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Investigation factors affecting the first recurrence of coronary artery disease in patients undergone angioplasty using cox survival model

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Abstract

Background: The incidence of restenosis in patients suffering from coronary artery disease after undergoing angioplasty is of paramount importance. Accordingly, this study aimed to investigate factors affecting the time of the first incidence of restenosis in patients undergone angioplasty in the city of Zanjan, Iran.

Methods: This retrospective cohort study was conducted on 421 patients who referred to Ayatollah Musavi hospital in Zanjan for angioplasty during 2009 to 2012. The time of the incidence of restenosis after angioplasty constituted the dependent variable of the study. Independent variables of the study included signs of diabetes, hypertension, hyperlipidemia, kidney disease, carotid stenosis, lung disease, anemia, angina history, and MI. The Cox regression model with the significance level of 0.05 was deployed for the statistical analysis.

Results: According to the Cox regression model, hazard ratio of the first incidence of restenosis in patients with hypertension and angina was 22.8% and 29.5% less than other patients, respectively. However, hazard ratio of the first incidence of restenosis was 7.4 times more in patients suffering from carotid stenosis than other patients ($p<0.05$).

Conclusion: The results of this study revealed that as time goes on, the risk of the incidence of restenosis in angioplasty patients increases such that patients' survival decreases dramatically after a year. To determine the role of effective factors on the incidence of restenosis, conducting a prospective interventional study is highly recommended.

Keywords: Angioplasty, Cardiovascular Disease, Restenosis, Survival, Cox Regression.

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Introduction

The heart, as the primary organ for supplying body's blood, requires nutrition and oxygen. This critical and fundamental need is mainly fulfilled by coronary arteries. Narrowing or blockage of coronary arteries, defects blood supply to the heart, and leads to heart failure and heart attack. The walls of blood vessels are normally characterized by flat, slick, and delicate surface; however, age increase along with other additional factors such as smoking, hyperlipidemia, hypertension and diabetes lead to the deposition of cholesterol in the blood vessel walls. This buildup of cholesterol in blood vessels is referred to as "dubbed plaque". Plaque formation in blood vessels results in the narrowing and hardening of blood vessels, and blood supply failure (1).

One of the most important treatments that have revolutionized the field of cardiology is the use of stent (2,3) or angioplasty, which for the first time, was used in 1997 by Gurnitzing (4). This treatment significantly eliminated the need to undergo coronary artery bypass graft surgery in patients

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with coronary artery disease; and in fact, it was conceived as an alternative to the coronary artery bypass graft surgery.

Compared to the coronary artery bypass graft surgery, angioplasty is both less expensive and minimally invasive. Moreover, after angioplasty, patients are required to stay in hospital only for one or two days, and they can return to their daily life very soon. Given the minimal risk and the high success rate of angioplasty, almost 400000 patients in the U.S.A undergo angioplasty annually. What is worth mentioning with regard to angioplasty is the incidence of restenosis, which necessitates the need for retreatment (5). In fact, none of the heart's valve meets all of the criteria of an ideal valve, and as time passes, heart valve problems may develop and necessitate retreatment (6).

Restenosis is a complex phenomenon and many factors are involved in its development. From among different factors leading to the development of restenosis, diabetes mellitus, small-diameter arteries, incomplete dilation of stenosis, arterial elasticity, occluded left anterior descending coronary arteries, and thrombus-containing stenosis are the most prevalent factors (7).

In most of the previous studies, restenosis has been regarded as a dichotomous variable and the time of the incidence of restenosis has not been taken into consideration. However, in using survival analysis, the dependent variable is the time of the incidence of the restenosis, and right-censored data are taken into account as well (8).

The bulk of research in this field mainly focuses on identifying the risk factors in patients who have undergone angioplasty, but the results are conflicting. Given the importance and high prevalence of the incidence of acute clinical outcomes and complications of angioplasty and the importance of assessing the survival rate of the patients with heart diseases, this study aimed to predict the time of the first incidence of acute clinical complications of angioplasty. Moreover, this study used the survival analysis, particularly Cox survival model, to investigate the effect of other related independent variables and predict the time of the first incidence of the clinical outcomes and complications of angioplasty.

Methods

In this retrospective cohort study, we examined the medical records of 421 patients who had undergone angioplasty in Ayatollah Musavi hospital in Zanjan during 2009 to 2012, whose record existed in the hospital.

To conduct this study, at the first stage, a researcher-administered information list was prepared. In the next stage, patients' demographic information along with other information such as whether patients suffered from diseases related to heart (diabetes, hypertension, hyperlipidemia, kidney disease, carotid stenosis, lung disease, anemia, angina history, and MI (Myocardial Infarction)), and time of the first incidence of restenosis were included in the form. Then by directly contacting the patients (using the phone number mentioned in their medical record), we examined the patients in terms of their vital status and the date of the second incidence of restenosis (if any) was recorded. Those patients who did not experience the second incidence of restenosis or were not considered for participation (due to death, lost to follow-up, etc.), were regarded as right censored data and were recorded.

In this study, the time of the incidence of restenosis after angioplasty constituted the dependent variable. Independent variables of the study included history of diabetes, hypertension, hyperlipidemia, kidney disease, carotid stenosis, lung disease, anemia, angina history, and MI. Given that hazard ratio was reported for each of the dependent variables, the Cox regression model, with stepwise estimation method was used in R software, to determine the effective factors on the time of the incidence of restenosis in patients who have undergone angioplasty. Significance level was set at 0.05.

Data analysis and the recording process

were done confidentially and anonymously.

Results

The mean±SD age of the participants were calculated to be 60.6±10.5 yrs. (range of 36 to 87 yrs.). Sex ratio of the patients was 2.2 (male to female ratio). Table 1 displays the prevalence and distribution of the dependent and underlying variables by gender.

The results of the performed statistical tests revealed a significant relationship between diabetes ($p<0.001$), hypertension ($p<0.001$) and gender.

As time goes on, the risk of restenosis increases significantly and dramatically in patients who have undergone angioplasty (Fig. 1). Given that the survival data are skewed to the right, median, instead of mean, was used as a measure of central tendency. Kaplan-Meier estimator indicated that the median time for the first incidence of restenosis after angioplasty was 218 days, with the standard deviation of 32 days. Moreover, the mean of the survival time and its standard deviations were 459 and 33 days, respectively.

The results of the Cox regression model on the data of the patients suffering from coronary arteries are represented in Table 2. The results revealed a significance of only three variables under investigation; namely, hypertension (0.27), carotid stenosis (0.001), and angina (0.32).

The results of Table 2 demonstrate that the hazard ratio for the first incidence of restenosis in patients with hypertension was 22.8% less than patients who did not have

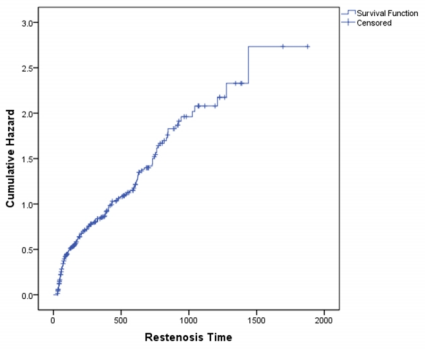

Fig. 1. Cumulative Hazard Function for the First Incidence of Restenosis in the Patients Undergoing Angioplasty in Ayatollah Musavi Hospital in Zanjan, Iran, during 2009 to 2012

hypertension ($p=0.027$). Moreover, the hazard ratio for the first incidence of restenosis in patients with carotid tension was 7.4 times more than patients who did not suffer from carotid tension ($p=0.001$). Finally, the hazard ratio for patients with angina was 29.5% less than patients who were not afflicted with angina ($p=0.032$).

Discussion

This study aimed at examining the effective factors on the time of the first incidence of restenosis in patients who have undergone angioplasty in Ayatollah Mosavi hospital in Zanjan (Iran). The findings of this study revealed that hypertension and angina decrease hazard ratio, while carotid tension leads to an increase in the hazard ratio for restenosis. No significant relationship was observed between hazard ratio for the first incidence of restenosis and other variables such as diabetes, hyperlipidemia, kidney disease, anemia, and MI).

Suffering from angina is conceived of as

Table 1. Frequency Distribution of the Patients Undergoing Angioplasty by their Medical History and Gender

Gender	Diabetes	Hypertension	Hyperlipidemia	Kidney disease	Carotid stenosis	Lung disease	Anemia history	Angina history	MI history
Male	12.5%	49.1%	91.7%	3.8%	2.7%	0.1%	1%	84.8%	45.7%
Female	32.6%	75.8%	86.4%	5.3%	2.8%	0.8%	0.1%	88.6%	25.8%
All	18.8%	57.5%	90.0%	4.3%	2.7%	0.2%	0.7%	86.0%	39.4%

Table 2. The Effect of Hypertension, Carotid Tension, and Angina on the Hazard Ratio for Restenosis in Patients who had Undergone Angioplasty

Variables	Regression coefficient	Standard error	p	Hazard ratio	95 % CI for hazard ratio
Hypertension	−0.259	0.117	0.027	0.772	(0.614 , 0.970)
Carotid Stenosis	2.003	0.593	0.001	7.413	(2.319 , 23.702)
Angina History	−0.349	0.163	0.032	0.705	(0.512 , 0.970)

having the experience of chest pain in the past or suffering from it as a chronic disease at the time of angioplasty and angiography. To put it differently, coronary artery stenosis develops gradually; accordingly, atherosclerotic plaques leading to the coronary artery stenosis are stable. However, as for the acute coronary syndrome, such as unstable angina or heart attack, atherosclerotic plaques leading to the stenosis were unstable and angioplasty was performed in an unstable condition. Accordingly, this lends credit to the argument that the hazard ratio for the first incidence of restenosis in acute coronary syndrome is higher, compared to the hazard ratio of chronic angina (9).

The investigation on patients suffering from both carotid tension and coronary artery stenosis revealed that coronary artery stenosis is a comparatively more extensive phenomenon, which can extend and lead to the involvement and affliction of other vessels of the body. In fact, in these patients, the inclination for developing coronary artery stenosis and the formation of atherosclerotic plaque increases, and it leads to the involvement of other vessels of the body. Accordingly, in patients suffering from carotid tension, the extent of the coronary artery stenosis and the number of involved vessels are more, and they are more likely to develop atherogenesis. Accordingly, the hazard ratio for the first incidence of restenosis in these patients was more than patients who were not afflicted with carotid tension in their medical history (9).

Patients with coronary artery disease who have undergone angioplasty are under continuous surveillance and take blood pressure controlling medications from beta-blocker group, AC inhibitors or calcium channel blocker group, which have anti-anginal effects and fall under the rubric of antianginal drugs. Given that patients who have undergone angioplasty take the above-mentioned medications regularly after the angioplasty, the risk of the incidence of restenosis in patients with high blood pressure decreases.

In another study conducted along the same line of research, Yusefnezhad et al., using Cox regression model, identified a significant relationship between hyperlipidemia and MI variables on the one hand, and the hazard ratio of restenosis on the other. This finding is in line with and confirms the findings of this study. However, in the study carried out by Yusefnezhad et.al, the effect of diabetes was identified to be significant, which is contrary to the findings of this study. The reason can be attributed to the fact that in this study, the number of patients with diabetes was comparatively lower than the patients of the study conducted by Yusefnezhad et al (7).

In another piece of research, using chi-square test, Hasani et al., quite contrary to the results of this study, identified the effect of diabetes as being significant, and the effect of angina as insignificant. The difference in the composition of the population and the deployed statistical methods can be invoked to account for the observed differences in the results of the two studies. Moreover, the effect of MI was detected to be insignificant, which is in line with the findings of this study (10).

In a systematic review carried out by Groschel et al., on 4,185 patients, hypertension was identified as the most determining factor in the incidence of restenosis, which in terms of significance, is in line with the findings of this study. However, the two studies contradict in terms of the significance of diabetes and hyperlipidemia variables. To explain the observed differences between the results of the two studies, we can refer to the fact that the prevalence of hyperlipidemia and diabetes was comparatively more in the systematic review, compared with their prevalence in this study (11).

In most of other researches, conducted in this field, the effect of diabetes was identified and reported to be significant (7,10,11, 13,15,16,20). However, some other researches, in line with the findings of this study, detected the effect of this variable as being insignificant (14,18,19).

In a considerable number of researches, the effect of hypertension was revealed to be insignificant (7,12,14,15), which does not confirm the results of this study; however, in a number of researches conducted in this field, the effect of this variable was found to be significant (11,19,20).

The effect of unstable angina was proved to be significant in most of the researches carried out in this field (14,17,18,20), which lends credibility to the findings of this study; and only in one of the related researches, the effect of this variable was not proved to be significant (10).

In the above-mentioned study, the effect of hyperlipidemia was detected as being insignificant, which is in line with the results of some other researches carried out in this field (7,12,15). However, the results of some other researches revealed a significant effect of this variable, which proves to be at odds with the results of this study (11, 19,20).

With respect to the effect of MI, which was proved insignificant in this study, it can be observed that the investigations of other related studies have come to the same conclusion (7,10,12,14,18,19).

With regards to the reasons for the observed differences and contradictions between the results of this study and the findings of other related researches, we can maintain that different composition of the population, difference in the composition of the independent variables, and the use of different statistical methods can be invoked to account for them.

Conclusion

The most important feature of this study, distinguishing it from previously conducted studies, is using a rather large population (421 patients), performing survival analysis and accordingly taking the time of the incidence of restenosis and right censored data into account. However, the retrospective nature of the study, incompleteness of the medical records of some patients, and not having access to the data of some of the effective factors were the limitations of this study. Moreover, this present aimed to investigate the effects of different variables only on the first incidence of restenosis, which can be considered as one of the drawbacks of this present study. Having the above limitations in mind, conducting introspective study, in which the effects of other effective and aggravating factors are investigated, is highly recommended. In terms of the statistical models, it is suggested that instead of focusing on the first incidence of restenosis, information on the recurrences of restenosis be used; and for data analysis, the recurrent event data model be exploited.

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