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Multilevel models for clinical registers concerning STEMI patients in a complex urban reality: a statistical analysis of MOMI^2 survey

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Abstract

In this work we describe statistical analyses conducted on MOMI^2 (MOnth MOnitoring Myocardial Infarction in MIlan) survey, a collection of data concerning patients admitted with STEMI (ST-Elevation Myocardial Infarction) diagnosis in one of the hospitals belonging to the Network in Milan urban area. The main goal of the analyses is statistical exploration, description and model of collected data in order to answer specific clinical questions (i.e. whether the result of certain healthcare policy is less or more effective than another one, whether the logistic organization or time scheduling of Emergency Room (ER) and rescue units can be improved, etc). Such results can be used as an effective support to decisional process for clinical and organizational governance. The fundamental result of this study is not only the use of advanced and innovative statistical tools, but also the social impact of the achieved results thanks to the synergic interaction between statisticians and physicians.

Keywords: `In-hospital mortality, Generalized Linear Mixed Models, Data Mining, ST-Elevation Myocardial Infarction, Random Effects.`

AMS Subject Classification: `62P10, 62J12, 62H30`

1. Introduction.

Over recent years there has been a growing interest in the use of performance indicators in health-care; they may measure some aspects of the health-care process, clinical outcomes or disease incidence. In response, a sizeable literature has emerged questioning the right use of such indicators as a measure of "quality of care", as well as stating more specific criticism of the statistical methods used to obtain estimates adjusted for patient case-mix. The purpose of the present work is to highlight how advanced statistical methods can be used to identify suitable models for complex data coming from clinical registers, taking into account variability between institutions and adjusting for case-mix.

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Several examples, available in clinical literature (see [1–3]), make use of clinical registers to evaluate performances of medical structures. These databases are very useful: they enable people concerned with the health-care governance to plan activities on real epidemiological evidence and needs: in fact, they provide the knowledge of the number of cases and incidence, of the survival etc., concerning a specific disease.

In general, health-care service scheduling is strictly connected with a deep knowledge of current health needs, of innovative surgery practices efficacy and measurement of clinical outcomes. Randomized clinical trials are usually carried out to test efficacy of new drugs, technologies and procedures in standard practice. Nevertheless, sometimes we cannot generalize their results because exsperimental conditions or number of inpatients involved are not representative of real population and settings. So the use of pathology registers concerning diseases of shared interest becomes more and more important in order to get the real clinical practice on inpatient population.

In 2005, February 11th, the *Piano Cardio-Cerebro Vascolare* has been approved in Lombardia Region through D.G.R.20592 [4]. This law set favorable conditions for using clinical registers in health-care process planning. In fact several clinical registers have been made in Lombardia Region up to now. In next sections we will describe the disease which MOMI^2 survey, the clinical register we analized in this work, is concerned to, then the survey structure and contents, and finally the statistical analysis performed on it.

1.1. *ST-Elevation Myocardial Infarction*

The Acute Myocardial Infarction with ST-segment Elevation (STEMI) is a disease characterized by a great incidence (650 - 700 events per month have been estimated only in Lombardia Region) and serious mortality (Italy 8%, data coming from *Istituto Superiore della Sanità*). In fact, it is one of the main causes of death all over the world.

In general, the Acute Myocardial Infarction (AMI) belongs to a wider class of diseases called Acute Coronary Syndromes (ACS). These pathologies are caused by a stenotic plaque detachment, which causes a coronary thrombosis and a sudden critical reduction of blood flow in coronary vessels. This process causes a widespread necrosis of myocardial tissues and leads to an inadequate feeding of myocardial muscle itself.

A case of STEMI can be diagnosed through the electrocardiogram (ECG), observing the elevation of ST segment. Up to now, Thrombolitic teraphy and Percutaneous Transluminal Coronary Angioplasty (PTCA) are the

most common procedures. The former one consists in a pharmacological treatment which causes a breakdown of the blood clots, while in the latter one an empty and collapsed balloon on a guide wise, known as *Balloon* catheter, is passed into the narrowed or obstructed vessels and then inflated to a fixed size. The balloon crushes the fatty deposit, so that the vessel can be opened up, the blood flow improved, and then balloon is collapsed and withdrawn. As we will see, in our data on Milan reality, patients always undergo directly to a PTCA procedure avoiding the Trombolysis, even if the two treatments are not mutually exclusive.

A good practice can be evaluated by observing firstly the in-hospital survival of inpatients, then quantifying the reduction of ST segment elevation one hour later the surgery: if the reduction is larger than 70% we could consider the procedure effective. Both survival and quantity of myocardial tissue saved from damage depend strongly on time saved during the process. The main focus of the next section is the explanation of the time role in the AMI health-care process.

1.2. *The AMI health care process*

A clinical register selects a population of subjects; in our case, we are dealing with the population of patients admitted in one of the hospital belonging to the Milan Network of cardiology divisions with STEMI diagnosis. For these subjects, we would like to comprehend and quantify the influence of healthcare process they are undergoing to on their in-hospital survival and reperfusion efficacy. In order to find suitable evaluating indexes of clinical performances, we would like to know which mechanisms and variables have to be measured during the health-care process.

Performance indicators in clinical context are based on the understanding the relationship between process variables and outcomes. Here the process is the service offered to a subject affected by STEMI in the time interval between the symptom onset and the surgeon practice, while the outcome is the health of patient at the end of the process, measured in terms of survival and therapy effectiveness. In the MOMI^2 study, we found that prehospital and in-hospital times strongly influence the outcomes of health-care processes. This confirms a previous clinical guess and it is a fundamental motivation to make a wider effort to understand the covariates we can act on in order to decrease these time procedures.

A subject affected by an infarction can move to the hospital by himself or can be moved to the hospital by 118 (the National free number for medical emergencies) rescue units. In the first case, the patient has to pass

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through the ER iter, which is longer and more difficult, while in the second one it could be overcome by activating the so called Fast-Track, i.e. to go directly to the Emodynamics or CathLab, where doctors have been already informed about the patient situation and are prepared to his incoming.

Let us call "Symptom Onset to Door time" the time since symptom onset up to the arrival at ER, and "Door to Balloon time" (DB time) the time since the arrival at ER up to the surgical practice of PTCA; it is possible to reduce the first one only through awareness campaigns to call 118 as soon as possible, and the latter one through the adoption of several policies, organizational and logistic for both 118 units and ER. By the way, clinical literature strongly stresses the connection between in-hospital survival and procedures time (see [5–7] and [8]): 90 minutes for Door to Balloon time in case of primary PTCA and 10 minutes for first ECG time are the actual gold standard limits suggested by the AHA/ACC guidelines (see [7,9]). Particularly, in our case both Symptom Onset to Door and Door to Balloon time will play the role of clinical performance indicators, and we will highlight and quantify their influence with respect to the outcome variables.

2. The MOMI^2 survey

The MOMI^2 project arises from a collaboration between the Working Group for Cardiac Emergency (ACEU) of Lombardia Region, Dispatch Center of 118 and Niguarda Ca' granda hospital, concerning the management of the Network, activated in the Milan urban area since 2001, in order to connect the territory to hospitals by a centralized coordination of the emergency resources. Its primary aims are promoting the best utilization of the different reperfusion strategies, reducing transport and decisional delays connected with logistic matters and therapies, and increasing the number of patients undergoing primary PTCA before 90 minutes since the arrival at Emergency Room (see [7]). Difficulties in reaching these goals are primary due to the fact that Milan urban area is a complex territory with high density of population (2.9 million residents and 1 million commuters daily) and a great number of hospitals (n = 27). 23 of them have a cardiology division and a Critical Care Unit; 18 offer a 24 hour available Cath Lab for primary PTCA, 5 are completed with a Cardiac Surgery unit.

The aim of this innovative project is the activation, on the Milan urban area, of a register on Acute Myocardial Infarction to collect also process indicators (Symptom Onset time, first ECG time, Door to Balloon time and so on). The main purpose of the study is the identification and development of new diagnostic, therapeutic and organizational strategies to be

applied (by Lombardia Region, 118 and hospitals) to patients with STEMI, in order to improve the occurrence of clinical outcomes and the health-care offer to the patients. In order to do this, it is necessary to understand which organizational aspects can be considered as predictive of reduction time to treatment. Therefore, a special attention is focused on the way of admittance; five different types of patients can be pointed out:

- **self-presented** patients, i.e. patients who came to the hospital by themselves;
- patients delivered by advanced rescue units with tele-transmission of ECG (**ARU** + **tele-ECG**), i.e. by rescue units with doctors on it and equipped with LIFEPACK 12, a box which enable clinicians to make ECG and forecast it to the Dispatch Center and to the hospital where the patient will be admitted to;
- patients delivered by advanced rescue units (**ARU**), i.e. by a rescue unit with doctors on it but without ECG tele-transmission equipment;
- patients delivered by basic rescue unit (**BRU**), i.e. the common ambulances;
- patients **transferred**, i.e. patients admitted to a certain hospital and then undergone to angioplasty in another one.

Beyond the way of admittance, several other information can be found in the MOMI^2 dataset: for example, demographic data as age and sex, clinical data like declared symptoms, Killip class (which quantifies in four cathegories the severity of infarction) and received therapy, organizational data like way of admission and activation of Fast-Track, data concerning all procedure times and finally, clinical outcomes: in-hospital survival and reperfusion efficacy.

The MOMI^2 survey is then a retrospective observational study. Anyway, it is a study that enables us to give a "real time" feedback on the monitored activities. In fact the MOMI^2 survey is composed by six collections, planned and made during six monthly/bimestral periods. In particular:

$MOMI^2$.1:	90 pcs.	Jun 1st - Jun 30th 2006
$MOMI^2$.2:	147 pcs.	Nov 15th - Dec 15th 2006
$MOMI^2$.3:	220 pcs.	Jun 1st - Jul 31st 2007
$MOMI^2$.4:	131 pcs.	Nov 15th - Dec 15th 2007
$MOMI^2$.5:	120 pcs.	Jun 1st - Jun 30th 2008
$MOMI^2$.6:	133 pcs.	Jan 28th - Feb 28th 2009

The whole dataset collects data concerning 841 patients.

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3. The Statistical Analysis

We start with a brief description of the whole database (for deeper analysis and details see [10–12]). There was a great number of patients treated with PTCA reperfusion therapy with a low in-hospital mortality (6.17%, 47 missing data), an extensive use of primary PTCA (75.52% of overall angioplasty, 32 missing data), and a continuous attempt to reduce DB time. Almost 60% of overall patients (66.38% of primary angioplasty) met the guidelines recommendations with a DB time smaller than 90 minutes. Table 1 shows the proportion of subjects in each collection have been treated by the guidelines gold standard of 90 minutes. Even if there is no statistical evidence, a growing trend can be seen across six collections. This result has been achieved under constant monitoring of data.

Table 1. Proportion of patients undergone primary PTCA within 90 minutes, stratified by $MOMI^2$ collections.

	DB < 90 min
$MOMI^2 1$	54.09%
$MOMI^2 2$	63.72%
$MOMI^2 3$	65.16%
$MOMI^2 4$	73.03%
$MOMI^2 5$	76.82%
$MOMI^2 6$	64.15%

As we will see below, data show that the DB time is greatly influenced by organizational pre-hospital and in-hospital elements. In particular, we found that timing of the first ECG, way of transport to hospital, pre-alert, direct Fast Track to the Cath Lab and presentation at hospital during work time, are all conditions under which probability of a DB time smaller than 90 minutes grows up. Of particular interest is the finding that execution and transmission of pre-hospital ECG (18.12% of patients) as well as triage within 10 minutes from ER presentation (59.56% of patients) are the two most important predictive factors in reducing DB time.

Then we will focus our readings on the dependence between the principal performance indicators (in particular times to treatment) and clinical outcomes. Other studies concerning this kind of problem have found conflicting results regarding the relationship between mortality and time to reperfusion with PTCA. Some investigators have found lower mortality for shorter onset-to-balloon times for all patients or just certain subgroups such as high-risk patients [13]. Other studies found no lower mortality for shorter symptom onset to balloon time but did find lower mortality for shorter DB time [6]. Finally, some studies failed to find an association be-

tween mortality and pre-hospital and in-hospital times [14]. We detected a statistical evidence for connection between outcomes and times (both concerning symptom onset and in-hospital times); in particular, data pointed out the dependence between survival and Symptom Onset to Balloon time and between the efficacy of reperfusion therapy and DB and Symptom Onset to Door times. Finally, no statistical evidence of dependency has been detected between two responses of interest: in-hospital survival and reperfusion efficacy (Fisher exact test: p-value = 0.24).

The analysis we performed on database can be divided in two part: firstly an explorative and descriptive section, where correlation patterns among covariates have been explored; then a modeling section, where the use of a Generalized Linear Mixed-Effects Model (GLMM) is proposed, in order to explain the outcomes of interest by means of the other suitable covariates of the dataset, taking into account the overdispersion induced by the grouped nature of data. Results of GLMM analysis implemented on MOMI^2 data will concern only in-hospital survival outcome. For further details on analyses of both responses with Generalized Linear Models and Generalized Additive Models, see [10,15,16].

3.1. *Descriptive Analysis*

The MOMI^2 database is composed by six collections of data. The cohort consists of 841 patients: 3.19% of patients are treated only with thrombolitic therapy, 91.15% with any kind of angioplasty, and 5.66% are not treated. Outcomes of interest are in-hospital survival and effectiveness of reperfusion therapy. Neither the first nor the second one seem to be correlated with the choice of the therapy (Fisher exact test [17] p-values for indipendence are 34.42% for mortality and 66.69% for effectiveness of reperfusion). Because of the specific clinical requests in the following analysis we will focus our readings on patients undergone primary angioplasty. We counted out patients with "transferred" as way of admittance, because, concerning time of intervenction, they represent a different population with respect to all other patients. So the population considered for all the following analyses consists of 536 statistical units.

Let look now at summary statistics of this reducted database. In Table 2 is reported the in-hospital survival stratified by different collection period.

Stratification by sex is coherent with literature [13,14]: 73.7% male patients and 26.3% female. The age of population, similar across all collections, ranges from 30 years (min) to 93 years (max). The mean is 63.7 years

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Table 2. Mortality of six $MOMI^2$ collections.

	Mortality
$MOMI^2 1$	8.9%
$MOMI^2 2$	3.1%
$MOMI^2 3$	4.0%
$MOMI^2 4$	9.5%
$MOMI^2 5$	2.9%
$MOMI^2 6$	3.8%

and the standard deviation 12.3 years.

Moreover, data confirm results of clinical literature about STEMI: we have greater incidence in male population than in female one; dependencies between Symptoms and Sex and between Symptoms and Age can be detected (respectively Fisher exact test p-values are 0.00205 and 0.0424), which say that women tend to have more frequently atypical symptoms and that the more atypic symptomatology is the older people are. For these tests, four categories for age have been chosen ([30,50),[50,65),[65,80) and over 80), according to literature.

Anyway, we have already said that we are mostly interested in Symptom Onset to Door and Door to Balloon times. Particularly, we are interested in the second one, because is the one which can be influenced by a more effective organization of logistic, economical and clinical resources of hospitals and 118. Way of in-hospital admission, transmission of ECG within 10 minutes, on-hour or off-hour timing and Fast-Track activation are correlated with DB time. Figure 1 shows the flanked boxplots of DB time distribution stratified by these variables and the p-values of Wilcoxon test for stochastic order among distributions.

Dependence between the DB time and factors we can act on in order to reduce it has been also explored by means of CART [18]. Indeed a CART analysis using Gini's impurity index splits groups satisfying or not the limit of 90 minutes for DB time in terms of time of first ECG within or not 10 minutes (see also [9]).

In fact the distribution of the DB time in the population of patients with the first ECG within 10 minutes is confirmed to be stochastically inferior to the corresponding distribution in patients with the first ECG after 10 minutes; this stochastic order between distributions is confirmed by Wilcoxon non parametric comparison test (p-value $= 1.22 \times 10^{-14}$). A random forest analysis (see [19]) applied to CART predictors has been performed in order to asses the discriminatory power of covariates. As we can see in Figure 2, a confounding effect between covariates detected by classification analysis

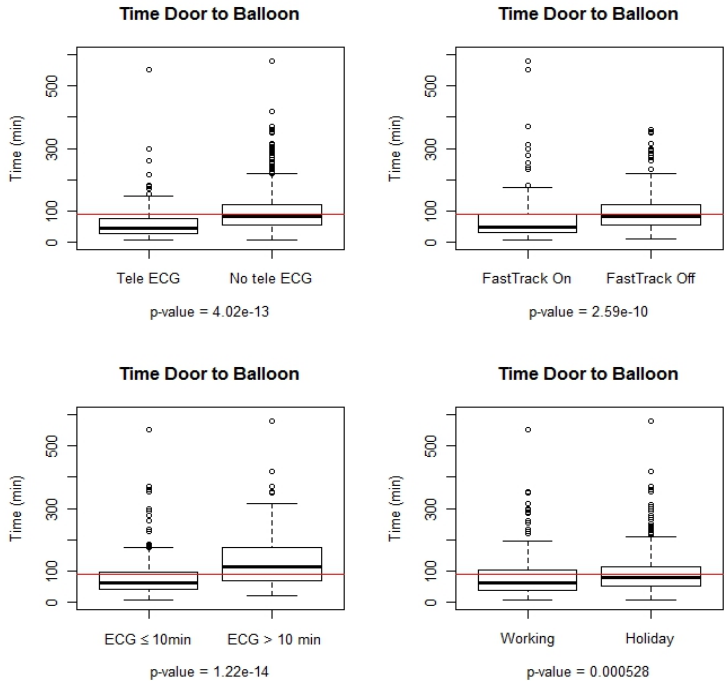

Fig. 1. Flanked Boxplots of DB time distribution stratified by relevant covariates: way of admission with or without tele-transmission of ECG (higher left panel), Fast Track on/off (higher right panel), ECG before/after 10 minutes (lower left panel), Working/Holiday admission days (lower right panel).

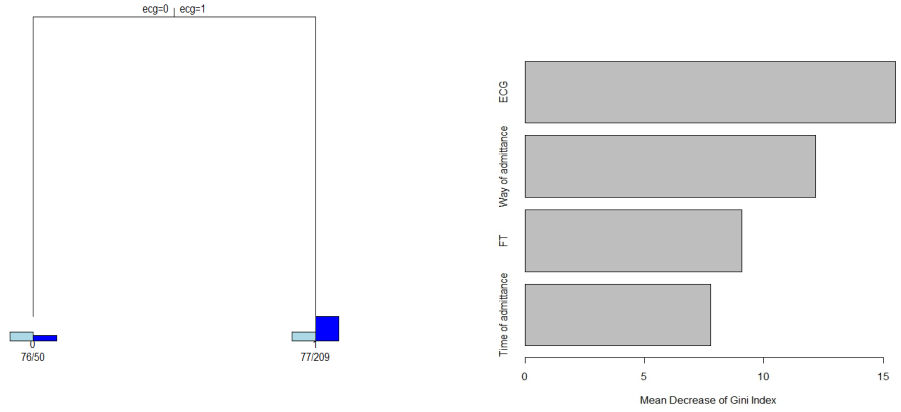

Fig. 2. CART (left panel) and Random Forest on CART predictors (right panel), assessing discriminatory power of covariates.

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(the way of in-hospital admittance and the time of first ECG) is pointed out. In fact the exact Fisher test, performed on the contingency table of the way of hospital admittance and a binary variable indicating whether the time of first ECG is within or not 10 minutes, shows a strongly statistical evidence (p-value $= 2.14 \times 10^{-11}$) of dependence between these two covariates. This means that these two covariates are saying the same thing, in fact we can discriminates rescue units on their capability of doing and sending ECG. Then, all these signals highlight the same matter: in order to make DB time lower than 90 minutes, it is fundamental to make and transmit ECG as soon as possible.

In Figure 3 the mean time of first ECG and the mean time from ECG to Balloon for each hospital involved in the MOMI^2 study are reported; yellow, red and green squares represent, respectively, the overall mean above all hospital and two fictitious examples of bad and good behaviour. The radius of points is proportional to the number of treated patients. This graph not only enables health-care governance to monitor and evaluate hospitals' inner organization, adjusting for volume of patients, but also shows to hospitals their position with respect to the other ones or to the gold standard.

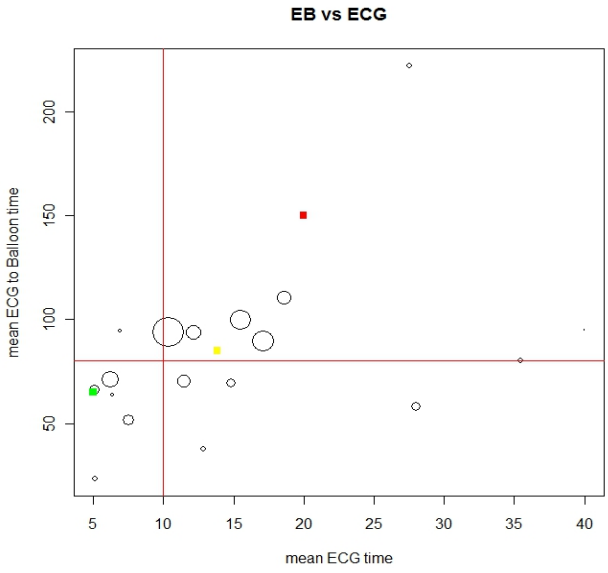

Fig. 3. Benchmark of hospitals' timing data.

So continuosly monitoring hospitals' performance could help medical insti-

tutions to reach the gold standard imposed or suggested from the health governance faster.

3.2. *Generalized Linear Mixed Models*

In this section we would like to build a suitable model for MOMI^2 data. We considered a GLMM [20,21] as a statistical technique to model binary response of grouped data. GLMMs are an extension of Generalized Linear Model [17]. In Generalized Linear Models, a function of response's conditional expected value is assumed proportional to a linear predictor. A GLMM adds to the linear predictor one or more random effects, whose realizations are drawn from some common unknown parametric distribution. In literature [20,22–24], these models are widely used to deal with intrinsically grouped data because they take into account the overdispersion due to the grouped nature of data, putting a random effect on the grouping factor. Specifically, the use of such models is intended to (i) overcome small sample problems by appropriately pooling information across grouping factor, introducing some bias or shrinkage, (ii) provide a statistical framework that allows one to quantify and explain outcome variability between or within each grouping level, and (iii) provide more reliable estimates of performance.

Let Y_{ij} be the binary outcome of subject i of j-th group, and p_{ij} the related probability of success. A GLMM could be written in the following way:

$$logit\left(\mathbb{E}\left[Y_{ij}|b_j\right]\right) = logit(p_{ij}) = \beta_0 + \sum_k \beta_k x_{ijk} + b_j$$

where x_{ijk} are significant covariates (we will consider hereinafter the process of model selection using stepwise methods); $b_j \sim \mathcal{N}(0, \sigma_b^2)$ are additive random effects Normally distributed. The first two terms of the linear predictor ($\beta_0 + \sum_k \beta_k x_{ijk}$) are commonly called fixed effect.

We fitted a Generalized Linear Mixed Model on survival outcome; the hospital of admission is the grouping factor assumed as an additive random term with Normal distribution.

In order to choose significant covariates for the model, we considered stepwise regression methods (AIC criterion) on the fixed effect part of the model and clinical best practice. These criteria pointed out the logarithm of Symptom Onset to Balloon time (logOB) (p-$value = 0.1838$), killip (p-$value = 0.0038$) and age (p-$value = 8.27 \times 10^{-5}$) of patient as significant factors in order to explain survival probability from a statistical and clinical

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point of view (see also [8]). The killip variable is now a binary categorization of Killip class, whose values are zero for less severe (Killip class 1 or 2) and more severe (Killip class 3 or 4) infarction.

Therefore, calling Y_{ij} the binary random variable representing in-hospital survival of patient $i = 1, \ldots, 536$ treated in the hospital $j = 1, \ldots, 17$, the model fitted is:

$$logit\left(\mathbb{E}\left[Y_{ij}|b_j\right]\right) = logit(p_{ij}) = \beta_0 + \beta_1 age_i + \beta_2 \log(OB)_i + \beta_3 killip_i + b_j$$

where $b_j \sim \mathcal{N}(0, \sigma_b^2)$ is the Normal random effect of the grouping factor (i.e. hospital where *i-th* patient is admitted to). In Table 3 estimates of fixed effects coefficients and standard deviation of random effect are reported with corresponding 95% confidence intervals.

Table 3. Model parameters estimates and relatives asymptotic confidence intervals.

		estimate	Asymptotic CI (95%)
Intercept	$\hat{\beta}_0$	12.957	[7.867,18.047]
Age	$\hat{\beta}_1$	-0.105	[-0.157,-0.052]
log(OB)	$\hat{\beta}_2$	-0.402	[-0.986,0.182]
Killip	$\hat{\beta}_3$	-1.719	[-2.885,-0.553]
Std. Dev.	$\hat{\sigma}_b$	0.261	/

Using the estimated coefficients reported in Table 3, we can draw the estimated survival probability surfaces for the patients (Figure 4).
For both killip classes (less or more severe infarction) we represent three different cases: from left to the right, we consider a realization of random effect equal to $-2\hat{\sigma}_b$, 0 and $+2\hat{\sigma}_b$ respectively. We could interpret these three cases as estimated previsions for patients treated in a "bad", "mean" and "good" hospital respectively.

Now, starting from this model, we can

a) consider a "typical" patient and see how his estimated survival probability changes from one hospital to another one, in order to quantify the loss/gain in terms of estimated survival probability when a hospital behaves similar to the "bad"/"good" condition;
b) compute the variation in estimated survival probability for different "case-mix", i.e. different features of patient, for each typology of hospital.

For point (a) we computed estimated survival probability for a typical patient, i.e. a subject with mean Symptom Onset to Balloon time (307.15 min), mean age (63.66 years), Killip class 1 or 2 (less severe case, first co-

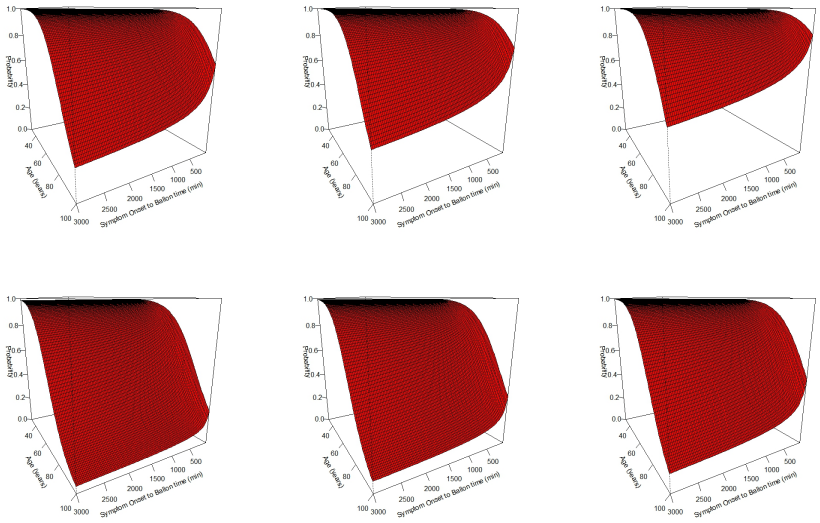

Fig. 4. Estimated survival probability surfaces for less severe (upper line) and more severe (lower line) class of Killip: "bad hospital" (left), "standard hospital" (central), "good hospital" (right).

lumn) and Killip class 3 or 4 (more severe case, second column). Results are reported in Table 4.

Table 4. Survival Probability of typical patient in the three different type of structure.

	Killip 1 or 2	Killip 3 or 4
"bad" hospital	0.9692	0.8496
"mean" hospital	0.9815	0.9050
"good" hospital	0.9889	0.9414

For point in case (b), fixing three different Symptom Onset to Balloon times (280, 305 and 335 min, i.e. mean Onset to Door time plus 65, 90 and 120 min of DB) for each hospital typology in both cases of less severe (Killip class 1-2) and more severe infarction (Killip class 3-4), we can see how differently estimated survival probability decreases as age increases (Figure 5).
Particularly, if we fix age equal to 50, 64 and 80 years, we can summarize infos of previous pictures, as shown in Tables 5 and 6 (first part of the Table for the "bad" hospital, second part for the "mean" hospital, third part for the "good" hospital).
This analysis enables us to see and quantify how survival probability decreases as age and Onset to Balloon time increase in the three different contexts.

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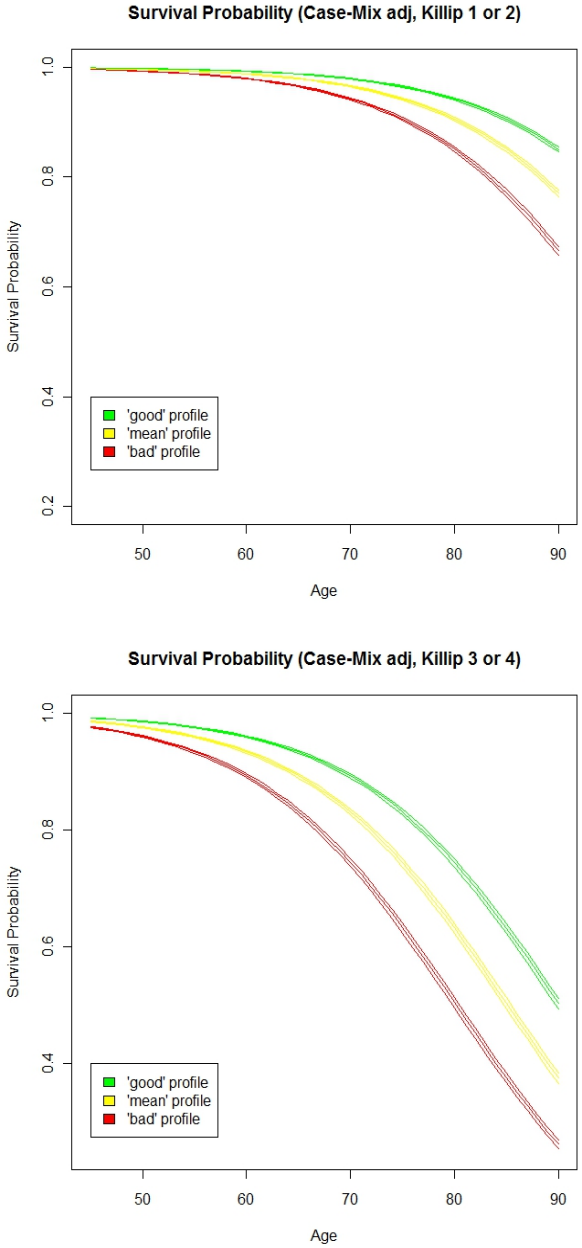

Fig. 5. Estimated survival probability for less severe (upper panel) and more severe (lower panel) class of Killip and different case-mix (age [45,90] years, OB = 280, 305, 355 minutes) in "bad" (red), "mean" (yellow) and "good" (green) hospital.

Table 5. Survival Probability for different case-mix in the three different types of structure: less severe infarction.

Age / OB time	280 min	305 min	335 min
50 years	0.9927	0.9925	0.9922
64 years	0.9693	0.9682	0.9607
80 years	0.8548	0.8505	0.8456
Age / OB time	280 min	305 min	335 min
50 years	0.9957	0.9955	0.9953
64 years	0.9815	0.9809	0.9802
80 years	0.9085	0.9056	0.9023
Age / OB time	280 min	305 min	335 min
50 years	0.9974	0.9973	0.9972
64 years	0.9889	0.9886	0.9881
80 years	0.9436	0.9418	0.9397

Table 6. Survival Probability for different case-mix in the three different types of structure: more severe infarction.

Age / OB time	280 min	305 min	335 min
50 years	0.9609	0.9596	0.9581
64 years	0.8498	0.8453	0.8404
80 years	0.5134	0.5048	0.4954
Age / OB time	280 min	305 min	335 min
50 years	0.9764	0.9756	0.9747
64 years	0.9051	0.9021	0.8987
80 years	0.6402	0.6322	0.6234
Age / OB time	280 min	305 min	335 min
50 years	0.9859	0.9854	0.9848
64 years	0.9414	0.9395	0.9374
80 years	0.750	0.7435	0.7362

Now, let us observe that the ratio between partial derivatives of odds with respect to covariates of interest corresponds to the ratio of coefficients of GLMM. In fact, being the odds

$$\begin{aligned} odds &= \frac{p_{ij}}{1-p_{ij}} \\ &= \exp\left\{\beta_0 + \sum_k \beta_k x_{ijk} + b_j\right\} \end{aligned}$$

we have

$$\frac{\frac{\partial odds}{\partial x_{(ij)k}}}{\frac{\partial odds}{\partial x_{(ij)h}}} = \frac{\beta_k \exp\left\{\beta_0 + \sum_k \beta_k x_{ijk} + b_j\right\}}{\beta_h \exp\left\{\beta_0 + \sum_k \beta_k x_{ijk} + b_j\right\}} = \frac{\beta_k}{\beta_h}$$

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In our case

$$\frac{\beta_{kil}}{\beta_{age}} = 16.38 \qquad \frac{\beta_{kil}}{\beta_{logOB}} = 4.27 \qquad \frac{\beta_{age}}{\beta_{logOB}} = 3.82$$

These ratios can be interpreted as "relative incidence coefficients"; they quantify the ratio between strength of covariates in prediction of outcome. For example, we can see that a variation in killip is 16 times more effective than a unit variation of age in the decrease of estimated survival probability. This turned out as an effective way to communicate results of statistical models to clinicians.

Dealing with binary unbalanced data leads to some troubles with Maximum Likelihood estimation. The `R` [25] package `lme4` [26,27] used for analyses, adopts the Laplace approximation of likelihood ([28–30]). Several different techniques of estimation are proposed in [21] to solve these problems, such Penalized Quasi Likelihood and Marginal Quasi Likelihood approximation, numerical integration of likelihood or bayesian hierarchical formulation. Anyway, since we deal with grouped data, the latter one seems the best practice in order to overcome estimation bias [24].

4. Conclusions

The results of this study support the effort of acting on some covariates in order to attain an improvement in performance indicators (such as the reduction of DB time) and so to increase the probability of a successful treatment. Analogously it would be strongly important to persuade the population to call the free emergency number as soon as possible after the Symptom onset. The analysis conducted on this survey stress that it is useful to take advantage of the great flexibility and power of mixed effects models, in the analysis of grouped data. This work has also pointed out process indicators, useful to compare institutional performances: these represent an important aid for people who are concerned with health-care governance.

More details on statistical models and techniques used to analyze the whole data set collected in the MOMI^2 observational studies can be found in [10,15,16].

The analysis conducted on MOMI^2 survey has already carried out remarkable results: it led Lombardia Region to establish that reduction of in-hospital times in AMI procedure should be checked in evaluating hospital health-care processes. Moreover, *Progetto PROMETEO* (PROgetto Milano

Ecg Teletrasmessi ExtraOspedaliero) started in December 2009. Its goal is to provide all Basic Rescue Units operating on Milan urban area with the ECG tele-transmission equipment. This program is fundamental in order to detect further cases, initially not classified as STEMI. This idea comes directly out of the evidence provided by MOMI^2 results on fundamental ECG's role in improving survival outcome of STEMI, and highlights how the effort of monitoring data from a statistical perspective has a deep social impact. Finally, the extension of the MOMI^2 paradigm of collecting and analyzing data to all Cardiology Divisions operating in Lombardia Region has been approved and ratified in the Strategic Program "Exploitation, Integration and Study of current and future health databases in Lombardia for Acute Myocardial Infarction". In fact a new register (STEMI Archive, [31]) has been designed for data collection on AMI; this register enriches the prototype of MOMI^2 collection with some more clinical information and can be directly linked to the administrative database (Public Health Database) in order to integrate information and reconstruct clinical history for each patient in a complex longitudinal data (for further details on analyses of integrated data, see [32]).

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