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Abstract

Studies of variations in health care utilization and outcome involve the analysis of multilevel clustered data, considering in particular the estimation of a cluster-specific adjusted response, covariates effect and components of variance. Besides reporting on the extent of observed variations, those studies quantify the role of contributing factors including patients and providers characteristics. In addition, they may assess the relationship between health-care process and outcomes. In this article we present a case-study, considering a Bayesian hierarchical generalized linear model, to analyze MOMI^2 (MOnth MOnitoring Myocardial Infarction in MIlan) data on patients admitted with ST-Elevation Myocardial Infarction diagnosis, in order to predict survival probabilities. We obtain posterior estimates of the regression parameters, as well as of the random-effects parameters (the grouping factor is the hospital the patients were admitted to), through an MCMC algorithm. The choice of covariates is achieved in a Bayesian fashion as a preliminary step. Some issues about model fitting are discussed through the use of predictive tail probabilities and Bayesian residuals.
Keywords: Bayesian hierarchical models, Multilevel data analysis, Bayesian generalized linear mixed models, Logistic regression, Health services research.
AMS Subject Classification: 62F15, 62P10, 62J12

1 Introduction

Over recent years there has been a growing interest in the use of performance indicators in health care research, since they may measure some aspects of the health care process, clinical outcomes or disease incidence. The purpose of the present work is to show how advanced statistical methods can be employed in the analysis of complex data coming from clinical registers. Several examples, available in clinical literature (see, for instance, Hasday *et al.*, 2002, and Saia *et al.*, 2009), make use of clinical registers to evaluate performances of medical institutions, because they enable people concerned with the health care governance to plan activities on real epidemiological evidence and needs and evaluate performance of structures they manage, providing knowledge about the number of cases, incidence, prevalence and survival concerning a specific disease.

The disease we are interested in is the Acute Myocardial Infarction with ST-segment Elevation (STEMI): it consists of 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. STEMI is characterized by a great incidence (650 - 700 events per month have been estimated only in Lombardia Region) and serious mortality (Italy 8%), and in fact it is one of the main causes of death all over the world. A case of STEMI can be diagnosed through the electrocardiogram (ECG), observing the elevation of ST segment, and treated by Thrombolytic teraphy and/or Percutaneous Transluminal Coronary Angioplasty (PTCA), which up to now are the most common procedures. The former one consists of a pharmacological treatment which causes a breakdown of the blood clots, while in the latter one an empty and collapsed *balloon* on a guide wire, 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 opening up the blood vessel to improved flow, and is then collapsed and withdrawn. The patients in our dataset always undergo directly to a PTCA procedure avoiding the Thrombolysis, even if the two treatments are not mutually exclusive. Anyway, good results for any of the two treatments can be evaluated by observing first the in-hospital survival of inpatients, and then quantifying the reduction of ST segment elevation one hour later the intervention (if the reduction is more than 70%, the procedure is considered effective). Concerning hearth attacks, both survival and quantity of myocardial tissues saved from damage strongly depend on time saved during the process. In this work, we will focus on the survival outcome. However, time has indeed a fundamental role in the overall STEMI health care process. By *Symptom Onset to Door time* we mean the time since symptoms onset up to the arrival at Emergency Room (ER), and *Door to Balloon time* (DB time) is the time since the arrival at ER up to the surgical practice of PTCA. Clinical literature strongly stresses the connection between in-hospital survival and procedures time (see Cannon *et al.*, 2000, Jneid *et al.*, 2008 and MacNamara *et al.*, 2006): 90 minutes for DB time in case of primary PTCA (i.e. PTCA without any previous pharmacological treatment) is the actual gold standard limit suggested by

the American Hearth Association (AHA)/American College of Cardiology (ACC) guidelines; see Antman *et al.*, 2008.

The presence of differences in the outcomes of health care has been documented extensively in recent years. In order to design regulatory interventions by institutions for instance, it is interesting to study the effects of variations in health care utilization on patients outcomes, in particular examining the relationship between process indicators, which define regional or hospital practice patterns, and outcomes measures, such as patients survival or treatment's efficacy. If the analysis of variations concerns in particular the comparison of the performance of health care providers, it is commonly referred to as *provider profiling* (see Normand *et al.*, 1997, Racz and Sedransk, 2010). The major aim of this work is to measure the magnitude of the variations of health care providers and to assess the role of contributing factors, including patients and providers characteristics, on survival outcome. Data on health care utilization have a "natural" multilevel structure, usually with patients at first level and hospitals forming the upper-level clusters. In this formulation, there are two main goals: one is to provide cluster-specific estimates of a particular response, adjusted for patient's characteristics, while the other one is to derive estimates of covariates effects, such as differences between patients of different gender or between hospitals. Hierarchical regression modelling from a Bayesian perspective provides a framework that can accomplish both these goals. In particular, this article considers a Bayesian generalized linear mixed model (Zeger and Karim, 1991) to predict the binary survival outcome by means of relevant covariates, taking into account overdispersion induced by the grouping factor. We illustrate the analysis on a subset of data collected in the MOMI^2 survey on patients admitted with ST-Elevation Myocardial Infarction (STEMI) diagnosis in one of the structures belonging to the Milano Cardiological Network, using a logit model for the survival probability. For this analysis, patients are grouped by the hospital which they were admitted to for their infarction. Assuming a Bayesian hierarchical approach for the hospital factors yields modelling dependence among the random-effects parameters, but also using the dataset to make inferences on hospitals which do not have patients in the study, borrowing strength across patients, as well as clustering the hospitals. A Markov chain Monte Carlo (MCMC) algorithm is necessary to compute the posterior distributions of parameters and predictive distributions of outcomes, as well as to use other diagnostic tools, such as Bayesian residuals, for goodness-of-fit analysis. The choice of covariates and link functions was suggested first in Ieva and Paganoni (2009), according to frequentist selection procedures and clinical know-how; however, it was confirmed here using Bayesian tools. We found out that Killip first, and then age, have a sharp negative effect on the survival probability, while the Symptom Onset to Balloon time has a lighter influence on it. The resulting variability among hospitals seems not too large, even if we underlined that 4 hospitals have a more extreme effect (one has a positive effect, while the remaining three have a negative effect) on the survival then the others.

To the best of our knowledge, this study is the first example of a Bayesian analysis of data arising from linkage between Italian administra-

tive databanks and clinical registers. This paper shares the same framework of hierarchical generalized linear mixed models as in Daniels and Gatsonis (1999), who examined differences in the utilization of coronary artery bypass graft surgery for elderly heart attack patients treated in hospitals.

The paper is organized as follows. Section 2 illustrates the dataset about STEMI in Milano Cardiological Network, while Section 3 describes the main features of the proposed model, with a short discussion on covariate selection. In Section 4 and 5 we discuss prior elicitation and Bayesian inferences, respectively. Finally, Section 6 describes results of the inference on quantities of interest with a discussion. All the analyses have been performed with WinBUGS (Lunn *et al.*, 2000; see also `http://www.mrc-bsu.cam.ac.uk/bugs/`) and R (version 2.10.1, R Development Core Team 2009) programs.

2 The STEMI dataset

A net connecting the territory to hospitals, by a centralized coordination of the emergency resources, has been activated in the Milano urban area since 2001. The aim of a monitoring project on it is the activation of a register on ST-Elevation Myocardial Infarction (STEMI) to collect process indicators (Symptom Onset to Door time, first ECG time, Door to Balloon time and so on), in order to identify and develop new diagnostic, therapeutic and organizational strategies to be applied to patients with STEMI by Lombardia Region, hospitals and 118 organization (the national toll-free number for medical emergencies). To reach this goal, it is necessary to understand which organizational aspects can be considered as predictive of time to treatment reduction. In fact, organizational policies in STEMI health care process concern both 118 organization and hospitals, since a subject affected by an infarction can reach the hospital by himself or can be taken to the hospital by 118 rescue units.

So, in order to monitor Milano Cardiological Network activity, times to treatment and clinical outcomes, the data collection MOMI^2 was planned and made on STEMI patients, during six periods corresponding to monthly/ bimonthly collections. For these units, information concerning mode of admission (by ambulance or on his/her own), demographic features (sex, age), clinical appearance (presenting symptoms and Killip class at admittance), received therapy (Thrombolysis, PTCA), Symptom Onset to Door time, in-hospital times (first ECG time, DB time), hospital organization (for example, admission during on/off hours) and clinical outcome (in-hospital survival) have been listed and studied. The Killip classification is a system used in individuals with an Acute Myocardial Infarction, in order to risk stratify them in four severity classes. Individuals with a low Killip class are less likely to die within the first 30 days after their myocardial infarction than individuals with a high Killip class. The whole MOMI^2 survey consists of 840 statistical units, but in this work we only focus on patients undergone primary PTCA and belonging to the third (Jun 1st - Jul 31th 2007, 154 patients) and fourth (Nov 15st - Dec 15th 2007, 93 patients) collections only. Among the resulting PTCA-patients, we selected those who had their own hospital admission registered also in the Public Health Database of Lombardia Region, in order to confirm the reliability of infor-

mation collected in the MOMI^2 register. Finally, the dataset considered consists of 240 patients.

Previous frequentist analyses on MOMI^2 survey (for further details see Grieco *et al.*, 2008, Ieva, 2008, and Ieva and Paganoni, 2010) pointed out that age, total ischemic time (Symptom Onset to Balloon time, denoted by OB) in the logarithmic scale and killip of the patient, categorized as binary variable, corresponding to 0 for less severe (Killip class equal to 1 or 2) and 1 for more severe (Killip class equal to 3 or 4) infarction, are the most significant factors in order to explain survival probability from a statistical and clinical point of view. This choice was confirmed using Bayesian variable selection procedure; see the next section for more details.

The main goal of our study is to explain and predict, by means of a Bayesian random-effects model, the in-hospital survival (i.e. the proportion of patients discharged alive from the hospital). We have a dataset of $n = 240$ patients who were admitted to $J = 17$ hospitals after a STEMI event. The number of STEMI patients per hospital ranges from 1 to 32, with a mean of 14.12. Each observation y_i records if a patient survived after STEMI, *i.e.* $y_i = 1$ if the i-th patient survived, $y_i = 0$ otherwise. In the rest of the paper, $\boldsymbol{y}$ denotes the vector of all responses $(y_1, \ldots, y_n)$. The dataset is strongly unbalanced, since 95% of the patients survived. The observed hospital-survival rates ranges from 75% to 100% with a mean of 93%. These high values are explained because they are in-hospital survival probabilities, a follow-up data being not available yet. The dataset contained some missing covariates, with proportions of 7%, 24% and 2% for age, OB and killip respectively. The missing data for age and logOB were imputed as the empirical means (64 years for age, 553 minutes for OB), while we sampled the missing 0-1 killip class covariates from the Bernoulli distribution with probability of success estimated from the non-missing data. After having imputed all the covariates, the mean value of age and OB did not change, while the proportion of patients with less severe infarction (killip=0) was 94%. Finally, we had no missing data concerning hospital of admission and outcome.

3 A Bayesian generalized mixed-effects model

We considered a generalized mixed-effects model for binary data from a Bayesian viewpoint. For a recent review on this topic, see Chapters 1-3 in Dey *et al.* (2000). For each patient $i = 1, \ldots, n$, let Y_i be a Bernoulli random variable with mean p_i, which represents the probability that the i-th patient survived after STEMI. The p_i's are modelled through a logit regression with covariates $\mathbf{x} := \{\boldsymbol{x}_i\}$, $\boldsymbol{x}_i := (1, x_{i1}, x_{i2}, x_{i3})$ which represent the age, the Symptom Onset to Ballon time in the log scale (logOB) and the killip, respectively, of the i-th patient in the dataset. Moreover, age and logOB have been centered. Since the patients come from J different hospitals, we assume the following multilevel model, with the hospital as a random effect:

$$Y_i | p_i \overset{ind}{\sim} \text{Be}(p_i), \qquad i = 1, \ldots, n, \tag{1}$$

and

$$\text{logit}(p_i) = \log \frac{p_i}{1-p_i} = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \beta_3 x_{i3} + b_{k[i]}, \qquad (2)$$

where $b_{k[i]}$ represents the hospital effect of the i-the patient in hospital $k[i]$. We will denote by $\boldsymbol{\beta}$ the vector of regression parameters $(\beta_0, \beta_1, \beta_2, \beta_3)$. It is well-known that (1)-(2) have a latent variable representation (see Albert and Chib (1995)), which can be very useful in performing Bayesian inference, as well as in providing medical significance: conditioning on the latent variables $Z_1, \ldots, Z_n$, the $Y_1, \ldots, Y_n$ are independent, and, for $i = 1, \ldots, n$,

$$Y_i = \begin{cases} 1 & \text{if } Z_i \geq 0 \\ 0 & \text{if } Z_i < 0 \end{cases}, \qquad (3)$$

where

$$Z_i = \boldsymbol{x}_i^T \boldsymbol{\beta} + b_{k[i]} + \varepsilon_i, \quad \varepsilon_i \overset{iid}{\sim} f_\varepsilon, \qquad (4)$$

being $f_\varepsilon(t) = \mathrm{e}^{-t}(1+\mathrm{e}^{-t})^{-2}$ the standard logistic density function. The same class of models, however without considering random effects, was applied in Sousa and Migon (2004) to a similar dataset of patients after acute myocardial infarction.

As mentioned in the previous section, the choice of covariates was first suggested in Ieva and Paganoni (2009), using frequentist model choice tools. However, we have considered it also in a Bayesian framework, using the Gibbs variable selection method by Dellaportas *et al.* (2002). But first, as a default analysis, we considered covariates selection via the R package BMA (Raftery *et al.* (2009)). A subgroup of 197 patients with 11 non-missing covariates was processed by the function `bic.glm`, and 7 covariates were selected (age, OB time, killip, sex, admission during on/off hours, ECG time, number of previous hospitalizations). For this choice of covariates, the non-missing data extracted from the 240-patients dataset consists of 217 units, which were again analyzed via `bic.glm`. The posterior probability that each variable is non-zero was very high (about 40%) for age and killip, while they were smaller than 7% for the others. Moreover, the highest BICs resulted for models including age, killip and sex. Since sex is strongly correlated with age in our dataset (only old women are in), at the end, we agreed with the choice of covariates in Ieva and Paganoni (2009), considering only age and killip, while the OB time was strongly recommended by clinical and health care utilization know-how.

As a second analysis, we considered only covariates which have non-missing values for all patients (age, OB time, killip, sex, admission during on/off hours, number of previous hospitalizations), to be analyzed using the Gibbs variable selection method. The linear predictor assumed in the right hand-side of (2) to select covariates can be represented as

$$\eta = \beta_0 + \sum_{1}^{6} \gamma_j \beta_j x_{ij}, \qquad (5)$$

where $(\gamma_1, \ldots, \gamma_6)$ is a vector of parameters in $\{0, 1\}$. Of course, a prior for both the regression parameter $\boldsymbol{\beta}$ and the *model index* parameter $\boldsymbol{\gamma}$ must be elicited, so that the marginal posterior probability of $\boldsymbol{\gamma}$ suggests which

variables must be included in the model. We assumed different "noninformative" priors for the logit model with the linear predictor (5), as suggested in Ntzoufras (2002), implementing a simple BUGS code to compute the marginal posterior distributions for each γ_j, $j = 1, \ldots, 6$, and posterior inclusion probabilities. However the analysis confirmed the previous selected model.

4 The prior distribution

As mentioned in the previous sections, one of the aim of this paper is to make a comparison among the patients survival probabilities treated in different hospitals of the Milano Cardiological network. Such an aim can be accomplished if, for instance, we assume the hospital each patient was admitted to as a random factor. We make the usual (from a Bayesian viewpoint) random-effects assumption for the hospitals, that is, the hospital effect parameters b_j's are drawn from a common distribution; moreover, since no information is available at the moment to distinguish among the hospitals, we assume symmetry among the hospital parameters, *i.e.* $b_1, \ldots, b_J$ can be considered as (the first part of an infinite sequence of) exchangeable random variables. Via Bayesian hierarchical models, not only we will model dependence among the random-effects parameters $\boldsymbol{b} := (b_1, \ldots, b_J)$, but it will also be possible to use the dataset to make inferences on hospitals which do not have patients in the study, borrowing strength across patients. As usual in the hierarchical Bayesian approach, the regression parameter $\boldsymbol{\beta}$ and the hospital parameter $\boldsymbol{b}$ are assumed a priori independent, $\boldsymbol{\beta}$ is given a (multivariate) Gaussian distribution and $\boldsymbol{b}$ is given a scale-mixture of (multivariate) Gaussian distributions; more specifically:

$$\begin{aligned} &\boldsymbol{\beta} \perp \boldsymbol{b}, \quad \boldsymbol{\beta} \sim MN(\boldsymbol{\mu}_\beta, V_\beta) \\ &b_1, \ldots, b_J | \sigma \overset{iid}{\sim} \mathcal{N}(\mu_b, \sigma^2), \quad \sigma \sim U(0, \sigma_0). \end{aligned} \tag{6}$$

Observe that the prior assumption on $\boldsymbol{b}$ is that, conditionally on the parameter σ, each hospital effect parameter has a Gaussian distribution with variance σ^2; here the uniform prior on σ is set as an assumption of ignorance/symmetry on the standard deviation of each hospital effect. The Gaussian prior for $\boldsymbol{\beta}$ is standard, but its hyperparameters, as well as the hyperparameter of the prior distribution for σ, will be given informatively, using available information from other MOMI^2 collections (see Section 6.2 for more details). On the other hand, a more standard prior for b_j would be a scale-mixture of normals, mixed by an inverse-gamma distribution for σ^2, with parameter (η, η) for small η. However, this prior has been criticized (for instance, see Gelman, 2006), mainly because the inferences will not result robust with respect to the choice of η, and the prior density (for all small η), as well as the resulting posterior, are too peculiar. In what follows, the parameter vector $(\boldsymbol{\beta}, \boldsymbol{b}, \sigma)$ will be denoted by $\boldsymbol{\theta}$.

5 Bayesian inference

Based on given priors and likelihood, the posterior distribution of $\boldsymbol{\theta}$ is given by

$$\begin{aligned}\pi\left(\boldsymbol{\theta}|\boldsymbol{y},\mathbf{x}\right) &\propto \pi\left(\boldsymbol{\theta}\right)\mathcal{L}(\boldsymbol{y}|\boldsymbol{\theta},\mathbf{z},\mathbf{x})f(\mathbf{z})\\ &= \pi(\boldsymbol{\beta})\pi(\boldsymbol{b}|\sigma)\pi(\sigma)\prod_{i=1}^{n}(\mathbb{I}_{(0,+\infty)}(z_i))^{y_i}(\mathbb{I}_{(-\infty,0]}(z_i))^{1-y_i}\prod_{i=1}^{n}f_\varepsilon(z_i-\boldsymbol{x}_i^T\boldsymbol{\beta}-b_{k[i]}).\end{aligned} \tag{7}$$

We are interested in predictions, too. This implies (i) considering the posterior predictive survival probability of a new patient coming from an hospital already included in the study, or (ii) the posterior predictive survival probability of a new patient coming from a new $(J+1)$-th hospital. We have

$$\mathbb{P}(Y_{n+1}=1|\boldsymbol{y},\boldsymbol{x},b_j)=\int_{\mathbb{R}^5}\mathbb{P}(Y_{n+1}=1|\boldsymbol{\beta},b_j,\boldsymbol{x})\pi(\boldsymbol{\beta},b_j|\boldsymbol{y})\,d\boldsymbol{\beta}db_j,\quad j=1,\ldots,J, \tag{8}$$

for a new patient with covariate vector $\boldsymbol{x}$ coming from the j-th hospital in the study, and

$$\mathbb{P}(Y_{n+1}=1|\boldsymbol{y},\boldsymbol{x})=\int_{\mathbb{R}^5}\mathbb{P}(Y_{n+1}=1|\boldsymbol{\beta},b_{J+1},\boldsymbol{x})\pi(\boldsymbol{\beta},b_{J+1}|\boldsymbol{y})\,d\boldsymbol{\beta}db_{J+1}, \tag{9}$$

where

$$\pi(\boldsymbol{\beta},b_{J+1}|\boldsymbol{y})=\int_{\mathbb{R}^+}\pi(b_{J+1}|\sigma)\pi(\boldsymbol{\beta},\sigma|\boldsymbol{y})d\,\sigma,$$

and $\pi(b_{J+1}|\sigma)$ is the prior *population* conditional distribution in (6).

As far as model checking is concerned, we will consider predictive distributions for patients already enrolled in the study in the spirit of *replicated data* in Gelman *et al.* (2004); more specifically, we will compute

$$\mathbb{P}(Y_i^{new}=1|\boldsymbol{y},\boldsymbol{x_i},b_{k[i]})\quad \text{for all } i=1,\ldots,n. \tag{10}$$

Here Y_i^{new} denotes the i-th "replicated data that could have been observed, or, to think predictively, as the data that we would see tomorrow if the experiment that produced y_i today were replicated with the same model and the same value of parameters that produced the observed data" (Gelman *et al.*, 2004, Sect. 6.3). Since we have a very unbalanced dataset, the following Bayesian rule is adopted: a patient is classified as *alive* if $\mathbb{E}(Y_i^{new}|\boldsymbol{y},\boldsymbol{x_i},b_{k[i]})$ is greater than the empirical mean $\bar{y}_n$. Then the coherence between the Bayesian rule and the dataset is checked.

Finally we computed the *latent* Bayesian residuals for binary data as suggested in Albert and Chib (1995). Thanks to the latent variable representation (3)-(4) of the model, we can consider the *realized* errors

$$e_i=Z_i-(\boldsymbol{x}_i'\boldsymbol{\beta}+b_{k[i]})\;i=1,\ldots,n, \tag{11}$$

obtained solving (4) w.r.t. ε_i. Each e_i is a function of the unknown parameters, so that its posterior distribution can be computed through the MCMC

simulated values, and later examined for indications of possible departures from the assumed model and the presence of outliers (see also Chaloner and Brant, 1988). Therefore, it is sensible to plot credibility intervals for the marginal posterior of each e_i, comparing them to the marginal prior credibility intervals (of the same level).

6 Data Analysis

In this section we illustrate the Bayesian analysis of the dataset described in Section 2, but first we give some details on computations and prior elicitation.

6.1 Bayesian computations

All estimates were computed via a Gibbs sampler algorithm; in fact in this case full conditional distributions were straightforward. The first 100,000 iterations were discarded, retaining parameter values each 80 iterations to decrease autocorrelations, with a final sample size equal to 5,000; we run the chains much longer (for a final sample size of 10,000 iterations), but the gain in the MC errors was relatively small. Some convergence diagnostics (Geweke and the two Heidelberger-Welch ones) were checked, together with traceplots, autocorrelations and MC error/posterior standard deviation ratios for all the parameters, indicating the MCMC algorithm converged. Code is available from the authors upon request.

6.2 Informative prior hyperparameters

Concerning information about hyperprior parameters, we fixed $\mu_b = 0$ regardless of any information, since, by the exchangeability assumption, the different hospital have the same prior mean (fixed equal to 0 to avoid confounding with β_0). As far as $\boldsymbol{\beta}$ is concerned, we have enough past data to be relatively informative in eliciting prior hyperparameters; they were fixed after having fitted model (1)-(2), under non-informative priors for θ, to "similar" data, i.e. 359 patients undergone primary PTCA whose data were collected during the other four MOMI^2 collections (MOMI^2.1, MOMI^2.2, MOMI^2.5, MOMI^2.6).

Therefore, for the present analysis, we fixed $\boldsymbol{\mu}_\beta = (3, 0, 0.1, -0.7)^T$, which are the posterior means of the regression parameters under the preliminary analysis. The matrix V_β was assumed diagonal,
$V_\beta = diag(2, 0.04, 0.5882, 3.3333)$, which, except for the second value, are about 10 times the posterior variances of the regression parameters under the preliminary analysis (0.04 is 100 times the posterior variance, in order to consider a vaguer prior for β_1). The prior hyperparameter σ_0 was fixed equal to 10, a value compatible with the support of the posterior distribution for σ in the preliminary analysis. Posterior estimates of $\boldsymbol{\beta}$, $\boldsymbol{b}$ and σ proved to be robust with respect to $\boldsymbol{\mu}_\beta$ and V, even when we fixed a non-diagonal matrix for V, assuming prior dependence through the regression parameters (the non-diagonal V elicited via the preliminary analysis as well).

6.3 Results

Summary inferences about regression parameters and σ can be found in Table 1, while the marginal posterior distributions are depicted in Figures 1-2. From Table 1 and Figure 1 it is clear that the marginal posteriors

		Informative prior	
		mean	sd
intercept	β_0	3.8160	0.5704
age	β_1	-0.0792	0.0324
log(OB)	β_2	-0.1527	0.3326
killip	β_3	-1.5090	0.8159
random effect std. dev.	σ	1.1770	0.7417

Table 1: Posterior means and standard deviations of the regression parameters and σ.

of β_1 and β_3 are concentrated on the negative numbers, confirming the naïve interpretation that an increase in age or killip class decreases the survival probability. The negative effect of the log(OB) is questionable, given its high variability, even if the posterior median of β_2 is -0.16. Anyway, it was indeed included because of its clinical relevance; moreover, it is the main process indicator in health care monitoring of STEMI procedures. Observe that the posterior mean of $\beta_0 + b_j$, which is the logit of the survival probability for a patient with "average" covariates from any hospital, is between 2.90 and 4.78, yielding a high posterior estimates of the survival probability from any hospital, as expected. By inspecting Figure 2 a shrinkage of a posterior density of σ with respect to the uniform prior can be observed, and this fact supports the conjecture of a low variability within medical institutions. As far as the marginal posterior distribution of the random effect parameters are concerned, Figure 3 displays the posterior median and mean (with 95% credibility intervals) of each hospital parameter b_j, $j = 1, \ldots, J$. In Table 2 we report

$$\tilde{p}_j = \min\{\mathbb{P}(b_j > 0|\boldsymbol{y}), \mathbb{P}(b_j < 0|\boldsymbol{y})\}, \quad j = 1, \ldots, J, \tag{12}$$

together with the signum of the posterior median of the b_j's. Low values of $\tilde{p}_j$ denote the posterior distribution of b_j is far from 0, so that the j-th hospital significantly contributes to the (estimated) regression intercept $\beta_0 + b_j$. In Figure 3 the credible intervals corresponding to $\tilde{p}_j$ less than 0.18 are depicted in yellow; it is clear that hospital 9 has a positive effect, while hospital 10, 11 and 15 have a negative effect on the survival probability.
Figure 4 displays medians and 95% credibility intervals for the posterior predictive survival probabilities (8) of four *benchmark* patients:

b_1	b_2	b_3	b_4	b_5	b_6	b_7	b_8	b_9	b_{10}	b_{11}	b_{12}	b_{13}	b_{14}	b_{15}	b_{16}	b_{17}
0.27	0.40	0.32	0.25	0.44	0.41	0.49	0.49	0.18	0.17	0.12	0.28	0.28	0.44	0.17	0.26	0.29
+	+	+	+	-	+	+	+	+	-	-	+	-	+	-	-	+

Table 2: Values of $\tilde{p}_j$ and the signum of the posterior median of each hospital parameters.

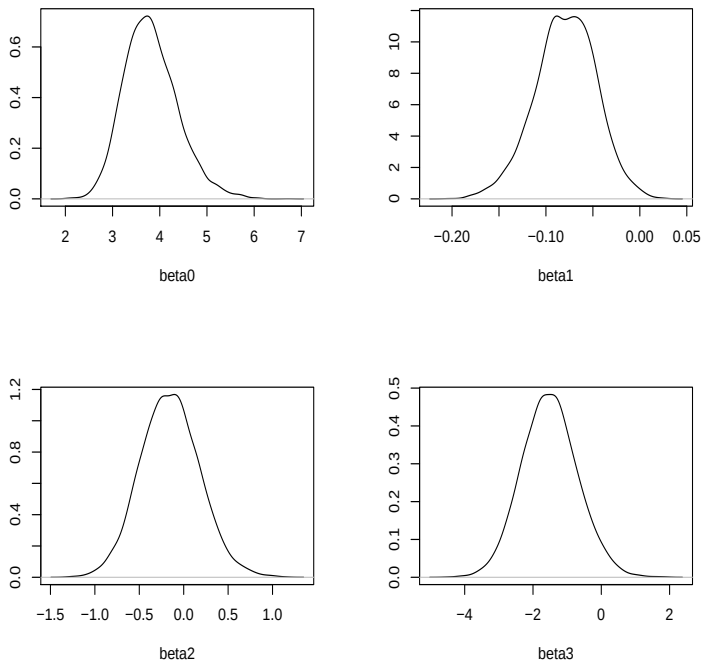

Figure 1: Marginal posterior density of the regression coefficients under the informative prior.

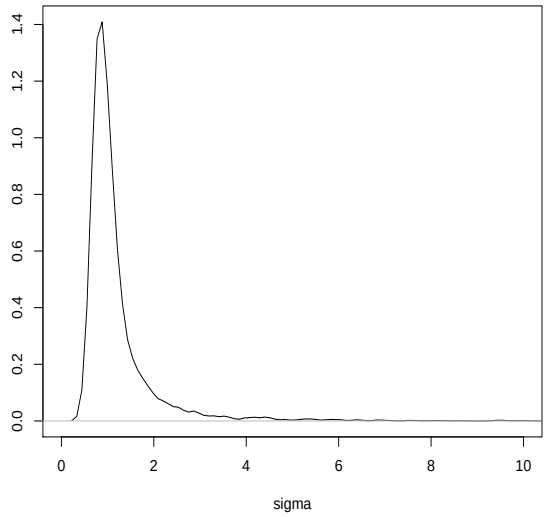

Figure 2: Marginal posterior density of σ under the informative prior.

(a) : $x_1 = 0$, $x_2 = 0$, $x_3 = 0$, *i.e.* a patient with average age (64 years), average OB (553 min.) and less severe infarction (Killip class 1 or 2);

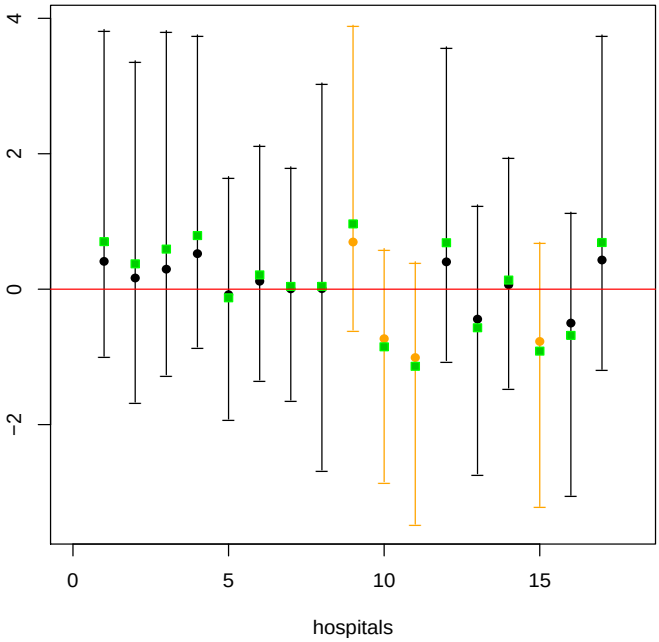

Figure 3: Posterior median (bullet), mean (green square) and 95% credibility intervals of all random effect parameters. The CI intervals for hospitals such that $\min(\mathbb{P}(b_j > 0|\boldsymbol{y}), \mathbb{P}(b_j < 0|\boldsymbol{y})) < 0.18$ are in yellow.

- (b) : $x_1 = 0$, $x_2 = 0$, $x_3 = 1$, *i.e.* a patient with same age and OB as (a), but with severe infarction (Killip class 3 or 4);
- (c) : $x_1 = 16$, $x_2 = 0$, $x_3 = 0$, *i.e.* an elder patient (80 years), with average OB (553 min.) and less severe infarction;
- (d) : $x_1 = 16$, $x_2 = 0$, $x_3 = 1$, *i.e.* an elder patient with average OB and severe infarction

coming from an hospital already in the study. The last credibility interval (in red in each panel) corresponds to the posterior predictive survival probability (9) of a benchmark patient coming from a *new random* $(J+1)$-th hospital. Moreover, from the figure it is clear that killip has a stronger (on average) influence on survival than age since, moving from left to right panels (same age, killip increased) the credibility intervals get much longer than moving from the top to the bottom panels (same killip, age increased).

Finally, as far as predictive model checking is concerned, we computed predictive values (10); the classification rule described in Section 5 gives an error rate equal to 27% (64 patients were erroneously classified as dead and only 1 patient was erroneously classified as alive). This rule can be generalized as follows: a patient is classified as alive if $\mathbb{E}(Y_i^{new}|\boldsymbol{y}, \boldsymbol{x_i}, b_{k[i]})$ is greater than a fixed threshold t; the choice $t = \bar{y}_n$ gives the 27% error rate. In this way, we were able to plot the ROC curve in Figure 5, *i.e.* the

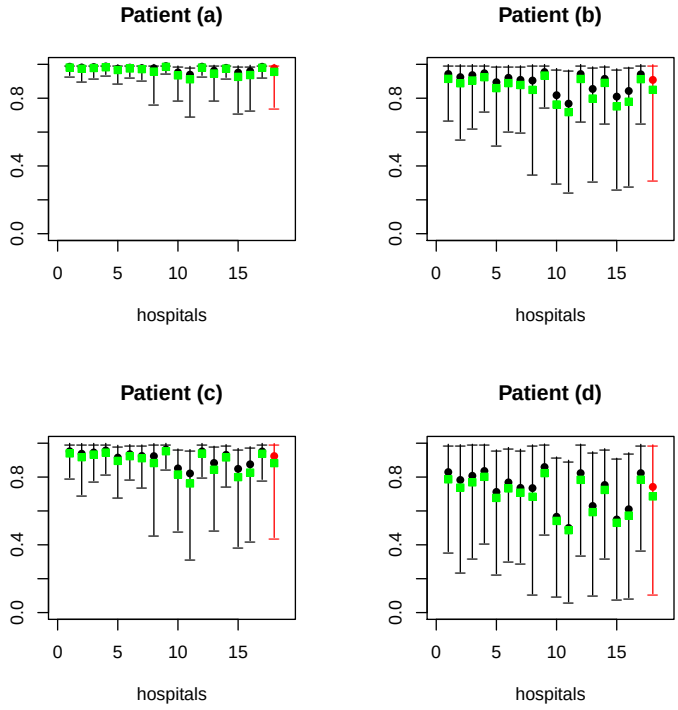

Figure 4: Posterior median (bullet), mean (green square) and 95% credibility intervals of the posterior predictive survival probabilities for 4 *benchmark* patients from each hospital in the study and from a *new random* hospital (the 18-th red CI).

True Positive Rate versus False Positive Rate, for a grid of values of the threshold t ranging from 0.5 to 1. As measure of goodness of fit we also computed the Brier score, the average squared deviation between predicted probabilities and outcomes, which is equal to 0.04. The Brier score, as well as the ROC curve in Figure 5, shows a fairly good predictive fit of our model.

Figure 6 displays the posterior distributions of the Bayesian residuals, see (11), for each observations, where the red line in the plot denotes the prior marginal distribution (logistic). The picture shows that there are no outlier among the patients who survived, since their densities cluster close to the prior density. More variability appears among the dead patients as far as posterior location and dispersion are concerned.

7 Conclusions

In this work we have considered a Bayesian hierarchical generalized linear model with random effects for the analysis of clinical and administrative data with a multilevel structure. These data arise from MOMI^2 clinical register, based on a survey on patients admitted with ST-Elevation Myocar-

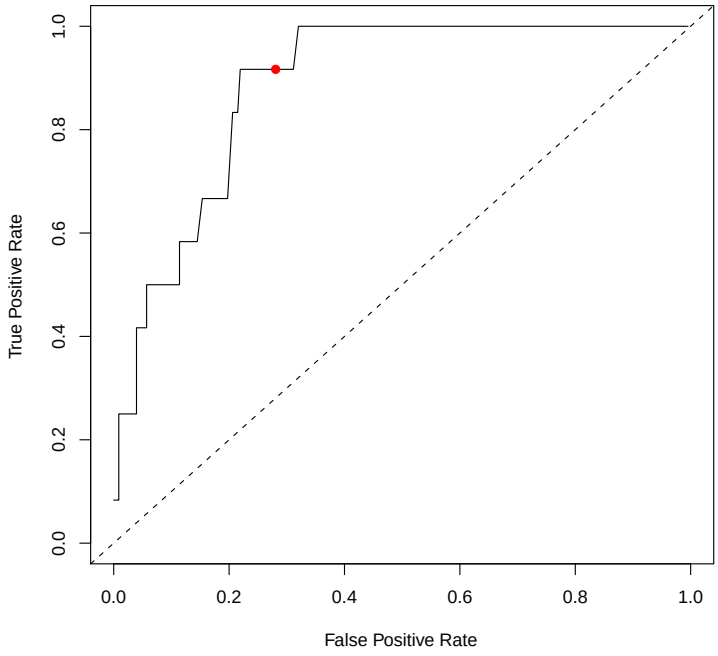

Figure 5: ROC Curve: True Positive Rate versus False Positive Rate, for binary classifiers with different thresholds. Red solid bullet corresponds to threshold equal to empirical estimation of survival probability.

dial Infarction diagnosis, integrated with administrative databanks. The analyses carried out on them could provide a decisional support to people concerned with cardiovascular health care governance. We adopted a Bayesian point of view to tackle the problem of modelling survival outcomes by means of relevant covariates, taking into account overdispersion induced by the grouping factor, i.e. the hospital where each patient has been admitted to. To the best of our knowledge, this study is the first example of a Bayesian analysis of data arising from linkage between Italian administrative databanks and clinical registers. The main aim of this paper was to study the effects of variations in health care utilization on patient outcomes, since the adopted model points out relationships between process and outcome measures. We also provided cluster-specific estimates of survival probabilities, adjusted for patients characteristics, and derived estimates of covariates effects, using Markov chain Monte Carlo simulation of posterior distributions of parameters; moreover we discussed model selection and goodness of fit. We found out that Killip first, and age, have a sharp negative effect on the survival probability, while the OB time has a lighter influence on it. The resulting variability among hospitals seems not too large, even if we underlined that 4 hospitals have a more extreme

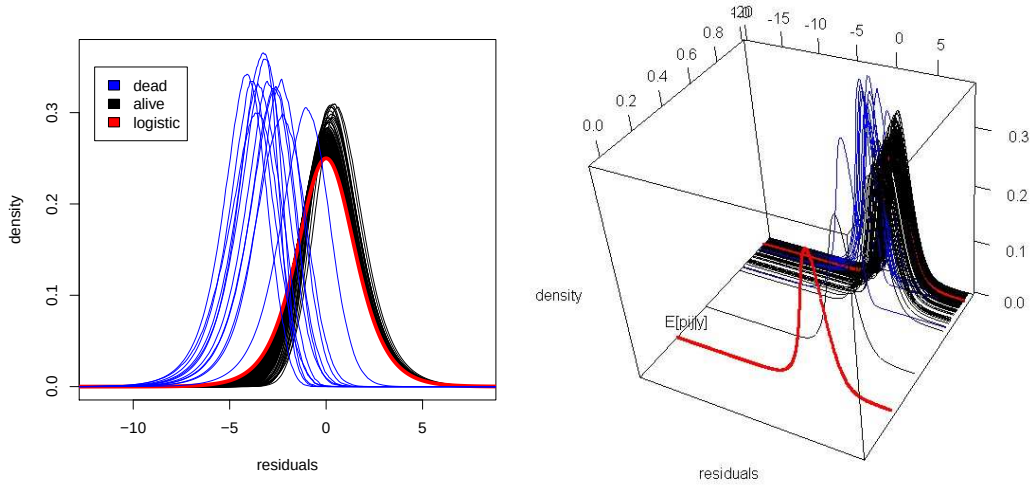

Figure 6: Posterior distributions of the latent Bayesian residuals against the fitted probabilities. The *blue* and *black* lines correspond to observations $y_i = 0$ and $y_i = 1$, respectively. The *red* line is the marginal prior distribution (logistic).

effect on the survival: in particular hospital 9 has a positive effect, while hospitals 10, 11 and 15 have a negative effect.

As far as negative features of the MCMC outputs are concerned, we found that the marginal posterior distributions of (β_0, b_j), for each j, are concentrated on lines of the whole parameter space, due to the "confounding" between the intercept parameter and the random-effects parameters. However the mixing and the convergence of the chain, under a suitable thinning, were completely satisfactory.

Finally, as further step of analysis, we are considering Bayesian nonparametrics to model the hospital effects, in order to find out a "better" hospital classification.

References

Albert, J.H. and Chib, S. (1993). Bayesian analysis of binary and polychotomous response data. *Journal of the American Statistical Association*, **88**, 669–679.

Albert, J.H. and Chib S. (1995). Bayesian residual analysis for binary response regression models. *Biometrika*, **82**, 747–759.

Antman, E.M., Hand, M., Amstrong, P.W., Bates, E.R., Green, L.A. et al. (2008). Update of the ACC/AHA 2004 Guidelines for the Management of Patients with ST Elevation Myocardial Infarction. *Circulation*, **117**, 269–329.

Cannon, C.P, C.M.Gibson, C.T.Lambrew, D.A.Shoultz, D.Levy, W.J.French, Gore J.M., Weaver W.D., Rogers W.J., Tiefenbrunn A.J. (2000). Re-

lationship of Symptom-Onset-to-Balloon Time and Door-to-Balloon Time with Mortality in Patients undergoing Angioplasty for Acute Myocardial Infarction. *Journal of American Medical Association*, **283**, 22, 2941-2947.

Chaloner, K. and Brant, R. (1988). A Bayesian approach to outlier detection and residual analysis. *Biometrika*, **31**, 651–659.

Daniels, M.J. and Gatsonis, C. (1999). Hierarchical generalized linear models in the analysis of variation in health care utilization. *Journal of the American Statistical Association*, **94**, 29–42.

Dellaportas, P., Forster, J.J. and Ntzoufras, I. (2002). On Bayesian model and variable selection using MCMC. *Statistics and Computing*, **12**, 27–36.

Dey, D.K., Ghosh, S. K. and Mallick, B.M. (Eds.) (2000). *Generalized linear models: a Bayesian perspective*. Chapman & Hall/CRC, Biostatistics Series, New York.

Gelman, A. (2006). Prior distributions for variance parameters in hierarchical models (Comment on Article by Browne and Draper). *Bayesian Analysis*, **3**, 515-534.

Gelman, A., Carlin, J.B., Stern, H.S., Rubin, D.B. (2004). *Bayesian Data Analysis.* Second Edition. Chapman & Hall/CRC, Boca Raton, Florida.

Grieco, N., Corrada, E., Sesana, G., Fontana, G., Lombardi, F., Ieva, F., Marzegalli, M., Paganoni, A.M. (2008). Predictors of reduction of treatment time for ST-segment elevation myocardial infarction in a complex urban reality. The MoMi2 survey. *MOX Report n. 10/2008*, Dipartimento di Matematica, Politecnico di Milano. Available at: `http://mox.polimi.it/it/progetti/pubblicazioni/quaderni/10-2008.pdf`.

Hasday, D., Behar, S., Wallentin, L. et al. (2002). A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the mediterranean basin. The euro heart survey of acute coronary syndromes. *European Heart Journal*, **23**, 1190–1210.

Ieva, F. (2008). Modelli statistici per lo studio dei tempi di intervento nell'infarto miocardico acuto. *Master Thesis*, Dipartimento di Matematica, Politecnico di Milano. Available at: `http://mox.polimi.it/it/progetti/pubblicazioni/tesi/ieva.pdf`.

Ieva, F. and Paganoni, A.M. (2009). A case study on treatment times in patients with ST-Segment Elevation Myocardial Infarction. *MOX-Report n. 05/2009*, Dipartimento di Matematica, Politecnico di Milano. Available at: `http://mox.polimi.it/it/progetti/pubblicazioni/quaderni/05-2009.pdf`.

Ieva, F. and Paganoni, A.M. (2010). Multilevel models for clinical registers concerning STEMI patients in a complex urban reality: a statistical analysis of MOMI^2 survey. *MOX-Report n. 08/2010*, Dipartimento di Matematica, Politecnico di Milano. Available at: `http://mox.polimi.it/it/progetti/pubblicazioni/quaderni/08-2010.pdf`.

Jneid, H., Fonarow, G., Cannon, C., Palacios, I., Kilic, T. et al. (2008). Impact of time of presentation on the care and outcomes of acute myocardial infarction. *Circulation*, **117**, 2502-2509.

MacNamara, R.L., Wang, Y., Herrin, J., Curtis, J.P., Bradley, E.H. et al (2006). Effect of Door-to-Balloon Time on Mortality in Patients with ST-Segment Elevation Myocardial Infarction. *Journal of American College of Cardiology*, **47**, 2180–2186.

Lunn, D.J., Thomas, A., Best, N., and Spiegelhalter, D. (2000). WinBUGS - a Bayesian modelling framework: concepts, structure, and extensibility. *Statistics and Computing*, **10**, 325-337.

Normand, S.T., Glickman, M.E. and Gatsonis, C.A. (1997). Statistical methods for profiling providers of medical care: issues and applications. *Journal of the American Statistical Association*, **92**, 803-814.

Ntzoufras, I. (2002). Gibbs variable selection using BUGS, *Journal of Statistical Software*, **7**, Isssue 7. Available at: `http://www.jstatsoft.org/`.

R Development Core Team (2009). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria.

Available at: `http://www.R-project.org`.

Racz, J., and Sedransk, J. (2010). Bayesian and Frequentist Methods for Provider Profiling Using Risk-Adjusted Assessments of Medical Outcomes, *Journal of the American Statistical Association* **105**, 489, 48–58.

Raftery, A., Hoeting, J., Volinsky, C., Painter, I., Yeung, K.Y. (2009). *BMA: Bayesian Model Averaging*.

Available at: `http://CRAN.R-project.org/package=BMA`.

Saia, F., Marzocchi, A., Manari, G., Guastaroba, P., Vignali, L., Varani, E. et al. (2009). Patient selection to enhance the long-term benefit of first generation drug-eluting stents for coronary revascularization procedures: insights from a large multicenter registry. *Eurointervention*, **5**, 1, 57–66.

Souza, A.D.P. and Migon, H.S. (2004). Bayesian binary regression model: an application to in-hospital death after AMI prediction. *Pesquisa Operacional*, **24**, 253–267.

Zeger, S.L. and Karim, M.R. (1991). Generalized linear models with random effects: a Gibbs Sampling approach. *Journal of the American Statistical Association*, **86**, 79–86.

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