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Research Article

Effect of Prognostic Factors on Survival Time of Patients of Cardiovascular Disease using Quantile Regression

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I N F O

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A B S T R A C T

Background: The study of survival time after the first myocardial infarction among cardiovascular disease patients are quite important for medical practitioners, planners and for the patients. This study tries to study the survival patterns and their risk factors using relatively new and advanced model.

Objective: The current paper conceived to accentuate the effect of prognostic factors on survival time of cardiovascular disease patients. using quantile regression technique.

Methods: Quantile regression model has been used to model survival time, McNemar's test for checking independence of linked attributes.

Results: The results showed our perceived notion that different prognostic factors have a different effect on patients' survival at varying locations of survival time. Like smoking has one effect at 10^{th} quantile and quite different effect at 75^{th} quantile of survival time after first myocardial infarction. McNemar test reveals that the initial status of hypertension has significant association with the current hypertension status of the patients, hypertensive patients are more likely to have heart failure which is in tandem with proven medical findings.

Conclusion: Unlike most of the well-known survival models, quantile regression models the survival time directly instead of modelling some other functions like hazard function or death density function. Therefore, its interpretation is easy and informative.

Keywords: Quantile Regression, CVD, DBP, SBP, McNemar

Introduction

The term cardiovascular disease is the general term used to define the problem with the blood vessels, circulatory system, and heart. Many of the cardiovascular problems occur when a substance called plaque build up inside the walls of the arteries, this is called atherosclerosis. Due to this process of atherosclerosis arteries gets narrower resulting in hindrance for blood to flow, this ultimately leads to heart attack and stroke. If blood flow stopped completely through any of the arteries, the part of heart muscle starts to die.

Heart attack or Myocardial Infarction (MI) or coronary thrombosis is a symptom where blood flow to a part of the heart is blocked due to the blood clot. The most frequent stroke, i.e. ischemic stroke is the symptom where blood vessels connecting the brain get plugged due to blood clots. Brain cells in the part of the brain that get blood supply from affected vessels start to die. This may results in dysfunction of activities controlled by that particular part of the brain like walking, sensation lessness, etc.[1]

Some other types of heart-related ailment are congenital heart disease: this is the general term used for deformities in the heart that are present since birth, like hole between the two chambers of heart, blood flow through the chambers are partially/ totally blocked etc., Arrhythmia: it denotes the irregular heartbeat, tachycardia when heart beats too fast generally above 100 beats/ minute, bradycardia when heart beats less than 60 beats/ minute, fibrillation when heart beats up/ down erratically. The arrhythmia may create an impediment to heart that results in inadequate pumping of blood to other parts of the body. Angina: it denotes the chest pain, mainly caused when heart muscles do not get an ample amount of oxygen-rich blood. It is not a disease but a symptom of cardiovascular disease beneath.[2]

In recent decades cardiovascular disease has become a focal cause of death and morbidity in India. Since life expectancy is low in India as compared to developed countries, cardiovascular affects the most productive midlife years. As per the global burden of disease study 2010, 24.8% of total deaths in India are due to CVD. Deaths per 100000 population due to CVD is 312 for males and 225 for females. Heart diseases continues to be the leading cause of death in India, the global burden of disease studies 2017. According to the findings of[3], leading risk factor for global burden of disease are blood pressure, tobacco smoking, and alcohol use account for 7.0%, 6.3% and 5.5% respectively. Dietary risk factor and physical inactivity account for 10% disease burden.

In fact for persons of age greater than 70 years, heart-related ailment accounts for 29.7% of total death. [ischemic heart disease (17.98%), stroke (8.95%), hypertensive heart disease (1.52%), rheumatic heart disease (0.9%), other cardiovascular and circulatory disease (0.35%)] global burden of disease study, 2017.

Some Common Diagnosis of Myocardial Infarction

Electrocardiogram (ECG) helps in determining what type of heart attack and where it has occurred.

Echocardiogram (ECHO) is used during and after a heart attack to see how the heart is pumping and also used to identify the area of heart where it is not pumping properly.

Cardiac Catheterization (CATH) is used to visualize the blocked arteries and also helps in deciding the medical procedures required.

Blood tests: When heart muscle cells are injured/blocked their contents like biochemical markers spills into bloodstream. So, by measuring the level of these markers, doctors can decide the approximate time extent of the heart attack.

Kusuoka H and Hoffman JI[4] discussed the various tools used in all aspects of cardiovascular disease. To check the difference between two or more regression lines analysis of covariance (ANCOVA) is suggested, Odds ratio and McNemar's test is used to check how much a particular drug reduces a risk, to predict the risk in a patient a logistic regression has been used.

Moye L[5] discussed in great details about statistical techniques used in cardiovascular diseases. Sanchis J et al.[6] explored some statistical methods like predictive modelling and Receiver Operating Characteristics (ROC) curve etc. Amugsi DA et al.[7] used quantile regression to estimate the effect of various prognostic factors on systolic and diastolic blood pressure. Bivariate analysis is used to check which variables are significantly associated with BP measures.

In regression analysis, one find the expected value of an explained variable (dependent variable) conditional on explanatory variables (prognostic factor). In ordinary least square regression prognostic factors have a constant effect on the dependent variable, but it is judicious to think that prognostic factors may have a different effect on various quantiles of dependent variable. Consider the effect of Blood Pressure (BP) on the survival time of cardiovascular disease patients. Obviously low as well as high BP will correspond to lower survival time, so the effect of BP varies for different survival interval, therefore it is contrived to think that usual regression would capture this phenomena. Again, consider the effect of Body Mass Index (BMI) on Systolic Blood Pressure (SBP), it is proved that both lower and higher BMI is associated with SBP.[8] So it is not true to assume that BMI will have a constant effect on SBP measurement. Therefore, if the conditional distribution of the dependent variable on the prognostic factors at different locations are to be studied the quantile regression has to be considered and it is imperative to use in thse types of situations. Quantile regression is an extension of ordinary least square regression, it enables to examine the effects of prognostic factors at various points of conditional distribution.

Koenker R and Basset Jr G[9] propounded quantile regression. Survival models like Cox-PH and AFT do not model the survival time directly but quantile regression models the conditional quantile of survival time directly, therefore interpreting the results are institutive and appealing. The quantile regression model allows the prognostic factors to have varying influence at different tails of the survival distribution.[10]

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Scharf FS et al.[11] used quantile regression to study the relationship between predator size and prey. Amugsi DA et al.[7] used quantile regression to jointly model the SBP and DBP based on age, salt intake, fruit consumed etc., the study was based on the female data of Ghana. Portnoy S[12] studied a generalization of Kaplan-Meier for quantile regression. Portnoy S and Portnoy G[13] and Xue X et al.[14] worked on censored quantile regression. Yang X et al.[15] suggested a method to handle left, right and doubly censored data simultaneously.

Data Source and Analytical Approach

Data Source

Data set is collected retrospectively during 2015-2016 at Dr. Ram Manohar Lohia (RML) hospital, New Delhi, which is a large hospital catering all kinds of patients from pan India. Patients, who experienced at least one Myocardial Infarction (MI) were included in the study. Initially, we had 580 cases but upon applying complete case analysis we were left with only 104 patients after excluding pregnant women, cancer patients, having chronic disease of kidney/lungs/liver/gastrointestinal tracts, etc. We have only the following variables, continuous: age at first MI, age at second/third MI (if more than one MI event occurred), Systolic Blood Pressure (SBP) in mmHg, Diastolic Blood Pressure (DBP) in mmHg, total serum in mg/dl [It is a chemical waste which is produced by muscle metabolism. If kidneys aren't functioning normally then creatinine may accumulate in blood. The normal range for creatinine in the blood may be between 0.84 to 1.21 milligrams per decilitre (74.3 to 107 micromoles per litre), range varies in men and women of different ages. In most of the cases, a high serum creatinine level means that kidneys aren't working well], fasting blood sugar in mg/dL, Body Mass Index (BMI), kg/m^2. And discrete - sex (Male/Female), smoking (No/Yes), alcohol (No/Yes), family history of MI (No/Yes), hypercholesterolemia (No/Yes), hypertension (No/Yes), angina (No/Yes), arrhythmias (No/Yes).

Analytical Approach

McNemar's Test

This test is used on nominal paired data. It is based on 2x2 contingency table with a dichotomous trait to determine whether column and row marginal totals are equal. It was first introduced by McNemar Q.[16]

Quantile Regression for Survival Analysis

In most of the cases of survival analysis, a model can be written as:

$$h(T_i) = x'_i\beta + u_i$$

T_i is survival time or time to event or time to onset of disease etc. $h(.)$ is monotonic transformation function, x_i and u_i are the prognostic factors and error term respectively.

Again, consider the quantile function for the transformed survival time $h(T)$:

$$Q_{h(T)}(\tau|x) = x'\beta(\tau)$$

$\tau \epsilon (0,1)$, Chaudhuri P et al.[17] suggested to treat $\beta(\tau)$ as coefficients vector of the standard linear model, the Cox-PH model, proportional odds and accelerated failure time model. Consider the linear location-scale models,

$$h(T_i) = x'_i\beta + (x'_i y)u_i$$

then a family of quantile regression can be written as:

$$Q_{h(T)}(\tau|x) = x'\beta + x'\gamma\, F^{-1}{}_u(T) = x\beta(\tau)$$

where $\beta(\tau) = \beta + \gamma\, F^{-1}(\tau)$.

The R-package, "quantreg" for censored quantile regression can be used to find the parameters of the above model, Koenker R et al.[18] In the package, there are three methods to deal with the censoring, namely Powell JL[19] for fixed censoring, Portnoy S[12] for fixed censoring Kaplan-Meier analogue, and Peng L and Huang Y[20] for random censoring, Nelson-Aalen analogue. Prognostic factors can be included on the model as:

$$\begin{aligned} Q_{\log T_i}(\tau|x_i) = {} & \beta_0(\tau) + \beta_1(\tau) * Age + \beta_2(\tau) * Sex + \beta_3(\tau) * Smoking + \beta_4(\tau) \\ & * Alcohol + \beta_5(\tau) * History_{MI} + \beta_6(\tau) * DM + \beta_7(\tau) \\ & * Hypercholoesterolemia + \beta_8(\tau) * HTN + \beta_9(\tau) * Obesity + \beta_{10}(\tau) \\ & * Angina + \beta_{11}(\tau) * Arrhythmias + \beta_{12}(\tau) * SBP + \beta_{13}(\tau) * DBP \\ & + \beta_{14}(\tau) * Total_{Serum} + \beta_{15}(\tau) * Blood_{Sugar} + \beta_{16}(\tau) * BMI \end{aligned}$$

Result

Table 1, gives the descriptive statistics of all the prognostic factors used in this study. Table 2, is the 2x2 contingency table between hypertension and heart failure. Odds of being hypertensive in heart failure cases = 8/5, similarly odds of being hypertensive in non-heart failure cases are = 51/40. Therefore, odds ratio will be (40*8)/(51*5)=1.2549. Odds ratio greater than 1 suggest that the odds of being hypertensive are positively associated with the adverse outcome (i.e. heart failure) compared to odds of being not exposed (non-hypertensive). We can see that hypertensive patients were 1.2549 times more likely to be the victim of heart failure compared to those who did not had problem of hypertension.

From McNemar's contingency Table 3, we observe that patients who have hypertension at the time of hospital admission (presenting hypertension) are more likely to have hypertension at the time of last contact and the two proportions are significantly different.

Smoking is proved to be the major cause of cardiovascular disease and it accounts for 25% death among cardiac patients. Main reason of blood clotting inside veins and arteries among smokers are the chemical substances found in cigarettes and nicotine products that thickens the blood

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itself Centers for Disease Control and Prevention.[21] From Table 4 it is observed smoking have negative effect on patient's survival with higher magnitude at lower quantiles of survival.

Table 1.Descriptives of Variable Under Study

		Frequency	Percent
Sex	Male	69	66.3
	Female	35	33.7
Smoking	No	51	49.0
	Yes	53	51.0
Alcohol	No	77	74.0
	Yes	27	26.0
History-MI	No	79	76.0
	Yes	25	24.0
DM	No	77	74.0
	Yes	27	26.0
Hyperchol-esterolemia	No	72	69.2
	Yes	32	30.8
HTN	No	45	43.3
	Yes	59	56.7
Angina	No	54	51.9
	Yes	50	48.1
Heart-failure	No	91	87.5
	Yes	13	12.5
Arrhythmias	No	80	76.9
	Yes	24	23.1
SBP (Mean±SD)	146.153 ± 23.67		
DBP (Mean±SD)	106 ± 27.04		
Total Serum (Mean±SD)	210.2 ± 44.68		
Blood Sugar (Mean±SD)	95.8 ± 34.25		
BMI (Mean±SD)	22.09 ± 2.57		

Association between alcohol consumption and heart related ailments a debatable issue. There are many studies that shows person who drinks light to moderate amounts of alcohol have lower death rates than non-drinkers, at the same time heavy drinkers have higher death rates from all causes including cardiovascular disease.[22-24] But some contradictory meta-analysis are also there in the literature.[25] As per WHO guidelines a person who takes more than three units of alcohol [one unit drink = half pint of beer/ large (5% alcohol), 100 ml of wine (10% alcohol), spirits 25 ml (40% alcohol)] should be advised to reduce the alcohol intake. From our study (Table 4) we find that for 10th quantile of survival alcohol has negative impact, then at 25th and 50th quantile alcohol has insignificant positive impact, so based on our limited data we are unable to reach at any conclusions as far as alcohol consumption is concerned. Among other reasons of this inconclusiness one most probable is that we didn't have amount of intake of alcohol. Family history of MI, Diabetes Mellitus (DM), arrhythmias and hypercholesterolemia all have negative impact on survival time of patients.

The most important risk factor for CVD patient is high blood pressure so is the higher mortality.[26-28] In our study also, there are 56.7% of the patients who are suffering from high BP.

There is numerous literature that shows angina is linked with risk of depression[29, 30] and it is well known that depression is the major risk factor for CVD patients.[31] From this study (Table 4) angina discerned out to be associated with lower survival time.

Cardiovascular disease is sometimes considered to be the "male" disease,[32] infect in economically developed countries male is two to five times more prone to cardiovascular disease than female in younger age group.[33] In our study also (from Table 4) being female have positive impact on survival as compared to male, although effect is being deprecated for at higher quantiles.

It is well established that increasing age acts as a catalyst to the cardiovascular disease. Dhingra Rand Vasan RS[34] beautifully used patient's age to predict the cardiovascular disease incidence by considering the different risk score. From Table 5, it reflects that age have different effect on patient's survival at various quantiles of survival time. Effect of age is decreasing on survival at all the quantiles significantly.

Systolic blood pressure has more risk on CVD than the diastolic blood pressure nevertheless it varies with sex and age.[35] SBP is the measure of pressure of blood vessels when heart beats, DBP measure the pressure of blood vessels when heart rests between two beats. Normal range for blood pressure is SBP<120 mmHg and DBP <80 mmHg; at risk (pre hypertension) SBP: 120-139 mmHg and DBP: 80-89 mmHg; high BP: SBP>140 mmHg and DBP>90 mmHg. DBP and SBP both have negatively significant relation with survival but SBP is more diminishing the survival time than DBP. There are plethora of research that found the linear relationship between cardiovascular disease and systolic/ diasytolic blood pressure.[27,36]

Total serum creatinine has small negative but significant effect on survival but note that at median quantile (50th quantile) it has insignificant effect.

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Table 2.Contingency Table Between Hypertension and Heart Failure

Yes		Heart_Failure		Total
		No		
HTN	Yes	8 (13.6%)	51 (86.4%)	59
	No	5 (11.1%)	40 (89.9%)	45
Total		13	91	104

Table 3.McNemar's Contingency Table

No		DM		Total	Sig.
		Yes			
Pres_DM	No	75 (91.5%)	7 (8.5%)	82	0.18
	Yes	2 (9.1%)	20 (90.9%)	22	
Total		77	27	104	
No		HTN		Total	
		Yes			
Pres_HTN	No	41 (74.55%)	14 (25.45%)	55	**0.031**
	Yes	4 (8.16%)	45 (91.83%)	49	
Total		45	59	104	
No		Angina		Total	
		Yes			
Pres_Angina	No	48 (78.7%)	13 (21.3%)	61	0.581
	Yes	6 (14.0%)	37 (86.0%)	43	
Total		54	50	104	
No		Arrhythmias		Total	
		Yes			
Pres_Arrhythmias	No	75(90.4%)	8 (9.6%)	83	0.581
	Yes	5 (23.8%)	16(76.2%)	21	
Total		80	24	104	

Table 4.Estimates of Parameters at Different Quantiles for model A

	Quantiles				
	10^{th}	**25^{th}**	**50^{th}**	**75^{th}**	**90^{th}**
Intercept	1.3854	1.43355	1.38007	0.82612	1.23544
Smoking	-0.32321	-0.10763	-0.09716	-0.04328	-0.03569
Alcohol	-0.07915	0.03906	0.11805	-0.02605	-0.017833
History MI	-0.09496	-0.16705	-0.1011	-0.39031	-0.26933
DM	-0.15238	-0.27673	-0.26588	-0.66908	-0.30705
Arrhythmias	-0.008329	-0.013078	-0.19674	-0.08473	-0.07995
Hypercholesterolemia	-0.22573	-0.00863	0.02865	-0.80112	-0.97894
HTN	-0.29078	0.00487	-0.2251	-0.72075	-0.15827
Angina	-0.40724	-0.09172	-0.35303	-0.79989	-0.52192
Sex	0.04167	0.10763	0.06159	0.023	0.0112

Bold faced numbers denote significant.

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Table 5.Estimates of Parameters at Different Quantiles for model B

	Quantile				
	10	25	50	75	90
Intercept	1.424	2.04738	0.76133	1.5182	1.87183
Age	-0.00855	-0.00334	-0.00132	-0.00219	-0.00494
DBP	-0.00174	-0.0034	-0.007	-0.0042	-0.00291
SBP	-0.041	-0.00395	-0.00183	-0.00846	-0.00441
Total Serum	-0.00042	-0.00023	-0.0011	-0.00124	-0.00068
Blood Sugar	-0.0113	-0.0011	-0.00178	-0.0015	-0.0013
BMI	-0.00282	-0.00863	-0.02865	0.00306	0.00326

Bold faced numbers denote significant.

Fasting blood sugar level is negatively associated with patient's survival with equal magnitude and direction at 10^{th} and 90^{th} quantile but at 10^{th} quantile blood sugar is significantly associated not at 90^{th} quantile.

BMI generally have U shaped relationship with death due to CVD, i.e. at lower and higher BMI there is inflated risk of mortality and morbidity. Higher BMI is associated with coronary heart disease, ischemic stroke in east Asians but it is weaker risk for south Asians.[8] Table 5, shows that in Indian patients also, BMI is having negative effect on survival time of CVD patients. Recently, a new prognostic factor of cardiovascular disease namely body surface index (BSI) has been discussed in great detail by Das et al.,[37] there it is found that BSI has significant association with mean SBP and Mean Central Venous Pressure (MCVP).

Conclusion

In modelling survival time data generally Cox-PH and AFT models are being used. But after contemplating various prognostic factors we sway with quantile regression and found that it is more diligent in describing the relationship between survival time and prognostic factors. Upon applying quantile regression, we get tangible benefits while interpreting the results which are at least as good as results that would have been obtained using traditional models. Results are appealing in the sense that we can observe the effects of prognostic factors quite impressively on various quantiles of survival.

Limitations

As per WHO guidelines we had no risk factors available like, low HDL-C (high density lipoprotein or good cholesterol), elevated triglycerides, albuminuria, C-reactive proteins, left ventricular hypertrophy, hyperuricaemia and fibrinogen, reduced sodium intake. We haven't considered modifiable and non-modifiable risk factors separately, if would have been considered that might had led to some improvement in estimation.

Conflict of Interest: None

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