In-hospital Death Prediction by Multilevel Logistic Regressin in Patients with Acute Coronary Syndromes

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Abstract

Background: The odds of death of patients with acute coronary syndromes (ACS) in non-PCI (percutaneous coronary intervention) hospitals in the Czech Republic change depending on a number of factors (age, heart rate, systolic blood pressure, creatinine, Killip class, the diagnosis, and the number of recommended medications and treatment of ACE-inhibitor or sartan).
Objectives: We present a detailed description of multilevel logistic regression applied in the derivation of the conclusion described in the Background, namely we compare multilevel logistic regression with logistic regression.
Methods: The above mentioned clinical findings have been derived on the basis of data from the three-year (7/2008-6/2011) registry of acute coronary syndromes ALERT-CZ (Acute coronary syndromes – Longitudinal Evaluation of Real-life Treatment in non-PCI hospitals in the Czech Republic). A total of 32 hospitals contributed into the registry. The number of patients with ACS (n=6013) in the hospitals varied from 15 to 827.
Results: The likelihood ratio test showed that the independence of medical outcomes across hospitals cannot be assumed ($p<0.001$, the variance partition coefficient VPC=8.9%). For this reason, we chose multilevel logistic regression to analyse data, specifically logistic mixed regression (the hospital identity was a random effect). The calibration properties of this model were very good (Hosmer-Lemeshow test, p=0.989). The total discriminant ability of the model was 91.8%.
Conclusions: Considering some differences among hospitals, it was appropriate to take into account patient affiliation to various hospitals and to use multilevel logistic regression instead of logistic regression.

Keywords

Multilevel logistic regression, acute coronary syndromes, risk factors, in-hospital death

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1 Introduction

During the past more than 10 years two important algorithms that estimate the risk scores in patients with acute coronary syndromes (ACS) have been derived [1]. The first is the risk score TIMI (Thrombolysis in Myocardial Infarction), which estimates the risk of death, myocardial infarction, or recurrent ischemia occurred by 14 days after hospitalization [2]. The risk score is available on the Web at http://www.timi.org/. The value of

the risk is estimated based on the following seven risk (binary) variables: at least 65 years of age, at least three risk factors for coronary artery disease (CAD) present (diabetes, cigarette smoking, hypertension, low HDL cholesterol, family history of premature CAD), known CAD, at least two episodes of angina chest pain in the last 24 hours, the use of aspirin in the last seven days, ST-segment deviation of 0.05 mV or more, and elevated serum markers for myocardial necrosis.

The second algorithm is the risk score of GRACE (Global Registry of Acute Coronary Events), which is available on the Web http://www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html [3]. To estimate the risk of death or myocardial infarction during hospitalization and in the following six months, eight variables are used: age, Killip class (a classification of seriousness of heart failure), systolic blood pressure, ST-segment deviation, cardiac arrest at admission, serum creatinine, elevated serum markers for myocardial necrosis and heart rate.

Monhart et al. [4] found that the odds of death in non-PCI (percutaneous coronary intervention) hospitals in the Czech Republic in patients with ACS change depending on a number of factors, on which are also based the risk scores TIMI and GRACE. Specifically, the odd of death depends on age, heart rate, systolic blood pressure, creatinine, Killip class, the diagnosis (ST-segment elevation myocardial infarction (STEMI), non-STEMI, unstable angina pectoris (UAP)), the number of the received recommended medications (aspirin, clopidogrel, unfractionated and low molecular weight heparin or fondaparinux, statin, beta-blocker) and treatment of angiotensin-converting-enzyme inhibitor (ACEI) or sartan. In this paper we present a detailed description of statistical analysis by multilevel logistic regression deriving these conclusions.

2 Material

ALERT-CZ (Acute coronary syndromes – Longitudinal Evaluation of Real-life Treatment in non-PCI hospitals in the Czech Republic) is a three-year registry of acute coronary syndromes (1 June 2008 - 30 July 2011), which had been organised by Cardiocentrum of 3rd Faculty of Medicine of Charles University in Prague under the auspices of the Czech society of cardiology. The participation of hospitals in the registry was voluntary. However, none of the hospitals was allowed to have any department of interventional cardiology (non-PCI hospitals). The intervention treatment (if indicated) was provided in any other PCI hospital. A total of 32 non-PCI hospitals from the Czech Republic were involved into the registry for a short time or over a long period.

Data collection was conducted using an electronic form. The application for data collection was created by European Centre for Medical Informatics, Statistics and Epidemiology, which also centrally collected anonymous data. In addition to the basic characteristic of patients (sex, age and cardiovascular risk factors), drug therapy (chronic, acute, at discharge), the severity of the disease, the clinic course of the disease, its complications and the treatment outcomes were recorded in the registry. A total of 7240 disease cases are in the registry. If a person has had more cases of ACS in the reference period, only the data of the first ACS (primarily admitted to non-PCI hospitals) was included in the present analysis (6013 patients).

3 Statistical methods

The influence of potential factors on in-hospital death was analysed using multilevel logistic regression (also called hierarchical logistic regression), and specifically using logistic regression with mixed effects (the identity of the hospital was a random effect), which belongs to generalized linear mixed models (GLMM). When estimating log-likelihood, Laplace and Gauss-Hermite approximations were used. In addition to multilevel logistic regression we also applied traditional logistic regression. To compare the two models we used likelihood ratio test and variance partition coefficient (VPC). Statistical significance of the individual predictors in the model was established using Wald test and likelihood ratio test. The overall fit of the model was assessed on the basis of the values of deviance, Akaike information criterion (AIC), Hosmer-Lemeshow test and ROC (receiver operating characteristic) curve with c-index. We also graphically analysed standardized Pearson residuals and estimated the coefficient of dispersion. In the text the symbol n indicates the number observations. For statistical analysis we used statistical software R version 2.8.0 (libraries lme4, MASS) [5].

4 Results

A total of 32 hospitals contributed into the registry. The number of patients with ACS (n=6013) in hospitals ranged between 15-827 and the time involvement in the registry varied between 0.2-3.0 years (media 2.6 years). The basic characteristics of the patients are shown in Table 1.

Our study was a multicentre study because patients were recruited from the different hospitals (centres). From this reason of hierarchical data organization (hospital-patient) there are possible two kinds of way of the statistical analysis, either to take account of the hierarchical data structure or not to take into account. Table 2 summarizes the results of multilevel logistic regression (taking into account the hierarchical structure of data) and logistic regression (not reflecting the hierarchical structure of data). Laplace approximation was used to estimate the parameters of multilevel logistic regression in Table 2 (the Gauss-Hermite approximation yielded the similar results).

When comparing the 95% confidence intervals in Table 2 it is seen at the first sight that there are not substan-

Table 1: Patients characteristics at admission.

Characteristic	Relative number	n
Age $\leq$ 70 years	53.5%	5987
Heart rate $\leq$ 80 pulses/min.	51.6%	5999
Systolic blood pressure $\leq$ 80 mmHg	58.9%	5985
Creatinine $\leq$ 100 μmol/l	39.3%	5907
Women	41.0%	6013
Diabetes mellitus	36.9%	5996
Hypertension	77.7%	5994
Hyperlipidemia	52.9%	5957
Smokers	28.0%	5925
Recurrence IM	29.5%	5990
Killip class I	74.3%	5996
STEMI	19.0%	5989
Five recommended drugs	41.1%	5922

tial differences between the results of both methods, at least in terms of significance. The intercept represents the odds of death in the "average" hospital, i. e. when the values of the explanatory variables are not taken into account. Specially, the continuous explanatory variables (age, systolic blood pressure) take on the value 0 and the categorical explanatory variables (heart rate, creatinine, Killip class, diagnosis, number of recommended drugs, ACEI/Sartan) are kept at the baseline level (hear rate $\leq$80 pulses/min, creatinine $\leq$100 μmol/l, Killip class = I, diagnosis = STEMI, number of recommended drugs = 5, ACEI/Sartan = Yes). The odds of in-hospital death were increased with increasing age. Patients with heart rate 80-155 pulses/min had the higher odds of death than patients with heart rate $\leq$80 pulses/min. Unlike persons with heart rate 80-155 pulses/min, whose the odds of death was not significantly different from persons with heart rate $\leq$ 80 pulses/min. Higher values of creatinine (over 100 μmol/l) increased the odds of death in comparison with creatinine 100 μmol/l and less. The odds of death were also increased with a higher Killip class, with decreasing number of recommended drugs (aspirin, clopidogrel, unfractionated and low molecular weight heparin or fondaparinux, statin, beta-blocker) received at admission, and if ACE-inhibitor or sartan therapy was not started early. On the other hand, the odds of death were decreased with increasing systolic blood pressure, and the lower odds of death were also observed among persons with final diag-

Table 2: Variables that influence the odds of in-hospital death.

Variables+)		n	Multilevel logistic regression			Logistic regression		
			Odds ratio	95% CI		Odds ratio	95% CI	
Intercept		5734	0.002	0.002	0.006	0.003	0.001	0.010
Age	[by 10 years]	5734	1.92	1.69	2.19	1.90	1.68	2.16
Heart rate [pulses/min]	$\leq$80	3265	1.00			1.00		
	(80-155]	2408	1.46	1.13	1.89	1.44	1.12	1.84
	>155	61	0.56	0.21	1.49	0.53	0.20	1.39
Systolic blood pressure	[by 10 mmHg]	5734	0.81	0.78	0.85	0.81	0.77	0.84
Creatinine [μmol/l]	$\leq$100	3567	1.00			1.00		
	>100	2167	2.29	1.76	2.97	2.41	1.87	3.11
Killip class	I	4251	1.00			1.00		
	II	1145	2.26	1.72	2.98	2.55	1.96	3.31
	III-IV	338	2.99	2.07	4.31	3.34	2.34	4.77
Diagnosis	STEMI	983	1.00			1.00		
	non-STEMI	3205	0.65	0.48	0.86	0.71	0.54	0.94
	UAP	1546	0.02	0.01	0.05	0.03	0.01	0.09
Number of recommended drugs	5	2362	1.00			1.00		
	4	1560	1.52	1.04	2.23	1.16	0.80	1.66
	3	1039	2.83	1.93	4.14	2.08	1.46	2.96
	2	532	2.91	1.86	4.55	1.77	1.17	2.68
	0-1	241	8.07	4.90	13.30	5.36	3.37	8.52
ACEI/Sartan	Yes	3995	1.00			1.00		
	No	1739	1.82	1.37	2.42	1.78	1.36	2.33

+) If we applied to the ordinal explanatory variables (heart rate, Killip class, diagnosis and number of recommended drugs) the orthogonal polynomial contrasts (under the assumption that the levels are equally spaced), there was also significant polynomial effects of those variables on the odds of death.

Table 3: Akaike information criterion (AIC), deviance and degree of freedom (df).

Model	AIC	Deviance	df	Reduction		p
				Deviance	df	
Multilevel logistic regression						
Intercept	3152.9	3148.9	5732			
Age	2849.1	2843.1	5731	305.8	1	< 0.001
Heart rate	2787.5	2777.5	5729	65.6	2	0.004
Systolic blood pressure	2471.6	2459.6	5728	317.8	1	< 0.001
Creatinine	2325.7	2311.7	5727	147.9	1	< 0.001
Killip class	2211.0	2193.0	5725	118.7	2	< 0.001
Diagnosis	2053.5	2031.5	5723	161.5	2	< 0.001
Number of recommended drugs	1913.3	1883.3	5719	148.1	4	< 0.001
ACEI/Sartan	1898.5	1866.5	5718	16.9	1	< 0.001
Logistic regression						
Intercept	3174.3	2988.9	5733			
Age	2861.0	2699.9	5732	289.0	1	< 0.001
Heart rate	2799.0	2652.4	5730	47.5	2	< 0.001
Systolic blood pressure	2484.6	2371.7	5729	280.7	1	< 0.001
Creatinine	2333.3	2283.8	5728	87.8	1	< 0.001
Killip class	2213.6	2173.8	5726	110.0	2	< 0.001
Diagnosis	2082.9	2039.3	5724	134.5	2	< 0.001
Number of recommended drugs	1968.6	1940.6	5720	98.6	4	< 0.001
ACEI/Sartan	1953.2	1923.2	5719	17.4	1	< 0.001

noses non-STEMI and UAP (compared with the diagnosis STEMI). The only substantial difference between both methods was in the number of the received recommended drugs. Logistic regression did not identify significantly higher odds of death in persons with four received recommended drugs compared with persons with five drugs (OR=1.16; p=0.435). In contrast, multilevel logistic regression showed this difference as a significant (OR=1.52;

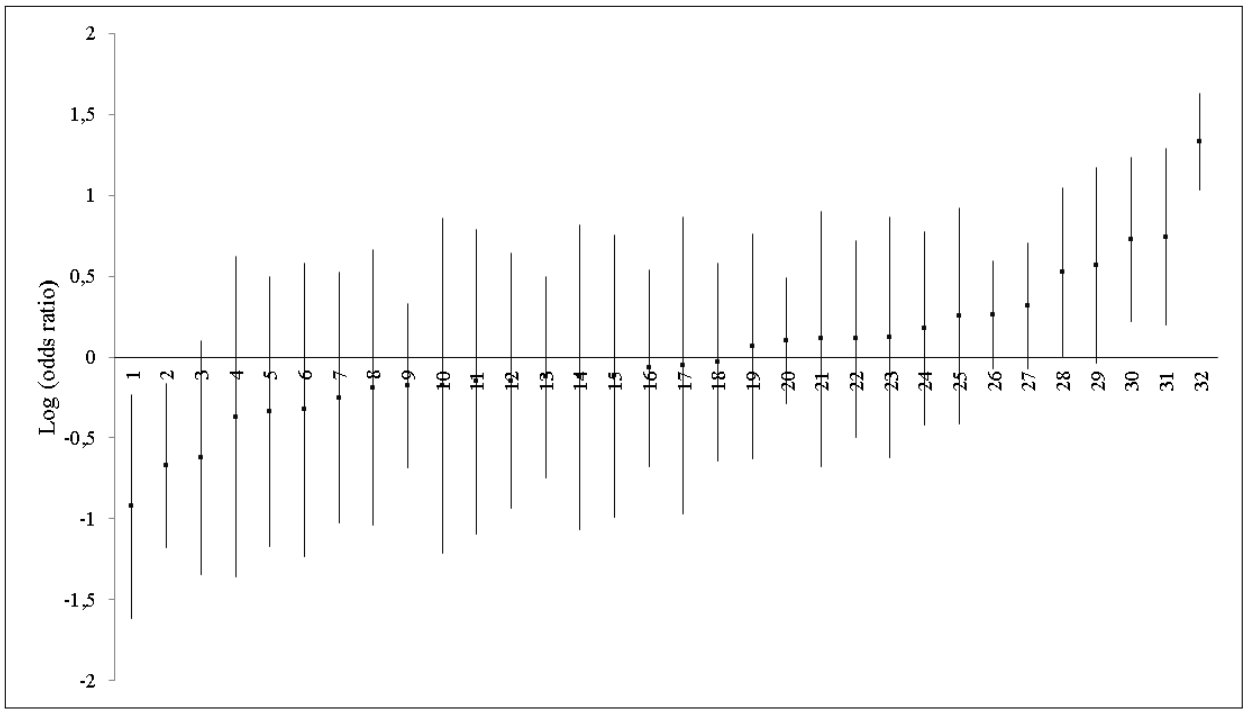

Figure 1: 95% confidence intervals of the natural logarithm of odds ratio of in-hospital death in the 32 hospitals (multilevel logistic regression).

p= 0.031). With the exception of this single difference in significance, let us note that the values of the estimated odds ratio are strongly shifted between both methods in some cases (e.g. in the number of recommended drugs).

The Akaike information criterion in Table 3 is the index that is used for the evaluation of the complexity of the model. Lower values of AIC indicate better model. Deviance measures the appropriateness of the model. The reduction in deviance for each variable, added sequentially first to last, is shown in Table 3. Each variable reduced the deviance significantly. Overall, the significant part of deviance was explained by the final multilevel logistic and logistic regression models (in both cases p<0.001).

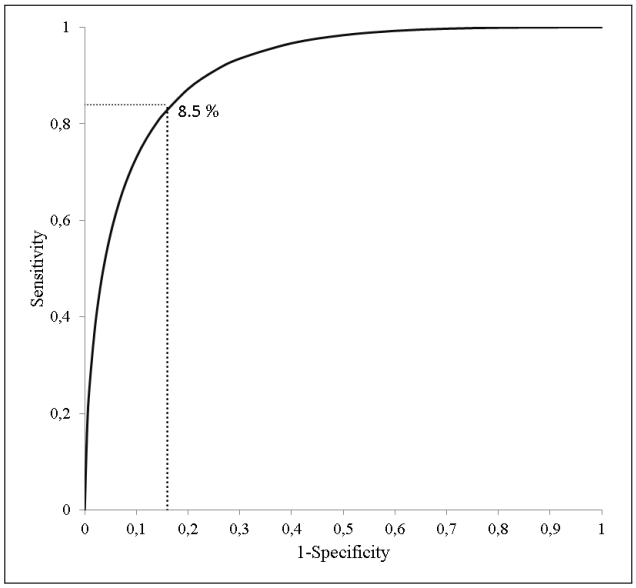

Figure 2: ROC curve - dotted lines mark sensitivity of 83.9% and specificity of 84.0% with threshold risk value of 8.5% (multilevel logistic regression).

When we compare the log-likelihoods of both model, the log-likelihood of multilevel logistic regression (-933.2; df=16) is significantly higher than that of logistic regression (-961.6; df=15), p<0.001. From this reason, we maintain that there is a statistically significant difference in the odds of death among hospitals. Because the VPC is 0.089, we estimate that 8.9% of the total residual variance is due to just hospitals. Although from the statistical point of view, this is a significant difference, from a clinical point of view, the difference may not be significant.

Let us go specify the differences among hospitals. Model of multilevel logistic regression includes, in addition to the intercept of Table 2, which is common for all hospitals, yet another intercepts specific to each hospital (hospital random intercept). Figure 1 illustrates the estimated natural logarithms of odds of in-hospital death in individual hospitals compared to zero value representing the "average" hospital. For a large part of the hospitals, their 95% confidence intervals overlap zero. In fact this means that the odds of in-hospital death in these hospitals did not differ from the average at the 5% significance level. The hospitals, whose 95% confidence intervals do not overlap zero and are above (bellow) the zero line, have the above-average (below-average) odds of in-hospital death. It is, however, necessary to realise that the hospitals with the small sample size have the wide confidence intervals (their estimates values are less accurate) compared with the hospitals with the large sample size. For example, the 95% confidence interval of 10th hospital (n=15) is much wider than 32nd hospital (n=827).

Let us examine in detail the predictive properties of multilevel logistic model. Table 4 shows the observed and expected numbers of in-hospital death across the groups defined on the basis of the percentiles of the estimated risk (probability) of death. There was not any significant difference (Hosmer-Lemeshow test, p=0.989) between the observed and expected numbers of death, and therefore the calibration properties of the model are very good. The highest observed (44.6%) and expected (44.8%) numbers of death were in the group of people with a calculated risk higher than 21.5% (tenth percentile). The discrimination property of multilevel logistic regression model was evaluated by ROC curve, Figure 2. The curve for each value of risk represents the proportion of people with the positive test in the group of the not dead people (1-specificity),

Table 4: Observed and expected relative numbers of in-hospitality deaths (multilevel logistic regression).

			Relative number	
Risk percentile	**Risk**	**n**	**Observed**	**Expected**
1	<=0.03%	574	0.0%	0.0%
2	(0.03%, 0.13%]	573	0.0%	0.1%
3	(0.13%, 0.37%]	573	0.2%	0.2%
4	(0.37%, 0.75%]	574	0.5%	0.5%
5	(0.75%, 1.38%]	573	0.9%	1.0%
6	(1.38%, 2.53%]	573	1.7%	1.9%
7	(2.53%, 4.66%]	574	3.5%	3.5%
8	(4.66%, 9.07%]	573	6.3%	6.6%
9	(9.07%, 21.50%]	573	15.0%	13.7%
10	>21.50%	574	44.6%	44.8%

and the ratio of people with the positive test in the group of the dead people (sensitivity). The best results were achieved for the threshold risk value of 8.5%, when the values of sensitivity (83.9%) and specificity (84.0%) were high. This means that 83.9% of the dead patients had the risk at least 8.5% (positive test), and 84.0% of the not dead patients had the risk under 8.5% (negative test). The total discriminant ability of the model was 91.8% (size of the area under the curve, c-index=0.918).

5 Discussion

The task of our study was to determine what factors influence whether a patient with ACS dies or does not during his/her stay in non-PCI hospital. Because mortality in some studied subgroups was larger than 10% (e.g. Killip class IV), we preferred (binary) logistic regression to Poisson regression. To be able to apply the traditional logistic regression model, observations within a sample must be independent. In our case, this means that the entries in the registry are not correlated with each other. Our study, however, was a multicenter study (a total of 32 hospitals contributed to the registry). If we did not take into account of hierarchical (hospital-patient) data structure, we would automatically assume that therapeutic results (and hence the medical procedures) are not dependent on which hospital the patient resides. Is it possible to make this assumption? Statistical tests showed that the independence of the outputs cannot be entirely assumed among hospitals. Although the differences between hospitals were not essential from our point of view, it was preferable to apply multilevel logistic regression, namely the logistic mixed regression, which took into account of patient affiliation to various hospitals. Hospital equipment, its accessibility, quality medical personnel and adherence to guidelines can have influence on the medical results.

Principles of multilevel modelling were published e.g. in [8, 9, 10, 11, 12]. Other papers on multilevel modelling can be found at the UCLA website (University of California, Los Angeles, Institute for digital research and education) and at the web sites of the Centre for multilevel modelling in Bristol. Austin et al. compared traditional logistic regression with multilevel logistic regression for patients hospitalized with acute myocardial infarction in Ontario, Canada [13]. The authors emphasize that false inferences can be caused by ignoring data structure. Their logistic regression models increased a level of significance for the effects of variables measured at the hospital-level compared a level of significance indicated by the multilevel model. Multilevel models have been applied for statistical analysis in a number of studies dealing with cardiovascular indicators across hospitals, e.g. [14, 15].

Multilevel models are equivalently called hierarchical models. The term of multilevel models is the term general. It reflects that the model works with some levels of data dependencies, either in the framework of the clusters (in our case they are hospitals), or repeated measurements of individuals. Multilevel model estimates individual-specific effects so called random effects for each level of dependence. If there are both fixed effects, which are the same across all levels of dependencies, and random effects, we are talking about mixed models. Models involving just random effects are called random effect models (variance components model). Models without random effects are called fixed effect models. These are based on the assumption that the observations are independent. Generalized linear models, which are estimated using the maximum likelihood method, belong to fixed effect models. If the assumption of independence of data cannot be made, we can use instead of the maximum likelihood method the generalized estimating equations (GEE) method. GEE is able to take account of data dependence, although in a different way than multilevel models [9]. Unlike them, the dependencies are incorporated into the parameter estimates (fixed effects), which then represent the so-called population-average effects. Population-average model is often referred to as marginal model in contrast to mixed model called individual-specific model. GEE method extends the application of GLM to correlated data. Because our goal was to estimate the effects of predictors on the fate of specific individuals (individual-specific effects) and to quantify the impact of the hospitals, we preferred mixed regression model to GEE.

Let us go back to the conclusions of this model. An adverse effect on our findings may be the fact that many hospitals were not involved in the registry for all-time duration of the registry and in some hospitals there was a small number of patients (for this reason we could not analyse the data in a more complex model, such as with random effect of the trend of the age). The majority of patients (89%) did not have at disposal time from first symptoms of ACS to medical facility contact. The results may be also influenced by the length of stay in hospital (median 5 days, range 0-120 days), which can be dependent not only on the patient's health but also the strategic practices in hospitals. However, when we restrict to the odds of death in first 14 days from hospital admission (87% of deaths were registered in the first 14 days), the results were similar. Despite these shortcomings, our conclusions are more or less in the accordance with the risk scores TIMI and GRACE. Odds of death in patients with ACS in non-PCI hospitals influenced age, heart rate, systolic blood pressure, creatinine, Killip class, diagnosis, the number of the received recommended drugs and ACE-inhibitor or sartan treatment. More detailed clinical description of these conclusions is presented in another publication [4].

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