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# Recurrent Event Analysis of Coronary Artery Stenosis in Patients Undergoing Angioplasty

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## Abstract

**Background:** Restenosis after coronary angioplasty can have serious complications such as coronary artery bypass graft, myocardial infarction, and death.
**Objectives:** The present study aimed at investigating the factors affecting the recurrence of coronary artery stenosis in patients undergoing angioplasty using the recurrent event data analysis.
**Methods:** A cohort study was performed on patients undergoing coronary angioplasty from March 23, 2009, to January 21, 2011. All patients were followed up from angioplasty to January 21, 2015. First, each of the independent variables was entered into the univariate Cox model with a frailty component. Then, variables with p-values of less than 0.2 were entered into the multivariate analysis. The statistical analysis was done using R software, version 3.6, at the significance level of 0.05.
**Results:** The present study was conducted on 1,000 patients who underwent coronary angioplasty. We found that 441 patients experienced restenosis at least once in the study period. The mean survival time to the first event of restenosis was $44.08 \pm 1.06$ months. Patients with a history of diabetes, unstable angina, and myocardial infarction had a significantly higher hazard of restenosis compared to other patients ($P < 0.05$).
**Conclusions:** The results of the recurrent event survival analysis confirmed the significant role of risk factors such as a history of diabetes, unstable angina, and myocardial infarction. Therefore, training to enhance the patients' awareness and attitude seems necessary to prevent them from exposing whit known risk factors. The periodic follow-up of patients with risk factors and more ongoing care are also necessary.

*Keywords:* Angioplasty, Recurrence, Coronary Stenosis, Survival

## 1. Background

Percutaneous transluminal coronary angioplasty (PTCA), also called percutaneous coronary intervention (PCI), is a minimally invasive method for opening blocked or stenosed coronary arteries, which allows the unobstructed blood flow to the myocardium. Blocked arteries caused by plaque (fatty deposits) build-up can reduce the myocardial blood flow. Coronary artery disease develops when atherosclerosis affects the coronary arteries (1). The most important signs and symptoms of atherosclerosis are ischemic heart disease, ischemic stroke, and peripheral arterial disease, which are among the leading causes of death in the United States of America, the United Kingdom, and other European countries (2). Open-heart surgery and PTCA using the drug and non-drug-eluting stents are the two common methods for the treatment of coronary artery disease. Percutaneous transluminal coronary angioplasty is a less invasive and expensive method than coronary artery bypass surgery. Using PTCA, patients can return to their normal work routine sooner (3). About one to three years after PTCA, around 30% of patients develop vascular stenosis, which can lead to another PTCA, open-heart surgery, ischemic heart disease, or even death (4, 5). Some risk factors for the occurrence of restenosis include gender, age, smoking, diabetes, high blood cholesterol, high blood pressure, chronic kidney disease, unstable angina pectoris, myocardial infarction, location of coronary artery lesion, lesion's length, number of involved coronary arteries, type of implanted stents,

and their length (6-9).

## 2. Objectives

One of the statistical methods used for analyzing time-to-event data in the presence of censored data is the survival analysis that is mostly used for investigating the survival and hazard rates of patients based on different covariates (10). In the survival analysis in many medical situations, patients experience recurrent events such as the development of new tumors in cancer patients, the occurrence of ischemic attacks in coronary artery disease patients, re-hospitalization, and the incidence of recurrent opportunistic infections in HIV-positive patients (11-14). In the above-mentioned examples, the recurrent events of an individual are possible given the basic characteristics of the individual. As a result, the intervals between recurring events might be shorter for one individual than for another. Furthermore, the heterogeneity in incidence rates between different individuals might not be reflected in the measured baseline variables. Thus, we need an appropriate statistical model taking such correlations and heterogeneities into account. Hence, the frailty model is proposed for the analysis of recurring data (13, 15, 16). The present study aimed at investigating the factors affecting the recurrence of coronary artery stenosis in patients undergoing angioplasty by using recurring data analysis and considering frailty.

## 3. Methods

### 3.1. Data Collection

In the present cohort study, the population consisted of all patients who underwent angioplasty from March 2009 to January 21, 2011, in Ayatollah Musavi Hospital in Zanjan, Iran. All of the patients were followed up from the time of angioplasty to January 21, 2015, to investigate the time to the recurrence of coronary artery stenosis. The total number of patients was 1,174, of whom 174 patients were excluded due to information deficits, and 1,000 patients were analyzed. Patients were included if they underwent angioplasty for the first time and had no history of CABG. Independent variables in the information form were age, gender, employment status, place of residence, education level, income satisfaction level, history of smoking, drug use, diabetes, high blood pressure, carotid stenosis, high blood cholesterol, chronic kidney disease, unstable angina, and myocardial infarction.

The dependent variable was the time to coronary artery stenosis. The coronary artery stenosis was indicated for patients who were readmitted with chest pain symptoms and their angiographic results showed that they had more than 50% stenosis in at least one of the coronary artery. If a patient did not experience stenosis to the end of the study (January 21, 2015), his/her data would be considered the right-censoring data. The study was approved by the Ethics Committee of Tarbiat Modares University (ethical code IR.TMU.REC.2019.112)

### 3.2. Statistical Methods

To describe the data, we used the mean $\pm$ SD for continuous variables and the frequency and percentage for categorical variables. The proportional hazard assumption was checked using the Harrell and Lee test. This test is based on the correlation between Schoenfeld residuals and ordered failure times. The semi-parametric Cox proportional hazards model with frailty component was used for the recurrence of coronary artery stenosis.

In this study, the time interval between two consecutive events (gap time) was considered the response variable. First, each of the dependent variables was entered into the univariate Cox model with a frailty component. Then, each of them with a p-value of less than 0.2 (and a history of myocardial infarction) was entered into the multivariate Cox model with a frailty component. The significance level of 0.05 was used for the statistical analyses. The R software, version 3.6, was used for data analysis.

## 4. Results

The present study was conducted on 1,000 patients who underwent angioplasty. The mean follow-up period to the first event of restenosis was 2.18 $\pm$ 1.57 years. The sample included 694 (69.4%) male patients. The mean age of the patients was 60.67 $\pm$ 10.39 and their ages ranged from 33 to 87. Moreover, 914 (91.4%) patients had a history of high blood cholesterol, 560 (56%) a history of high blood pressure, 36 (3.6%) a history of acute renal failure, and 355 (35.5%) a history of myocardial infarction (Table 1).

In this study, 441 patients experienced restenosis at least once in the study period. The mean survival time to the first event of restenosis was 44.08 $\pm$ 1.06 months. Moreover, 106 patients experienced restenosis for the second time with a mean of 54.85 $\pm$ 1.48 months. Of the remaining 106 patients, 26 patients experienced restenosis for the third time, with a mean of 47.41 $\pm$ 3.09 months. Finally,

**Table 1.** Univariate Analysis of Cox Proportional Hazards Model with Frailty Component for Recurrence of Coronary Artery Stenosis[a]

| | Values | Hazard Ratio (95% Confidence Interval) | P Value |
|---|---|---|---|
| **Gender** | | 0.91 (0.77, 1.09) | 0.312 |
| Male | 694 (69.4) | | |
| Female | 306 (30.6) | | |
| **Age, y** | | 1.043 (0.88,1.23) | 0.614 |
| ≥ 60 | 486 (48.6) | | |
| < 60 | 514 (5.4) | | |
| **Place of residence** | | 1.15 (0.94,1. 41) | 0.178 |
| Urban | 767 (76.6) | | |
| Rural | 233 (23.3) | | |
| **Education level** | | 1.15 (0.93,1.42) | 0.188 |
| Diploma or upper | 164 (16.4) | | |
| Under diploma | 836 (83.6) | | |
| **Income satisfaction level** | | 0.97 (0.80,1.19) | 0.809 |
| Moderate or high | 801 (80.1) | | |
| Low | 199 (19.9) | | |
| **History of smoking** | | 1.01 (0.83,1.20) | 0.987 |
| Yes | 227 (22.7) | | |
| No | 723 (72.3) | | |
| **History of drug addiction** | | 1.30 (0.89,1.89) | 0.170 |
| Yes | 36 (3.6) | | |
| No | 964 (96.4) | | |
| **Diabetes** | | 1.25 (1.03,1.54) | 0.025 |
| Yes | 170 (17) | | |
| No | 830 (83) | | |
| **History of Hyperlipidemia** | | 0.98 (0.74, 1.29) | 0.881 |
| Yes | 914 (91.4) | | |
| No | 86 (8.6) | | |
| **History of hypertension** | | 1.02 (0.86,1.20) | 0.820 |
| Yes | 560 (56) | | |
| No | 440 (44) | | |
| **History of chronic renal failure** | | 1.49 (1.04,2.13) | 0.028 |
| Yes | 36 (3.6) | | |
| No | 964 (96.4) | | |
| **History of carotid stenosis** | | 1.22 (0.65, 2.27) | 0.548 |
| Yes | 15 (1.5) | | |
| No | 985 (98.5) | | |
| **Angina history** | | 1.20 (0.93,1.54) | 0.162 |
| Yes | 851 (85.1) | | |
| No | 149 (14.9) | | |
| **History of myocardial infarction** | | 1.11 (0.93,1.29) | 0.271 |
| Yes | 355 (35.5) | | |
| No | 645 (65.5) | | |

[a]Values are expressed as No. (%).

five out of 26 patients experienced restenosis for the fourth time.

The results of the univariate Cox analysis with a frailty component revealed that the hazard of restenosis was significantly higher for diabetic patients than for patients with no history of diabetes (hazard ratio: 1.25, 95% CI: 1.03 to 1.54). The hazard of restenosis was significantly higher in patients with a history of chronic renal failure than in patients without a history of chronic renal failure (hazard ratio = 1.49, 95% CI = 1.04 to 2.13) (Table 1).

**Table 2.** Multivariate Cox Model with Frailty Component for Recurrence of Coronary Artery Stenosis

| Risk Factor | Hazard Ratio | (95% Confidence Interval) | P Value |
|---|---|---|---|
| **Diabetic** | 1.23 | (1.01,1.51) | 0.041 |
| **History of chronic renal failure** | 1.42 | (1.01,2.04) | 0.051 |
| **History of myocardial infarction** | 1.25 | (1.03,1.51) | 0.024 |
| **Unstable angina history** | 1.35 | (1.02,1.79) | 0.040 |
| **History of drug addiction** | 1.27 | (0.86,1.85) | 0.221 |
| **Living in urban areas** | 1.06 | (0.86,1.31) | 0.542 |
| **Diploma or upper** | 1.11 | (0.90,1.39) | 0.331 |

The results of the univariate Cox analysis with a frailty component showed that the hazard of restenosis was higher in patients living in urban areas, with an education level of a diploma or higher, with a history of drug addiction, carotid stenosis, unstable angina, and myocardial infarction but not statistically significantly.

Diabetes, chronic renal failure, history of myocardial infarction, history of unstable angina, history of drug addiction, place of residence, and education level were entered into the multivariate Cox model with a frailty component as independent variables. The results of the analysis revealed that the hazard of restenosis was significantly higher for patients with a history of diabetes, myocardial infarction, and unstable angina ($P < 0.05$) (Table 2). Figure 1 represents the survival curve of patients with/without angina history and patients with/without diabetes.

## 5. Discussion

The present study aimed to identify factors affecting time to restenosis in angioplasty patients by using recurrent data analysis and considering the frailty component. The results of the study demonstrated that the hazard of restenosis was significantly higher for patients with a history of diabetes, unstable angina, acute renal failure, and myocardial infarction ($P < 0.05$). However, the effects of variables such as a history of coronary stenosis, high blood cholesterol, high blood pressure, smoking, place of residence, drug addiction, education level, age (older or younger than 60 years), and gender were not statistically significant. We found that 44% of the patients experienced restenosis at least once, 10.6% of them experienced it at least twice, 2.4% of them experienced it at least three times, and 0.5% of them experienced it four times. The mean follow-up time to the first event of restenosis was 2.18 years. In this period, the 56% success rate of the treatment method was lower than the results of a meta-analysis conducted by Christakopoulos et al. (17) reporting a 71% success rate in 3.8 years of follow-up. This can be due to the differences in medical equipment and the experience of the centers.

The frailty model has been deployed for the analysis of recurrent data in many medical studies such as the development of new tumors in cancer patients, re-hospitalization, recurrent seizures in patients with epilepsy, etc. Cui et al. (13) scrutinized parametric conditional frailty models for recurrent coronary heart disease events.

This model considers the correlation between the recurring times and the heterogeneity of the personal characteristics of individuals, which are not considered in the variables; thus, this model can lead to better estimates of the coefficient of covariates (18).

In this study, the effect of the history of diabetes was significant on restenosis; it is similar to many previously conducted studies (19-21). However, some studies argued that the effect of diabetes was not significant on restenosis (22, 23). The observed difference in the results can be attributed to the low prevalence of diabetes in the present study. In many systematic reviews such as those conducted by Aoyama et al. (24) and Ota et al. (25), the effect of acute renal failure was significant on restenosis and this is similar to the findings of the present study.

The results of the present study showed that the effect of the history of myocardial infarction was significant on the incidence of restenosis. This finding is in line with the findings of Kim et al. study (7). However, some other studies have reported the non-significant effect of the above-mentioned risk factor (26). The observed differences in the obtained results can be ascribed to using different statistical methods and different combinations of independent variables. Most of the studies have shown the significant effect of unstable angina on restenosis (27, 28); the results of the multivariate model in our study were also indicative of the significant effect of this risk factor. However, it is worth mentioning that some studies demonstrated the insignificant effect of this risk factor (26).

The effect of the history of high blood pressure was not significant on restenosis, which is in agreement with the results of most studies conducted in this regard (26). However, some other studies indicated the significant effect of this risk factor (20). The observed differences can be attributed to different combinations of independent

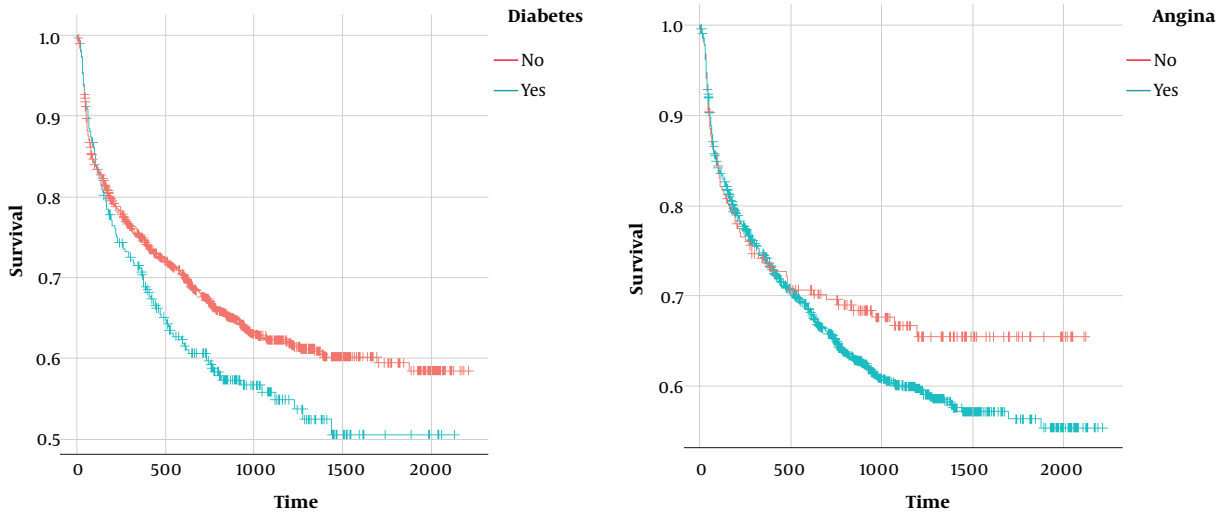


**Figure 1.** Survival Curve for Unstable Angina and Diabetes

variables used in data modeling and different definitions adopted for restenosis. In line with our study, some studies reported the non-significant effect of high blood cholesterol on restenosis (19, 26). However, some other findings are contrary to the present study results and emphasize the significant effect of this risk factor (29). A possible reason for the observed differences might be the high prevalence of high blood cholesterol in the present study (91.4%) or the difference between the deployed statistical methods.

Although the place of residence did not significantly affect restenosis, the hazard of restenosis was more for patients living in urban areas. This can be attributed to the higher pollution level in urban areas and their different lifestyles. The histories of smoking and drug addiction were proven to affect restenosis insignificantly; however, in some studies, the effects of these factors were reported to be significant (6).

The reason for the observed difference can be attributed to the fact that the patients in the current study possibly followed their doctors' orders and ceased smoking or drug use after angioplasty. One of the most important limitations of the present study is that the patients' records did not include information regarding the status and number of the involved coronary arteries and the features of the implanted stents.

### *5.1. Conclusions*

The results of recurrent event survival analysis with one frailty component confirmed the effects of risk factors such as a history of diabetes, unstable angina, acute renal failure, and myocardial infarction. Therefore, training to enhance the patients' awareness and attitude seems necessary to prevent them from exposing whit known risk factors. The periodic follow-up of patients with risk factor and more ongoing care are also necessary.

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## Footnotes

**Authors' Contribution:** Study concept and design: Ebrahim Hajizadeh, Abdollah Amirfarhangi, and Behrouz Beiranvand. Analysis and interpretation of data: Aliakbar Rasekhi and Abdollah Amirfarhangi. Drafting of the manuscript: Behrouz Beiranvand and Hajizadeh. Critical revision of the manuscript for important intellectual content: Ebrahim Hajizadeh and Abdollah Amirfarhangi. Statistical analysis: Behrouz Beiranvand, Aliakbar Rasekhi, and Javad Nasseryan.

**Conflict of Interests:** The authors declare that they have no conflict of interest in the publication of this article.

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