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The positive stable frailty model application to assess survival effect of health care reform on patients with acute myocardial infarction

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Abstract
Background: notoriously known worldwide leading cause of disability and mortality in adults cardiovascular diseases experience their rise in Ukraine, taking formidable death tall of 37 960 people with vicious rate 1 person per minute being the highest among European countries**.** Acute myocardial infarction (AMI) leads the way. The aim was to unveil the impact of ongoing health care reform to survival of patients with AMI incident in Vinnitsa region, Ukraine. **Data:** organised by cohort design. Control cohort comprised 400 patients with first episode of AMI treated in cardiological Vinnitsa city department on the eve of reform, namely 2005-2006 years. Experimental cohort consisted of 400 patients with first episode of AMI treated in Vinnitsa regional cardiological centre in 2008-2009 years at the moment of reform initiation and opening of the centre. Diagnoses comprised ICD-10 codes I21.0-I21.3, I21.4, I21.9, I22. The most pervasive localization happened to be anterior (33,2%), posterior (37,4%), and frontolateral (12,0%). AMI-related lethal cases happened in first 5 years from the hospitalization were investigated. In given time period 270 out of 800 patients died, that is 33,7%. **Methods:** positive stable frailty model processed by SAS macro. **Results:** after adjustment on important clinical and biological confounders the implementation of reform rendered hazard reduction effect of the largest magnitude among other covariates (β=-0,179, p=0,029). Basic risk of lethality because of reform dropped by 19,6%, saving additional 0,8788 survival months to patient in first 5 years from AMI incident. It was unveiled that main effect (84,2%) was related particularly to improvement in timeliness of medical care.

Keywords: acute myocardial infarction, survival, medical reform, Ukraine.

1. Introduction

By our preliminary investigations the linchpin of pivotal importance to improve survival in AMI patients is timeliness of treatment and hospitalization (RR=1,44) [2]. Related derivative is severity of patient's condition at hospitalization (RR=1,98), exigent administration of β-blockers (1-RR=0,549), along with reperfusion (1-RR=0,35). Treatment intensity and accomplishment is yet another significant factor to reduce lethality (RR=2,767) [3]. Widely discussed issues in research publications are effectiveness of intensive treatment procedures, thrombolytic therapy, PCI, CABG are most popular among them, as well as severity of patient's condition, comorbidity load (mostly measured by Charlson's index), ejection fraction and systolic blood pressure values at hospitalization, presence of pathological Q, instances of heart arrest before or at hospitalization, patient's gender and age [8].

Whereas ongoing health care reform (HCR) greatly influenced all abovementioned issues the necessity to make in process assessments is obvious. Many innovations were introduced in emergency care; actually highly interspersed services and facilities were united since 2009 into emergency medicine with compartmentalized budgeting, management, and greatly enhanced capabilities. Most efficiently it was implemented in Vinnitsa region. Another remarkable innovation was establishment of Vinnitsa regional centre of cardio-surgery in 2008. They serve procedures of percutaneous coronary intervention (PCI) free of charge. Among obvious advantages there are: extraterritorial organization of emergency cases management, attenuation of geographical disparity in coverage with emergency care services.

2. Materials and Methods

Data were organised by cohort design. Control cohort comprised 400 patients with first episode of AMI treated in cardiological Vinnitsa city department on the eve of reform, namely 2005-2006 years. Experimental cohort consisted of 400 patients with first episode of AMI treated in Vinnitsa regional cardiological centre in 2008-2009 years at the moment of reform initiation and opening of the centre. Diagnoses comprised ICD-10 codes I21.0-I21.3, I21.4, I21.9, I22. The most pervasive localization happened to be anterior (33,2%), posterior (37,4%), and frontolateral (12,0%) AMI. AMI-related lethal cases happened in first 5 years from the hospitalization were investigated. In given time period 270 out of 800 patients died, that is 33,7%. Relevant covariates such as trombolytic therapy, PCI and CABG procedures administration, severity of patient's condition, comorbidity load (measured by Charlson's index), ejection fraction and systolic blood pressure values at hospitalization, presence of pathological Q, instances of heart arrest before or at hospitalization, patient's gender and age were observed.

We have chosen flexible semi-parametric positive stable frailty (PSF) model to study survival effect of health care reform. Frailty model incapacitates the assessment of individual propensity to survive, incorporating unobserved patient's characteristic influenced survival differently across patients. Overlooking frailties entails biased and inefficient estimation of survival effects. Frailty model basically incorporates three main components:

1. Basic hazard function, changeable in time.
2. Function of factors, modifying basic hazard.
3. Frailty distribution.

These components were specified as following. We did not specify basic hazard function parametrically instead it was estimated semi-parametrically by the Aalen estimator [5]. Doing so, we avoided possibility of basic hazard function misspecification. We exploited classical exponential function of predictors that insures proper space of predicted survival values. We opted for positive stable distribution (PSD) of frailties:

$$f(z) = \frac{1}{\pi}\sum_{k=1}^{\infty}(-1)^{k+1}\frac{\Gamma(k\gamma+1)}{k!}z^{-k\gamma-1}\sin(k\gamma\pi) \quad \text{............(1)}$$

with z – frailties values, z≥0, γ – single parameter of PSD, that in fact is inverse dispersion measure (i.e. precision of PSD), with bounds 0 <γ≤1, Γ(•) – Gamma function. In special case with γ=1 distribution degenerates to constant mass point z=1, evidencing on the equal individual propensities to survive across cohort members. To the contrary, γ proximity to zero bares evidence on high heterogeneity of frailties distribution. We opted for PSD (1) yet for another reason. PSD is unique statistical distribution, that insures proportionality of survival effects in time after integration out frailties. In simple case of binary factor X hazard ratio at levels 1 against 0 doesn't depend upon time *t*:

$$\frac{\mu(t \mid X=1)}{\mu(t \mid X=0)} = e^{\gamma\beta} \quad \text{..(2)}$$

Besides, (2) secures simple proper expression in Laplace transformation: $L(u) = e^{-u^{\gamma}}$, exploited to derive unconditional survival function *S(t)*:

$$S(t) = e^{-H(t)^{\gamma}}, \quad H(t) = \int_0^t h(u)du \quad \text{........................(3)}$$

and *H(t)* – function of cumulative hazard *h(t).*

Model coefficients (survival effects) *β* and frailty dispersion parameter γ were reckoned by two semi-parametric methods: EM (*expectation-maximization*) and PL (*penalized likelihood*) algorithms. Each operates with classical log-likelihood function (LL) for PSF conditional proportionate hazards model:

$$L = \sum_{i=1}^{N}\sum_{j}^{M}\left\{I_{ij}\left[\beta X_{ij} + \ln h(t_{ij})\right] - z_i H(t_{ij})\exp(\beta X_{ij})\right\} \quad (4)$$

with i – patient's id number: i ϵ{1 … N}, N – sample size (800), j – month's id number: j ϵ{1 … M}, M =12x5=70, I_{ij} – right censoring indicator for *i*th patient in *j*th month (1 – demised, 0 – censored); z_i – *i*th patient's frailty score. While frailties are time constant, model may incorporate dynamic predictors X_{ij}. Full formulae (4) expression includes constants $I_{ij}*ln(z_i)$, latter don't influence (4) maximisation for their derivatives by *β* tantamount to zero. Maximisation of (4) constitutes M-step of EM algorithm. By derived vectors *β* and *H* E-step (*expectation*) takeovers. In E-step expected frailties scores $E(z_i|\beta,X_i)$ are calculated by formulae (Wang et al., 1995):

$$E(z_i) = \frac{E\left[z_i^{Di+1}\exp(-H_i z_i)\right]}{E\left[z_i^{Di}\exp(-H_i z_i)\right]} \quad \text{..............................(5)}$$

and $D_i = \sum_{j=1}^{M} I_{ij}$ is cumulative outcome (death / censored) of *i*th patient. In this study z_i assumes PSD with expectations [6]:

$$E\left[z^q \exp(-sz)\right] = \left(\gamma s^{\gamma-1}\right)^q \exp\left(-s^{\gamma}\right) J[q,s]$$
$$q = 0,1,\ldots; \quad s > 0$$
$$J[q,s] = \sum_{m=0}^{q-1}\Omega_{q,m}s^{-m\gamma} \quad \text{.........(6)}$$

wherein Ω_{qm} stands for polynominal of degree *m*. Having lethal case can happen once, D_i (5) values are confined to integers 0 or 1, in turn q_i (6) possible values 0, 1, and 2, therefore degree *m* in (6) are limited to 0 and 1, that greatly simplified calculus, whereas polynominal given recursively by:

$$\Omega_{q,0} = 1;$$
$$\Omega_{q,1} = \Omega_{q-1,1} + \Omega_{q-1,0}\left\{(q-1)/\gamma - (q-m)\right\}; \quad \text{............(7)}$$

Generally polynominal constituents numerous and can't be expressed in close form:

$$\Omega_{q,q-1} = \gamma^{1-q}\Gamma(q-\gamma)/\Gamma(1-\gamma); \quad \text{...........................(8)}$$

Putting reckoned by (5 – 7) expected scores z_i into (4) EM

algorithm proceeds to M-step with output of modified vectors *β* and *H* and so forth. Vector *H* we calculate by modification of Aalen estimator (Wang et al., 1995).
We modified the algorithm of SAS PS Frailty macro (available download http://www.biostat.mcw.edu/SoftMenu.html). The initiate values for zero step of algorithm were estimates of *β* and *H*, obtained by PL algorithm that greatly improved solving. Furthermore, instead of (8) with Gamma function we exploited much simpler close form polynominal expression (7).
In summary, the estimation routine proceeds with four consequent steps:

Step 0. Estimates of *β* and *H*, obtained by PL algorithm together with initial frailties scores z_i=1 (implying γ=1) are used as input to (8) to proceed with M-step.

Step 1. Fixes γ. Using the current values of γ, *β*, and *H* algorithm computes expected frailties scores $E(z_i|\beta,X_i)$ by formulae (5 – 7), E-step.

Step 2. Having z_i from Step 1 vectors *β* and *H* are updated by (4) (M-step).

Step 3. Iterates between Steps 1 and 2 until convergence of *β*.

Step 4. Repeats Steps 1-3 to construct the profile likelihood (9) dependent on γ only. Search for γ value that maximises (9). Maximisation was implemented by golden search method after set bounders on solution space by grid-search technique.

$$Lprofile = \sum_{i=1}^{N} \left\{ D_i \left[\ln\gamma + (\gamma - 1)\ln H_i \right] - \left[H_i \right]^{\gamma} + \ln\left\{ J\left[D_i, H_i \right] \right\} \right\} + \\ + \sum_{j=1}^{Mi} \left\{ I_{ij} \left[\beta(\gamma) X_{ij} + \ln h(t_{ij}) \right] \right\} \qquad (9)$$

3. Results and Discussion

Linear predictor is set by factors that indicate accessibility, timeliness, quality of services, as well as covariates known to be moderators of survival in AMI patients [7, 8] to make adjustment for. So we include covariates: treatment with thrombolytic therapy, PCI, CABG severity of patient's condition, comorbidity load (measured by Charlson's index), left ventricular ejection fraction (LVEF) and systolic blood pressure (SBP) values at hospitalization, presence of pathological Q, instances of heart arrest before or at hospitalization, patient's gender and age.
Estimates of significant effects of PSF model by EM algorithm are displayed in Table 1. Non-significant effects discarded from display.

Table 1: Estimates of significant effects by EM algorithm, PSF model

№	Factors	β	m	χ^2	df	p	RR
1	Health care reform	-0,179	0,082	4,777	1	0,029	0,836
2	Age (+1 over 40)	0,013	0,006	5,652	1	0,017	1,013
3	Gender (m=1/f=0)	-0,275	0,121	5,194	1	0,023	0,759
4	Delay in hospitalisation over 10 hours	0,362	0,118	9,485	1	0,002	1,436
5	Severe condition*	0,197	0,072	7,445	1	0,006	1,218
6	Charlson's index >=5	0,179	0,100	3,198	1	0,074	1,196
7	LVEF <=0,3*	0,333	0,119	7,880	1	0,005	1,395
8	SBP >170*	0,321	0,185	5,169	1	0,023	1,378
9	+Q	0,169	0,070	5,762	1	0,016	1,184
10	Heart arrest*	0,483	0,247	3,838	1	0,050	1,621
11	PCI, CABG	-0,271	0,103	6,905	1	0,009	0,763
12	Trombolytic therapy	-0,236	0,104	5,195	1	0,023	0,790

PSD dispersion parameter γ =0,305
*at hospitalization
Columns headers are:
β estimate of regression coefficient;
m standard error of regression coefficient estimate;
χ^2 chi-square distribution quintile serving test statistic on effect significance;
df test's degrees of freedom;
p chi-square test based significance of effect;
RR relative risk.

The main effect of interest was impact of health care reform, proving to be significant after adjustment for covariates (β=-0,179, p=0,029). By RR value (0,836), we can conclude that HCR decreased hazard of lethality by 19,6%, that is [1/RR-1]*100%.
Taking into consideration organizational functionals improved by HCR, it appeared that it's timeliness of treatment that was the crucial pivot in reduction of lethality (hazard) in AMI patients. In case of delay with hospitalization over 10 hours hazard experienced increase shift by 43,6%, that is [RR-1]*100%.
Effectiveness of thrombolytic therapy, PCI, CABG closely related to timeliness of administration, first 10-12 hours from incident in particular.
Administration of thrombolytic therapy in first 10-12 hours reduced basic risk of lethality by 26,6%, while timely performed PCI or CABG reduced hazard by 31,1%. It corresponds with conclusions of other researches, indicating up to two-fold reduction with distinct age model, i.e. maximal reduction in younger patients groups, and even increase in

hazard in patients aged above 70 [9, 10, 11, 12].

Severe patient's condition at hospitalization increased basic risk of lethality by 21,8%. Heavy comorbidity load (Charlson's index >=5) increased basic risk of lethality by 19,6% with marginal significance p=0,074. Independent researches stipulated RR approaching 2 with Charlson's index >=4 [13, 14]. That high RR values may be to some extend explained by the lack of adjustment for the other important confounders.

Low ejection fraction (values <= 0,3%) at hospitalization increased basic risk of lethality by 39,5%. Values of systolic blood pressure more than 170 mm. Hg at hospitalization increased basic hazard by 37,8%. Other studies [8, 10, 14] arrived at the likewise RR values with typical range 1,2-2,0.

Presence of pathological Q related to increased risk against basic hazard by 18,4%. Our findings coincide with other study indicating the range of RR typicality from 1,15 to 1,30 [3, 8].

Heart arrest before or at hospitalization increased basic risk of lethality by 62,1% with marginal significance p=0,05. As with Charlson's index marginal significance related to low frequency of conditions. Obtained value falls in line with published by other researchers given suggested boundaries of 1,2 – 1,8 [3, 8].

Every next year of age after 40 increased risk against basic hazard by 1,3% that agrees with other studies range of 1,01 – 1,07 [8]. Females experienced higher (by 31,7%) hazard against males ([1/0,759-1]*100%) that again supported by other researchers [7, 8].

Therefore after adjustment on important clinical and biological confounders the implementation of the model of medical care to patients with acute myocardial infarction in the process of HCR proved to reduce basic hazard significantly.

Still the most efficient way to demonstrate treatment effect in survival terms is to build up survival curves across cohorts. Besides observed curves we have analyzed impact of main components of HCR, that is improvements in acceptability and quality of medical care for AMI patients. We also made prognostication of the best survival outcomes assured by most intensive (unbounded) implementation of HCR.

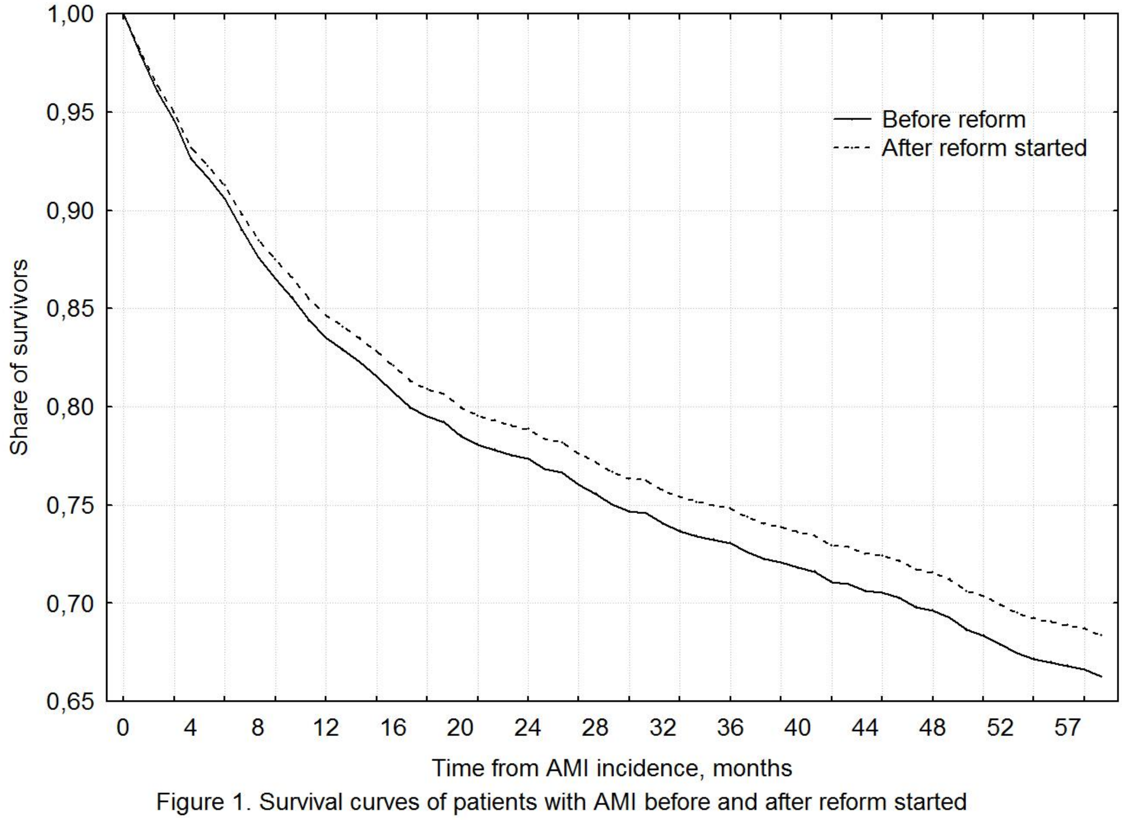

Figure 1. Survival curves of patients with AMI before and after reform started

Figure 1 displays observed survival curves of the members of control and experimental cohorts (before and after HCR). Positive effect of HCR is obvious and determined by difference in curves squares, that secures gain of 0,8788 months. It is tantamount to improvement in survival of 100 AMI patients by 87,88 months in first 5 years from the incidence of disease. Having about 2000 cases annually in Vinnitsa region the impact of HCR envisages gain of 1757,6 months in first 5 years from the incidence of disease annually throughout the region.

Taking into consideration organizational functionals improved by HCR, it's timeliness of treatment that was credited to be crucial in reduction of lethality in AMI patients with increase shift of 43,6% in case of delay with hospitalization over 10 hours.

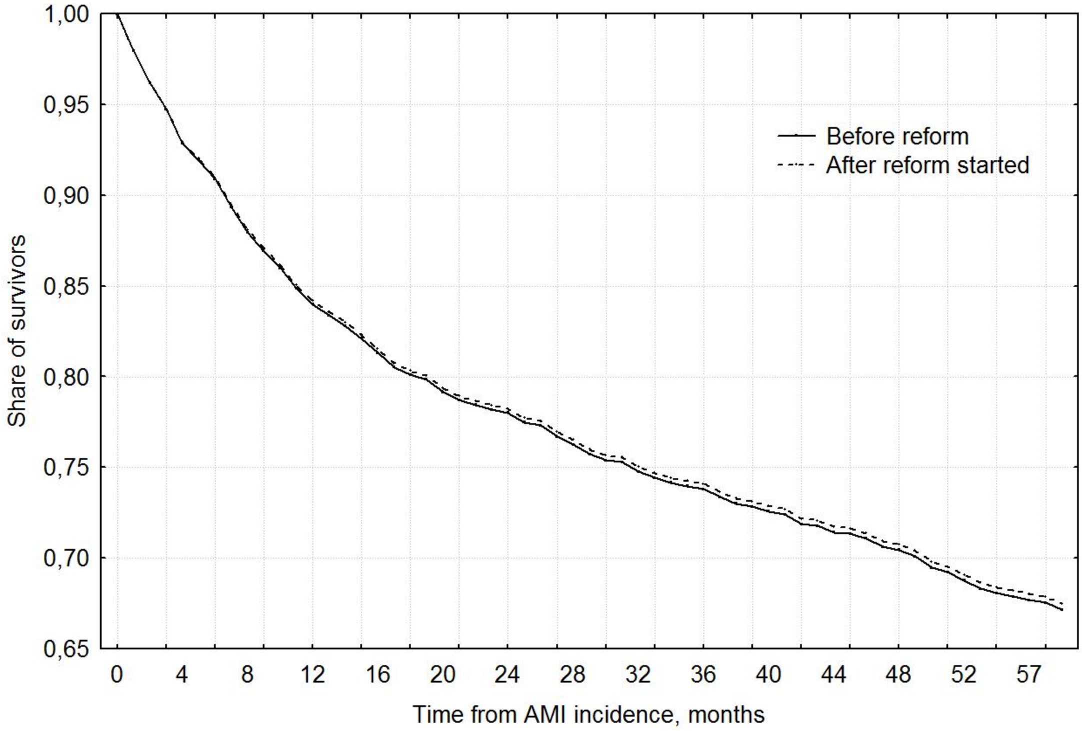

Figure 2. Survival curves of patients with AMI before and after reform started adjusted for timeliness of treatment

That's why we built up survival curves for control and experimental cohorts with adjustment for timeliness of care and graphed them by Figure 2. Obviously, impact of HCR reduced substantially to almost intangible 0,139 months of gain in first 5 years from the incidence of disease. It constitutes only 15,8% of total HCR impact. These percentages virtually related with improved treatment.

It stands to reason, that implementation of new doctrine in HCR is confined to resources, political will, community and physician support. Never do we have all flat out implementation. What we can do is to evaluate reserves to pursue in the frame of HCR. So we marked out maximal possible benefits for AMI patients given best possible scenario displayed by Figure 3. According to predictions we envisage survival improvement by 4,674 months of average gain per patient in first 5 years from the incidence of disease. That is on-going realization consolidates 18,8% only of the "maximal possible".

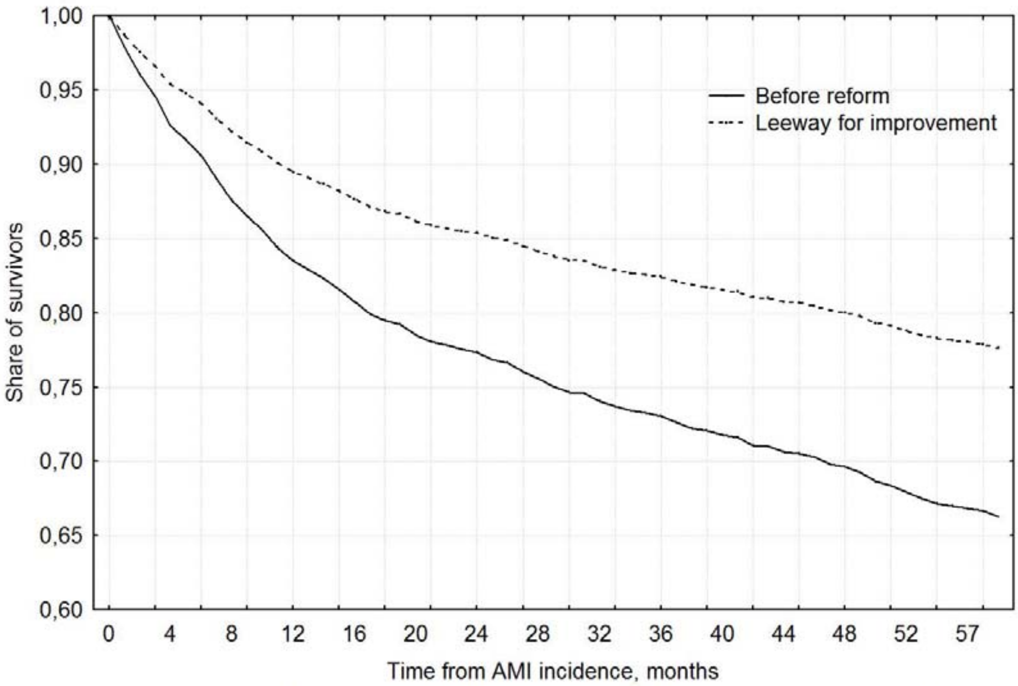

Figure 3. Survival curves of patients with AMI before reform started and by best scenario of reform implementation

All in all after adjustment on important clinical and biological confounders the implementation of the model of medical care to patients with acute myocardial infarction in the process of HCR in Vinnitsa region proved to reduce basic hazard significantly securing substantial gain in months of survival. Estimators are safeguarded against biases due to unobservable factors by taking into account frailties. HCR effect (β=-0,179, p=0,029) secures basic hazard reduction by 19,6%.
Among all organisational functionals of medical care it appeared that it's timeliness that of paramount importance in hazard reduction in patients with AIM. If patient was hospitalised with 10 hours delay or more basic risk of lethality increased by 43,6%. Effectiveness of administration of trombolytic therapy, PCI, and CABG closely related to timeliness of administration, especially to first 10-12 hours. Administration of trombolytic therapy in first 10-12 hours reduced basic risk of lethality by 26,6%, while timely performed PCI, and CABG reduced hazard by 31,1%. Severe patient's condition at hospitalization increased basic risk of lethality by 21,8%. All these covariates are time related and bare indirect evidence on importance of timeliness of treatment.
Further investigation of survival curves revealed that implementation of the HCR saved additional 0,8788 survival months to average patient in first 5 years from AMI incident that sum up to gain of 1757,6 months annually throughout the Vinnitsa region. It was unveiled that main effect (84,2%) was related particularly to improvement in timeliness of medical care.

4. Conclusions

1. The implementation of the model of medical care to patients with acute myocardial infarction in the process of HCR in Vinnitsa region proved to reduce basic hazard significantly securing substantial gain in months of survival. Estimators are safeguarded against biases due to unobservable factors by taking into account frailties. HCR effect (β=-0,179, p=0,029) secures basic hazard reduction by 19,6%.
2. Among all organisational functionals of medical care it appeared that it's timeliness that of paramount importance in hazard reduction in patients with AIM. If patient was hospitalised with 10 hours delay or more basic risk of lethality increased by 43,6%.
3. Effectiveness of administration of thrombolytic therapy, PCI, and CABG closely related to timeliness of administration, especially to first 10-12 hours. Administration of thrombolytic therapy in first 10-12 hours reduced basic risk of lethality by 26,6%, while timely performed PCI, and CABG reduced hazard by 31,1%. Severe patient's condition at hospitalization increased basic risk of lethality by 21,8%. All these covariates are time related and bare indirect evidence on importance of timeliness of treatment.

Investigation of survival curves revealed that implementation of the HCR saved additional 0,8788 survival months to average patient in first 5 years from AMI incident that sum up to gain of 1757,6 months annually throughout the Vinnitsa region. It was unveiled that main effect (84,2%) was related particularly to improvement in timeliness of medical care.

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