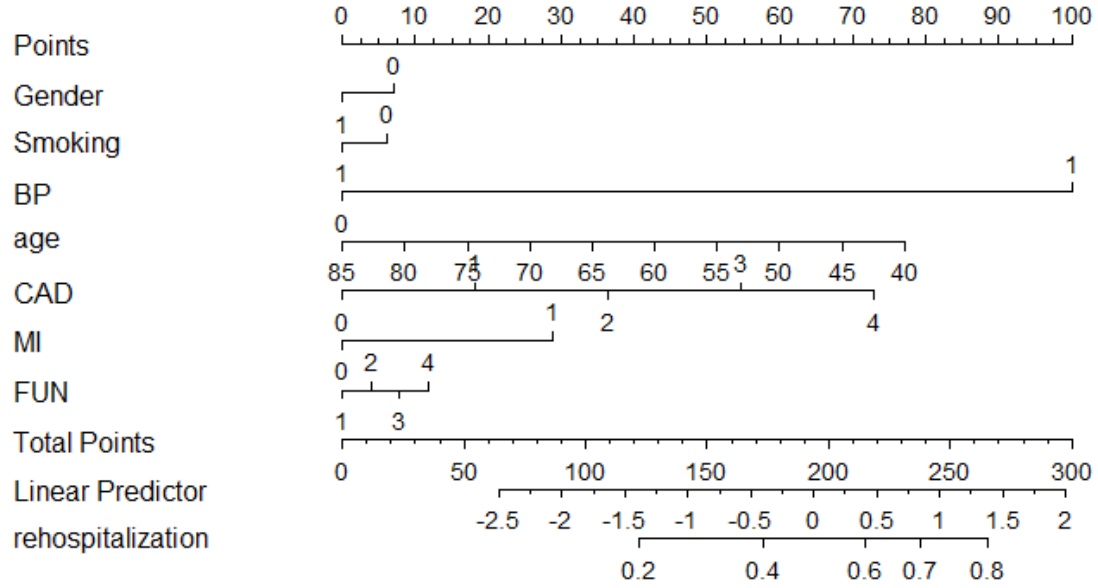

Fig 4. Nomogram for rehospitalization probability.

In order to understand results from Nomogram, consider the case of 80 year old non-smoker female patient with high blood pressure, with 1 vessel coronary artery disease having myocardial infraction having functional class 2 has points equal to 7+6+7+100+17+30+6 = 173 and probability of her rehospitalization is 0.4.

CONCLUSION

Heart failure is the foremost common disease all over the world and is leading cause of death in Pakistan as well. Many factors which cause heart failure are identified and factors which cause rehospitalization due to heart failure are less identified in Pakistan. For this study the required data depends on follow up time and also on censored data. The study can be of vital importance for patients of heart disease, medicine manufacturers and doctors in Asian regional, particularly in Pakistan.

The present report was prepared to study rehospitalization rate of heart failure patients and for the identification of risk factors which were responsible for increase in this rate. 257 patients have been selected from Faisalabad Cardiology Institute by following legal ethics for this purpose. Required information for this study was collected in the beginning of study and then patients were followed for 335 days. Kaplan Meier plot was constructed to study the pattern of rehospitalization rate and survival of patients after heart failure which showed high rehospitalization rate at initial 150 days of study. It can be concluded that growing age, renal dysfunction (having serum creatinine greater than its normal level 1.2) and high BP (higher than normal range) are the key factors contributing towards increased risk of rehospitalization among heart failure patients. No significant differences were found due to smoking status, diabetes, level of potassium, EF levels, platelets, BUN, level of Hb, level of Na and gender of patients.

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