The use of statistical analysis methods in assessing long-term prognoses in patients with acute coronary syndrome and contrast-induced nephropathy

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Abstract. Thus, using a rank correlation analysis, a preliminary analysis of the relationship between the increase / decrease in blood creatinine, blood urea, GFR (Cockcroft-Gault) and GFR (CKD-EPI) after coronary angiography with vascular events was performed. A Kaplan-Meier survival analysis demonstrated the statistically significant effect of contrast-induced nephropathy on the risk of death from myocardial infarction in patients with long-term acute coronary syndrome.

1. Introduction
Survival analysis is a set of statistical methods that allow you to evaluate any events that occur after a certain initial event (for example, the start of treatment) without the occurrence of a certain event (for example, it can be death, a relapse of a disease or a condition). This probability is called the probability of survival. At the end of the study and censoring variable, indicating the completeness of the data [1].

The STATISTICA package implements the procedure for constructing survival curves using the Kaplan-Meyer method [2], which is as follows. It is estimated that there are n patients. Let dti be the number of deaths at time ti, and nti the number of people observed at time ti, where i is the number of the time at which the event occurred. The survival curve is given by the following function:

\[ \hat{S}(t) = \prod_{t_i \leq t} \left(1 - \frac{d_{t_i}}{n_{t_i}}\right). \] (1)

2. Methods
The study included 323 patients with acute coronary syndrome who were treated in the cardiology department of the regional vascular center, of which 217 (67.1%) were men, 106 (32.9%) were women. The average age of the examined patients was 59.6 ± 9.2 years.

All patients underwent standard biochemical studies, including the assessment of lipid metabolism: total cholesterol; high and low density lipoprotein cholesterol; atherogenic index; triglycerides, creatinine and urea levels.
The complex of instrumental studies included recording ECG at rest, Holter ECG monitoring, ultrasound of the heart, ultrasound examination of the kidney, coronary angiography to assess the degree of damage to the coronary vessels, selective angiography of the renal vessels.

Statistical analysis of the results was carried out using a set of applied statistical programs Microsoft Office Excel 2010 (Microsoft Corp., USA) and STATISTICA 10.0 (StatSoft Inc., USA). In order to assess the type of data distribution, Kolmogorov-Smirnov analysis was used; for values of p > 0.05, the distribution was considered not different from the normal one.

Descriptive statistics were carried out to determine the following features: the data were presented as M ± SD (M is the arithmetic mean, SD is the standard deviation) with a normal distribution and in the form Me [Q1; Q3] (Me is the median, Q1 and Q3 are the first and third quartiles) with abnormal distribution. In the normal distribution of the sample, when comparing two independent samples, the Student criterion was used, and when different from the normal one, the Mann-Whitney test and χ² or the Leuven test with the determination of F. We also used logistic regression analysis with the calculation of relative risks (OR) and determination χ², the relationship was considered statistically significant at a value of p < 0.05.

Kaplan-Majer survival analysis was performed with the Gehan's Wilcoxon test, the test was considered statistically significant at a p value of <0.05.

3. Results
At the first stage, a preliminary analysis of the relationship between the increase / decrease in blood creatinine, blood urea, GFR (Cockcroft-Gault) and GFR (CKD-EPI) after coronary angiography with vascular events was performed. For this purpose, a rank correlation analysis was used. It was shown that an increase in creatinine did not have a statistically significant relationship with vascular events (Table 1).

Table 1. Results of rank correlation analysis of Δ creatinine and vascular events

| Sign                                  | Spearman r | T (N-2) | p      |
|---------------------------------------|------------|---------|--------|
| Nonfatal myocardial infarction        | -0.09      | -0.89   | 0.37   |
| Non-fatal brain stroke                | -0.11      | -1.12   | 0.26   |
| Fatal myocardial infarction           | -0.06      | -0.62   | 0.53   |
| Fatal brain stroke                    | 0.09       | 0.99    | 0.32   |
| Fatal and nonfatal myocardal infarcion| -0.10      | -1.09   | 0.28   |
| Fatal and non-fatal cerebral stroke   | -0.05      | -0.52   | 0.60   |
| Fatal vascular events                 | -0.01      | -0.10   | 0.92   |
| Nonfatal vascular events              | -0.11      | -1.21   | 0.23   |
| Fatal and non-fatal vascular events   | -0.10      | -1.08   | 0.29   |

However, as blood urea increased after coronary angiography, there was an increase in the likelihood of developing fatal vascular events and non-fatal ones (table 2).

Table 2. Results of rank correlation analysis of Δ urea and vascular events

| Sign                                  | Spearman r | T (N-2) | p      |
|---------------------------------------|------------|---------|--------|
| Nonfatal myocardial infarction        | 0.13       | 2.0     | 0.12   |
| Non-fatal brain stroke                | -0.12      | -1.26   | 0.21   |
| Fatal myocardial infarction           | 0.22       | 2.36    | 0.02   |
| Fatal brain stroke                    | 0.02       | 0.17    | 0.87   |
| Fatal and nonfatal myocardal infarcion| 0.01       | 0.11    | 0.91   |
| Fatal and non-fatal cerebral stroke   | -0.09      | -1.02   | 0.31   |
| Fatal vascular events                 | 0.21       | 2.21    | 0.029  |
| Nonfatal vascular events              | 0.23       | 2.49    | 0.014  |
| Fatal and non-fatal vascular events   | -0.05      | -0.5    | 0.61   |
The decrease in GFR after coronary angiography was associated with the subsequent development of non-fatal myocardial infarction, as well as non-fatal vascular events (table 3). In general, a decrease in GFR also influenced the development of all vascular events.

**Table 3.** The results of rank correlation analysis Δ GFR and vascular events

| Sign                                | Spearman r | T (N-2)  | p     |
|-------------------------------------|------------|----------|-------|
| Nonfatal myocardial infarction      | -0.25      | -2.71    | 0.008 |
| Non-fatal brain stroke              | 0.11       | 1.17     | 0.24  |
| Fatal myocardial infarction         | 0.07       | 0.71     | 0.48  |
| Fatal brain stroke                  | -0.09      | -0.97    | 0.33  |
| Fatal and nonfatal myocardial infarction | 0.24      | 2.61     | 0.01  |
| Fatal and non-fatal cerebral stroke | 0.05       | 0.53     | 0.59  |
| Fatal vascular events               | 0.02       | 0.19     | 0.85  |
| Nonfatal vascular events            | -0.26      | -2.79    | 0.006 |
| Fatal and non-fatal vascular events | -0.22      | -2.38    | 0.019 |

The decrease in GFR determined by the CKD-EPI method after CAG was also associated with the development of nonfatal myocardial infarction, nonfatal vascular events, all vascular events, as well as fatal and nonfatal myocardial infarction (table 4).

**Table 4.** Results of rank correlation analysis Δ GFR (CKD-EPI) and vascular events

| Sign                                | Spearman r | T (N-2)  | p     |
|-------------------------------------|------------|----------|-------|
| Nonfatal myocardial infarction      | -0.28      | 3.1      | 0.003 |
| Non-fatal brain stroke              | 0.10       | 1.1      | 0.28  |
| Fatal myocardial infarction         | 0.10       | 1.1      | 0.26  |
| Fatal brain stroke                  | -0.09      | -1.1     | 0.29  |
| Fatal and nonfatal myocardial infarction | -0.29      | 3.25     | 0.002 |
| Fatal and non-fatal cerebral stroke | 0.04       | 0.46     | 0.65  |
| Fatal vascular events               | 0.05       | 0.57     | 0.57  |
| Nonfatal vascular events            | -0.27      | 3.05     | 0.003 |
| Fatal and non-fatal vascular events | -0.26      | 2.91     | 0.004 |

In addition, it was shown that nephrosclerosis, defined as a difference in kidney length of more than 15 mm, is a factor associated with the development of non-fatal myocardial infarction, fatal and non-fatal myocardial infarction, as well as non-fatal vascular events and all vascular events (table 5).

**Table 5.** Results of a rank correlation analysis of nephrosclerosis (difference> 15mm) and vascular events

| Sign                                | Spearman r | T (N-2)  | p     |
|-------------------------------------|------------|----------|-------|
| Nonfatal myocardial infarction      | 0.21       | 2.19     | 0.03  |
| Non-fatal brain stroke              | 0.002      | 0.02     | 0.98  |
| Fatal myocardial infarction         | 0.02       | 0.20     | 0.84  |
| Fatal brain stroke                  | 0.14       | 1.49     | 0.14  |
| Fatal and nonfatal myocardial infarction | 0.19      | 2.04     | 0.044 |
| Fatal and non-fatal cerebral stroke | 0.07       | 0.75     | 0.45  |
| Fatal vascular events               | 0.09       | 0.94     | 0.35  |
| Nonfatal vascular events            | 0.19       | 1.99     | 0.049 |
| Fatal and non-fatal vascular events | 0.22       | 2.34     | 0.02  |
Nephrosclerosis, determined by a decrease in kidney size less than 90 mm, had an effect only on fatal myocardial infarction (table 6).

**Table 6. Results of rank correlation analysis of nephrosclerosis (<90mm) and vascular events**

| Sign                                      | Spearman r | T (N-2) | p   |
|-------------------------------------------|------------|---------|-----|
| Nonfatal myocardial infarction            | 0.13       | 1.36    | 0.18|
| Non-fatal brain stroke                    | -0.08      | -0.77   | 0.44|
| Fatal myocardial infarction               | -0.07      | -0.71   | 0.48|
| Fatal brain stroke                        | 0.22       | 2.36    | 0.02|
| Fatal and nonfatal myocardial infarction  | 0.07       | 0.74    | 0.46|
| Fatal and non-fatal cerebral stroke       | 0.04       | 0.44    | 0.66|
| Fatal vascular events                     | 0.06       | 0.57    | 0.57|
| Nonfatal vascular events                  | 0.07       | 0.71    | 0.48|
| Fatal and non-fatal vascular events       | 0.09       | 0.98    | 0.33|

Thus, renal factors in general and damage to the renal parenchyma during coronary angiography, in particular, are associated with the development of vascular events in the distant period, which justifies the transition to analysis of the role of contrast-induced nephropathy in predicting the course of cardiovascular pathology in this group of patients.

A Kaplan-Meier survival analysis showed a statistically significant effect of contrast-induced nephropathy on the risk of death from myocardial infarction (Figure 1).

![Figure 1](attachment:image.png)

**Figure 1.** Schedule of cardiovascular survival of patients (development of fatal cerebral stroke) in the presence or absence of CIN. Gehan's Wilcoxon Test WW = 39,0 Sum = 2542,0 Var = 220,09, Test statistic = 2,59, p = 0,009

When conducting a logistic regression analysis, it was shown that contrast-induced nephropathy increased the risk of further development of fatal and non-fatal infarction by 20% (table 7).
Table 7.-Logistic regression analysis of the effect of contrast-induced nephropathy on the risk of developing vascular events

| Sign                                      | Constanta B0 Est | Constanta B0 OR | Estimate | OR (unit ch) | OR (range) | $\chi^2$ | df | p    |
|-------------------------------------------|------------------|-----------------|----------|--------------|------------|----------|-----|------|
| Nonfatal myocardial infarction            | 2,17             | 8,8             | 24,1     | $3,0*10^{10}$ | $3,0*10^{10}$ | 2,24     | 1   | 0,13 |
| Non-fatal brain stroke                    | 2,48             | 12,0            | 24,1     | $2,9*10^{10}$ | $2,9*10^{10}$ | 1,67     | 1   | 0,19 |
| Fatal myocardial infarction               | 2,49             | 12,2            | 23,0     | $9,9*10^{7}$  | $9,9*10^{7}$  | 1,65     | 1   | 0,19 |
| Fatal brain stroke                        | 4,64             | 104             | -2,34    | 0,09         | 0,09       | 2,21     | 1   | 0,14 |
| Fatal and nonfatal myocardial infarction  | 1,57             | 4,83            | 25,9     | $1,8*10^{11}$ | $1,8*10^{11}$ | 3,91     | 1   | 0,047|
| Fatal and non-fatal cerebral stroke       | -2,37            | 0,09            | 0,06     | 1,06         | 1,06       | 0,003    | 1   | 0,95 |
| Fatal vascular events                     | -2,37            | 0,09            | 0,06     | 1,06         | 1,06       | 0,003    | 1   | 0,95 |
| Nonfatal vascular events                  | -1,6             | 0,19            | -25,4    | $1*10^{-7}$  | $1*10^{-7}$  | 3,36     | 1   | 0,07 |
| Fatal and non-fatal vascular events       | -1,12            | 0,33            | -1,07    | 0,34         | 0,34       | 1,27     | 1   | 0,26 |

When analyzing factors that could influence the formation of contrast-induced nephropathy, an interesting circumstance was that during the survival analysis it was shown that a more severe myocardial damage in the form of acute myocardial infarction contributed to the development of contrast-induced nephropathy during coronary angiography in compared with a less severe lesion in the form of unstable angina (Figure 2). One gets the impression of the presence of a mutually aggravating effect of CIN and coronary pathology on each other.

![Cumulative Proportion Surviving](image.png)

**Figure 2.** Survival chart of patients (development of contrast-induced nephropathy) with the development of unstable angina pectoris or myocardial infarction. Gehan's Wilcoxon Test WW = 1095,0, Sum = 4238*10², Var = 96921, Test statistic = 3,52, p = 0,0004
4. Discussion
According to the literature, the likelihood of developing kidney dysfunction in patients with cardiovascular disease is significantly higher than in the general population. Thus, according to NHANES III (Third National Health and Nutrition Examination Survey), a combination of any two risk factors for developing cardiovascular diseases leads to a decrease in glomerular filtration rate of less than 60 ml / min / 1.73 m² by a factor of 3.7, than with conserved kidney function. In addition, according to the results of a meta-analysis performed in 2002 by J. Suwaidi et al., in acute coronary syndrome, a slight decrease in renal function was accompanied by a higher mortality rate and frequency of repeated myocardial infarction during 6 months of follow-up [3].

According to the results of numerous clinical studies, the role of renal dysfunction as a factor worsening the prognosis in acute coronary syndrome has been proved. According to the Canadian register GRACE (Global Registry of Acute Coronary Events), in patients with myocardial infarction with ST segment elevation, a decrease in GFR to 30-60 ml / min increases the risk of death by 2.09 times; with GFR <30 ml / min, the probability of an adverse outcome increased by 4 times.

In addition, it has been proven that even moderate renal dysfunction is an independent predictor of myocardial infarction and death [4-6]. A retrospective analysis in 16,248 patients who underwent administration of a contrast medium showed that even a slight decrease in renal function can lead to a huge increase in mortality, regardless of other risk factors [7-9].

During the first year after administration of the contrast agent, the mortality rate in patients with chronic kidney disease that existed before the contrast remains very high. In particular, in the course of our work, it was demonstrated that the decrease in GFR after coronary angiography was associated with the development of subsequent non-fatal myocardial infarction, as well as non-fatal vascular events.

During the first year after administration of a contrast medium, the mortality rate in patients with chronic kidney disease, which existed before contrast, remains very high.

Mortality reaches 45.2% in the group of patients on hemodialysis, is 35.4% in patients with impaired renal function and 19.4% in patients with intact renal function. According to the Mayo Clinic register, mortality within 1 year after PCI is directly correlated with creatinine clearance, making up 1.5% among patients with creatinine clearance of more than 70 ml / min and 18.3% among patients with creatinine clearance of less than 30 ml / min [10].

According to our Kaplan-Meier survival analysis, we showed a statistically significant effect of contrast-induced nephropathy on the risk of death from myocardial infarction in patients with acute coronary syndrome.

5. Conclusion
Thus, using a rank correlation analysis, a preliminary analysis of the relationship between the increase / decrease in blood creatinine, blood urea, GFR (Cockcroft-Gault) and GFR (CKD-EPI) after coronary angiography with vascular events was performed. A Kaplan-Meier survival analysis demonstrated the statistically significant effect of contrast-induced nephropathy on the risk of death from myocardial infarction in patients with long-term acute coronary syndrome.

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