A hierarchical survival model to describe patterns and factors associated with HIV/AIDS Portuguese hospitalizations

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Abstract

Background

The beneficial effects of highly active antiretroviral therapy, increasing survival and the prevention of AIDS defining illness development are well established. However, the annual Portuguese intra-hospital mortality is still higher than expected. It is crucial to understand the hospitalization behavior to better allocate resources. This study aims to estimate the intra-hospital mortality attributable to the variation in hospitals performance, after adjusting for measurable risk factors.

Methods

The study population consists of all adult discharges with HIV infection in Portuguese hospitals from 2005 to 2007 that were collected from the diagnosis related groups database.

We used hospitalization level variables and group level variables to develop a hierarchical model. The hospitalization level variables were: age, gender, type of admission (urgent or planned), the type of diagnoses related group (medical or surgical), related HIV complication (pneumonia and/or tuberculosis), the patient's residence, the number of diagnoses, the number of procedures and the Euclidean distance from hospital to the centroid of the patient's ward. The characteristics for the Hospital including the number of beds, catchment area and hospital classification according to national health system were employed as group level variables.

Exploratory analyses with Kaplan-Meier were applied to estimate survival curves. Cox proportional hazard models and frailty models were used to identify independent predictors of intra-hospital mortality and to calculate hazard ratios.

Results

We studied 12,078 discharge records 15% of which were deaths. Estimation results show that all the hospitalization level variables are statistically significant at the 1% level, except the number of diagnoses and procedures. Considering the covariates of the hospital, two factors were associated with performance, size and hospital classification. There were significant frailty effects among hospitals, with hazard ratios varying between 0.67 and 1.34, and an estimated variance of 0.032.

Conclusions

Strong independent predictors of intra-hospital mortality were male gender, urgent admission, medical diagnoses related group and pneumonia. The fit of the estimated frailty model is better than the one estimated by the usual Cox model, suggesting that the clustering effect of hospitals is relevant. The quality of the health care in Portuguese hospitals reveals a satisfactory equity level, with only one hospital presenting a higher risk of death than the average.

Background

The introduction of highly active antiretroviral therapy (HAART) in late 1996 dramatically improved the prognosis of Human Immunodeficiency Virus (HIV) infected patients in most developed countries [1, 2]. Consequently, the estimated number of worldwide deaths due to HIV/AIDS is declining, which is attributable to the scaling up of antiretroviral treatment services. Nevertheless, HIV/AIDS remains a leading cause of mortality worldwide. In Portugal, although the access to treatment has been free of charge since 1996 and available in all hospitals since 2005, HIV/AIDS is one of the major reasons of death. Despite declining mortality over the last years, adult HIV prevalence is still high, ranging from 0.1% to 0.6% in Europe during 2007. Portugal is one of the countries with the highest prevalence (0.5%) [3], where 31667 (0.3%) cases of HIV/AIDS were notified in 2007 [4].

HIV/AIDS is one of the major financial burdens on health care system in all countries. In the United States of America the average annual HIV/AIDS charge per patient was estimated to be approximately $18.000 during 1996-2000 [5]. In Portugal, the hospitalizations related to HIV infection are also some of the most expensive; the average daily cost is around €825 and it is the second major diagnosis category (MDC) with higher average hospitalization time. The average length of stay (LOS) in Portuguese hospitals from the National Health Service (NHS) was 23 days in 2006 [6, 7]. Although this value is very high compared with other countries such as the USA or Canada where the average is around 5 days [5, 8], it is more similar compared with European countries such as Germany where the average LOS is 20 days [9].

In recent literature several approaches have been adopted to analyze LOS. Barbour et al. [5] used a multivariable linear regression model to study inpatients charges among HIV/AIDS. On the other hand Huang et al. [10] used a generalized linear mixed model to study LOS and costs and

Wang et al. [11] adopted a two-component Poisson mixture model to analyze maternity LOS. In this study, LOS will be considered the main vehicle that allows the study of intra-hospital mortality of HIV infected patients.

In the study of intra-hospital mortality one has to be aware that the risk of death cannot be assumed to be homogeneous but must be considered as a heterogeneous, i.e. a mixture of individuals with different hazards. In this particular case, the intra-hospital mortality may vary according to individual patient and hospital characteristics. The former can be taken into account including covariates at hospitalization level in a classical Cox Model. Differences in the health services can be assessed using hierarchical models, including variables at hospitalization and hospital levels, allowing the estimate of differences in outcome not fully explained by observed patient or other specific and known conditions. Hierarchical (or multilevel) models allow the partition of the random variability between and within hospitals. The hospital specific random error component is interpreted as representing differences in hospital performance. Consequently, hierarchical modeling is strongly advocated as a more appropriate statistical method for dealing with outcome data when hospitalizations are clustered within hospitals [12-15].

The aim of this paper is to describe patterns and factors associated with intra-hospital mortality attributed to HIV infectious disease. We propose the use of a hierarchical time survival model to analyze data of HIV discharges in Portuguese hospitals during 2005 to 2007.

To our knowledge, this is the first study using this type of methodology for HIV discharges in Portugal. This analysis is particularly relevant giving the burden associated with HIV namely, in the current context of costs cutting to within the National Health Service (NHS).

Methods

Data source

The data was provided by the Central Administration of Health System (ACSS) and refers to the Portuguese national database of the diagnosis related groups (DRG – All Patients v21.0). In the DRG database each record corresponds to a discharge episode and contains information about

the patient and information collected whilst the patient was in hospital: gender, age, principal and secondary diagnoses, the hospital where the patient was admitted, admission and discharge dates, type of discharge, ward (administrative sub-division of a county), county and district of the patient's residence, admission type, DRG type and procedures undergone.
Hospital characteristics were obtained by using data provided by ACSS and the Portuguese National Institute of Statistics.

Study Population

For this study, we considered all discharge registers that took place in Portuguese NHS hospitals, occurred from 1st January 2005 to 31st December 2007 and attended the following criteria:

a) Hospitalizations classified under the MDC 24 created for HIV infections patients, which incorporates the DRG 700-716;
b) Inpatients aged 18 years-old or older;
c) Geo-referenced cases, i.e., hospitalization with patient residence ward known;
d) Hospitalizations from hospitals with more than 10 discharges; all hospitalizations were included except the ones for transfers to another hospital to avoid including the inpatient episode twice, given that often the cause of the transfer was lack of procedure facilities;
e) Hospitalizations with LOS $\geq$ 1day.

Considering these criteria we selected 12,078 hospitalizations occurred in 43 public Portuguese NHS hospitals.

Dependent variable

The dependent variable considered in this analysis was the number of days between the hospital admission and discharge dates (LOS). Death was assumed to be the outcome of interest and censoring was considered when patient were alive at discharge.

Covariates

Discharge level variables

The discharge variables considered in this study were: the age of the patient on admission, gender, the type of admission (urgent or planned), the type of DRG (medical or surgical), the HIV infection related complication (pneumonia and/or tuberculosis), the patient's residential area (North, Centre, Lisbon and Tagus' valley and the South). Specific data on income,

education, and other components of socioeconomic status (SES) were not available. Therefore, we utilized the type of admission variable as a proxy for SES as in Barbour et al. [5]. The Euclidean distance from hospital to the centroid of patient's residential ward in kilometers was also calculated. In addition, the number of diagnoses and the number of procedures undertaken were also available for each hospitalization. In an exploratory analysis, age, the number of diagnoses and procedures were divided into two categories according to their median value (age: ≤ 39, >39 years; number of diagnoses ≤5, >5; and number of procedures ≤ 8, >8). The distance was categorized according to its average value of 13 km.

Group-level variables (hospital characteristics)

The following information was selected to characterize the NHS hospital: the hospital size (number of beds) and were analyzed via two categories, 500 beds maximum and greater than 500 beds; if the patient lived in the catchment area of the hospital classifications according to NHS administrative structure (hospitals offering more differentiated services denoted central, or not).

Statistical analysis

Descriptive statistics were computed for all variables: means, medians and standard deviations for continuous variables, and frequencies and percentages for categorical variables.

Kaplan-Meier (KM) estimators were applied to estimate survival curves and log rank tests and Peto tests were used for comparison between variables categories.

Cox proportional hazard models [16] were used to identify independent predictors of intra-hospital mortality and calculate hazard ratios (HR).

To take into account the left truncation of the survival discharges data we adopted the Cox model with a counting process approach and also included random effects to deal with covariates hierarchy denoted frailty models. This random effect can be thought of as a "frailty", increasing hospital's susceptibility to short survival time when it is large, and decreasing this susceptibility when it is small.

The equation $\lambda(t|\mathbf{x}) = z\lambda_0(t).\exp(\mathbf{x}\boldsymbol{\beta})$ describes the frailty model where $\mathbf{x}$ are the covariates matrix, $\boldsymbol{\beta}$ are the fixed effect vector and Z is a random variable representing an unknown random effect, and related to hospitals, with the unit mean and variance ξ. This random effects act multiplicatively on the baseline hazard and large values of ξ reflect a great degree of

heterogeneity among hospitals. Groups with frailty >1 tend to experience the event at a faster rate than under the basic Cox model, indicating in our case a poor hospital performance. On the other hand, when frailty is <1, survival times tend to be longer. It should be noted that when the variance of Z approaches zero, the model reduces to the basic Cox model. For model distributions purposes, we assumed that the frailties were distributed according to a gamma distribution [17]. One attractive feature of the gamma distribution is that it is mathematically tractable. Frailty models were treated as a penalized Cox model [18] and were estimated using survival package from R software [19].

We started by including in a basic Cox model only the hospitalization level and group level variables which were statistically significant at 10% level in KM analysis then the random effects were added. The comparison between the Cox model and the Frailty model was made by likelihood ratio (LR) test. All the statistical analysis were performed using R statistical software [20].

Results

Between 2005 and 2007 there were 14,165 HIV/AIDS discharges, but only 12,078 attended the inclusions criteria as shown in the diagram at Figure 1.

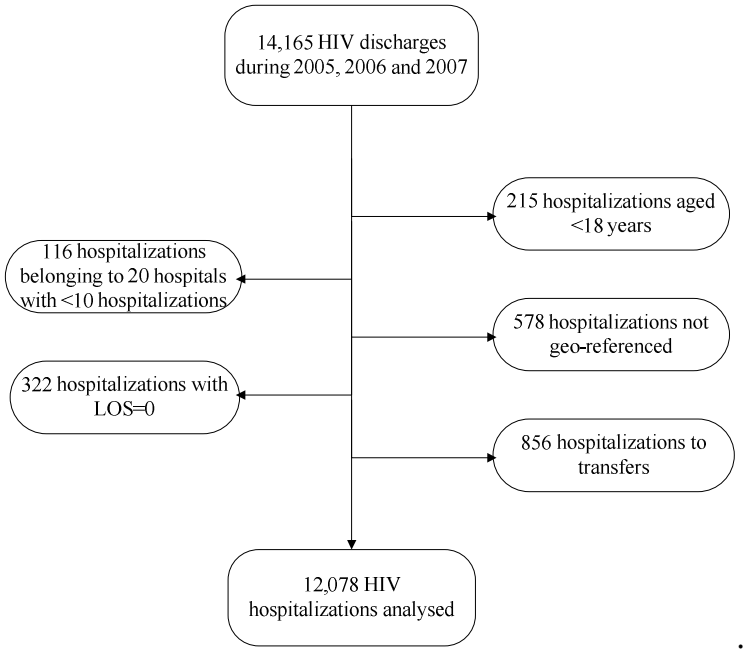

Figure 1: Selection profile of study population

The median LOS was equal to 12 days (interquartile range 6-24). Summary statistics of the hospitalization according to episodes and hospitals characteristics are given in Table 1.

Table 1: Characteristics of HIV discharges in NHS Portuguese hospitals

Variables (mean ± sd)	**n=12078**
Age; years	41.6 ± 11.5
LOS; days	19.2 ± 24.8
Number of diagnoses	6.2 ± 3.5
Number of procedures	8.2 ± 4.3
Gender (%)	
Male	8954 (74.1)
Female	3124 (25.9)
Year of discharge (%)	
2005	4111 (34.0)
2006	4124 (34.2)
2007	3843 (31.8)
Type of admission (%)	
Urgent	10281 (85.1)
Planned	1797 (14.9)
Type of DRG (%)	
Medical	11192 (92.7)
Surgical	886 (7.3)
Pneumonia (%)	2401 (19.9)
Tuberculosis (%)	2256 (18.8)
Hospital size (beds)	538.3 ± 360.1
Hospital catchment area	
Live in (%)	8998 (74.5)
Live out (%)	3080 (25.5)
Hospital classification	
Central	8206 (68.0)
Non central	3872 (32.0)

Out of 12,078 discharges, 8,954 (74.1%) were male and the median age was 42 years. The number of discharges decreased 7.8% in the last year. There were 10,281 (85.1%) urgent admissions and the majority of the discharges (92.7%) had medical DRG. Over these 3 years, the most common HIV related complications of pneumonia and tuberculosis accounted for 19.9% and 18.7% of the discharges, respectively. The endpoint death occurred in 15.2% (1,882) of the hospitalizations.

In the exploratory analysis with KM, older male, patients, urgently admitted and with medical DRG, were all associated with a quicker progression to death (Figure 2).

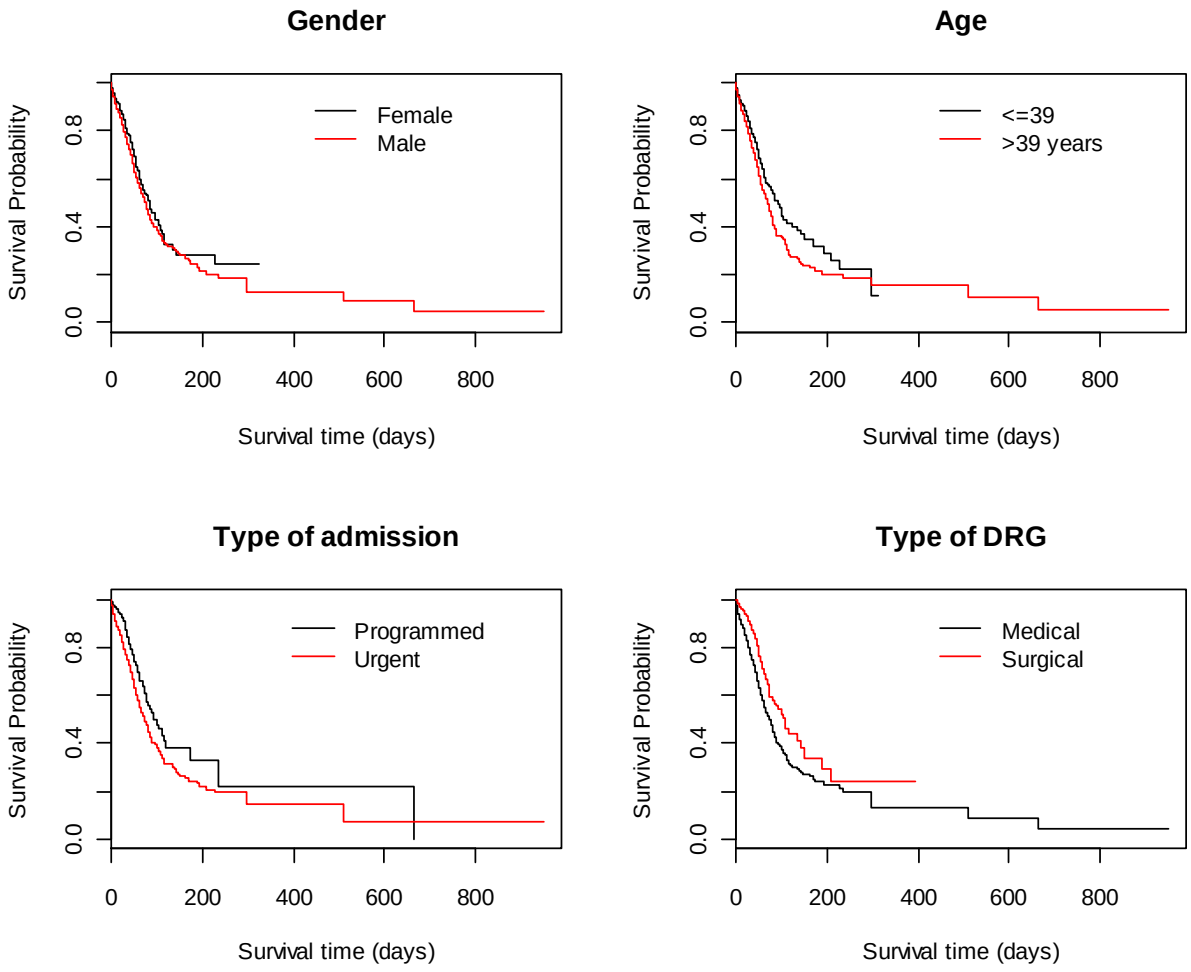

Figure 2: KM estimates of survival for selected variables: gender, age, type of admission and type of DRG

For these four variables log rank and Peto tests for KM survival differences were all highly significant ($p<0.001$). Greater number of diagnoses and procedures also presented lower survival. The main HIV related infection complication risk factor for survival was pneumonia and is also statistically significant, as can be seen from Table 2. Patients with tuberculosis showed a great median survival LOS and this was also statistically significant. The Euclidean distance from hospital to patient residential ward was also statistically significant at 5% level. The year of discharge and the administrative region did not reach statistical significant differences. All hospital characteristics were statistically significant at 10% level.

Table 2: Kaplan-Meier survival estimator of 12078 HIV hospitalizations

Variables	Median survival LOS (95% CI)	p-value Log Rank test	p-value Peto test
Gender			
Male	75 (69; 80)	<0.001	<0.001
Female	84 (73; 104)		
Year of discharge			
2005	76 (71; 87)		
2006	78 (69; 100)	0.357	0.405
2007	75 (68; 88)		
Age			
≤ 39	92 (83; 104)	<0.001	<0.001
> 39	71 (65; 76)		
Type of admission			
Urgent	75 (69; 80)	<0.001	<0.001
Planned	95 (77; -)		
Type of DRG			
Medical	75 (69; 80)	<0.001	<0.001
Surgical	110 (84; 191)		
Number of diagnoses			
≤ 5	83 (74; -)	0.040	0.080
> 5	75 (69; 80)		
Number of procedures			
≤ 8	100 (80; 140)	0.175	0.031
> 8	75 (69; 80)		
Pneumonia			
Yes	53 (48; 59)	<0.001	<0.001
No	87 (81; 100)		
Tuberculosis (yes)			
Yes	97 (83; 113)	<0.001	<0.001
No	69 (64; 78)		
Region			
North	75 (64; 85)		
Centre	78 (68; 135)	0.258	0.193
Lisbon and Tagus' valley	78 (70; 84)		
South	- (74; -)		
Distance			
≤ 13 km	75 (69; 80)	0.008	0.023
> 13 km	92 (75; 170)		
Hospital size			
N. beds ≤ 500	76 (70; 84)	0.089	0.078
N. beds > 500	79 (72; 85)		
Hospital catchment area			
Live in	75 (69;79)	0.009	0.014
Live out	87 (78; 110)		
Hospital classification			
Central	82 (75; 88)	<0.001	<0.001
Non central	71 (61; 79)		

According to KM analysis and taking into account that Euclidean distance and the catchment area were highly associated and that Euclidean distance does not represent the real distance between the hospital and the residential ward, we choose catchment area as a proxy of residential distance from hospital. So, the final model included the following variables: gender, age, type of admission, type of DRG, the number of diagnoses, the number of procedures, pneumonia, tuberculosis, hospital size, the hospital catchment area and the hospital classification.

Table 3 shows the HR for each covariate in survival models with and without frailty. As expected, men increase the risk by 27.0% in comparison to women. Each additional year of age only leads to an increase in risk of 1.3%. Urgent admission presents the higher risk, increasing it by >60% in comparison with programmed admission. Surgical DRG reduces the risk of death by 44%. Pneumonia is the most serious HIV related infection complication increasing risk by 43% and tuberculosis has a protective effect. Parameter estimates of individual covariates are quite similar for both models.

Table 3: Cox proportional hazards models for in-hospitals mortality

	No frailty		**Frailty**	
Variables	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Gender (male)	1.270 (1.13; 1.42)	<0.001	1.273 (1.14; 1.43)	<0.001
Age (years)	1.013 (1.01; 1.02)	<0.001	1.013 (1.01; 1.02)	<0.001
Type of admission (urgent)	1.698 (1.43; 2.02)	<0.001	1.591 (1.33; 1.91)	<0.001
Type of DRG (surgical)	0.569 (0.47; 0.69)	<0.001	0.560 (0.46; 0.68)	<0.001
Number of diagnoses	1.019 (1.00; 1.03)	0.012	1.021 (1.01; 1.04)	0.009
Number of procedures	0.996 (0.98; 1.01)	0.580	0.993 (0.98-1.01)	0.340
Pneumonia	1.428 (1.29; 1.59)	<0.001	1.431 (1.29; 1.59)	<0.001
Tuberculosis	0.780 (0.69; 0.88)	<0.001	0.783 (0.69; 0.88)	<0.001
Hospital size (>500 beds)	1.118 (1.01; 1.24)	0.033	1.144 (0.93; 1.41)	0.210
Live in catchment area	1.032 (0.92; 1.16)	0.590	1.011 (0.90; 1.14)	0.850
Central hospital	0.799 (0.72; 0.89)	<0.001	0.809 (0.66; 0.97)	0.022
Marginal likelihood	-9658.18		-9626.56	
Frailty variance			0.032	0.002

As regards hospital covariates, the catchment area is not statistically significant in both models. The hospital size only presents statistical significance in the Cox Model without frailty. Nonetheless, large hospitals (>500 beds) increased risk by greater than 12% in comparison with smaller hospitals. The central hospital is statistically significant at 5% level in both models and can be considered a protective factor decreasing the hazard by 20%.

When hospital frailties are included in the model, there is an increase in the marginal likelihood. For just one degree of freedom in the model, the likelihood increased from -9658.18 to -9626.56. The inclusion of a frailty effect expands the confidence intervals, and the catchment area and the hospital size lost statistical significance.

The estimated frailty variance (0.033) is significant and indicates the presence of a small variability among NHS hospitals (Figure 3). The HRs of hospitals estimated through the frailty effect varied from 0.67 to 1.34 are presented in Figure 3 with their respective confidence interval. In particular, there is only 1 hospital with frailty significantly above 1 and there is also 1 hospital with frailty significantly below 1. Hospital number 1 (with frailty significantly below 1) corresponds to a large teaching central hospital in a metropolitan area while hospital number 43 (with frailty significantly above 1) is a non central hospital in a smaller area.

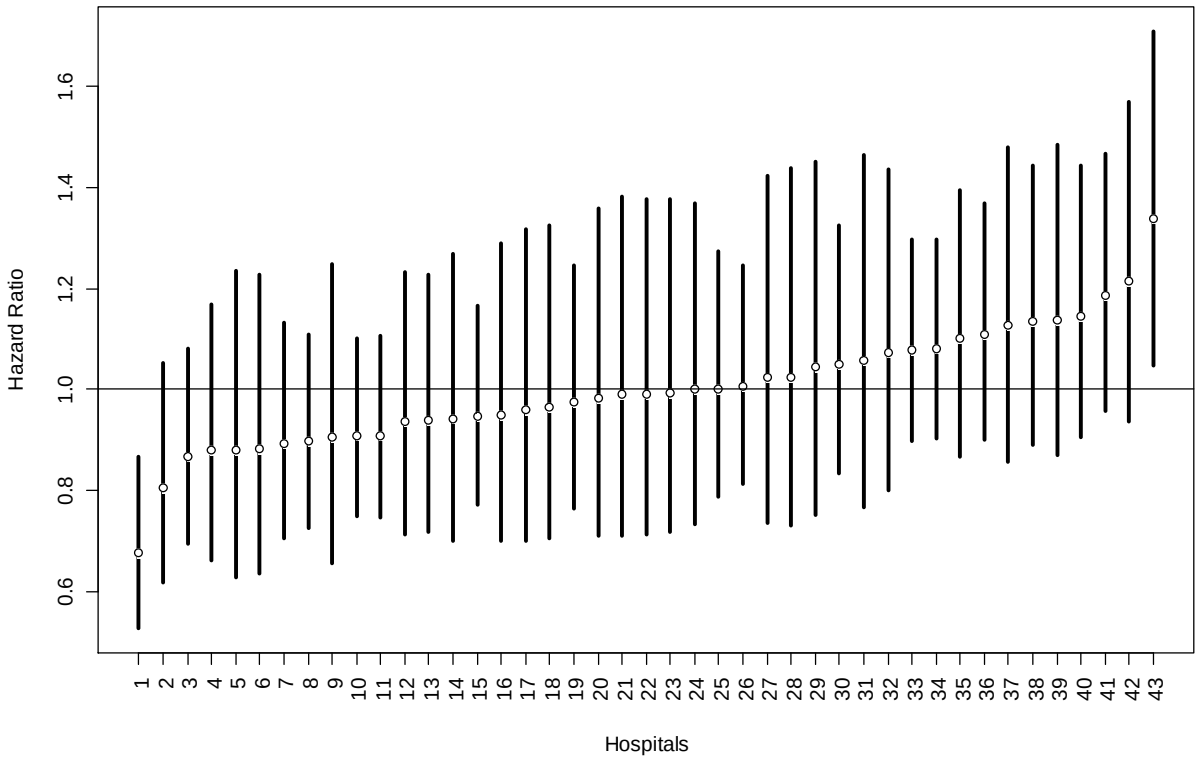

Figure 3. Frailty model estimates of HR of hospitals showing the point estimate (circle) and their respectively 95% CI band

Discussion

Since 1980, the healthcare systems in industrialized countries have been through deep changes to reduce excessive expenses in healthcare, particularly the expenses in hospitals. From several proposals, the classification given by Fetter et al. [21] was the one that got wider approval for evaluating the results of each hospital. In this classification, the leading diagnoses and the proceedings used during the hospital stay will be used to classify the patient in a DRG that determine the quota to be paid to the hospital.

Therefore, DRGs were created so that we can get a classification system of patients admitted to hospitals, according to the grouping in clinically homogenous classes and assuring a coherent typology, according to consumption and resource. Its development in Portugal is connected to the need of creating a hospital financing system integrated in the NHS.

This study was conducted to build a hierarchical model using data from the national DRG data base. Exploratory data analysis suggested that data set was adequate for the purpose of the study.

The Portuguese DRG data base started in 1994, but we only studied the period between 2005 and to 2007. Mortality was high in this study, and most deaths occurred within 3 months of hospitalization.

The discharge variables included in the model behaved as expected. Urgent admission has the highest risk. As it can be seen as a proxy for SES, this finding confirms the results obtained in previous studies where patients with urgent admission are of lower SES when compared to patients with programmed admission [22, 23].

Pneumonia was also a strong predictor of intra-hospital mortality in our study. Patients with pneumonia were 1.5 times as likely to die when compared with those without pneumonia. This result is in accordance with studies from Europe [24] and North America [25, 26] showing that pneumonia is an important predictor of mortality in patients with AIDS.

On the other hand, tuberculosis has been associated with improved survival [27-29]. In our study, tuberculosis was also a protective predictor of intra-hospital mortality, reducing the risk of death by 22%. This is because HAART significantly reduces the risk of developing active tuberculosis among HIV infected people [28].

The number of diagnoses and procedures for a particular patient is associated with the complications and co-morbidities that the patient had during hospital stay. A great number of

diagnoses or procedures usually indicate a more severe condition of the patient [30]. In this analysis only the number of diagnoses was statistically significant in both models.

The frailty model estimated a small variability among hospitals (range 0.67 to 1.34), although it is statistically significant.

Standard single-level models, usually adopted in these studies, treat all hospitalizations as independent observations. Actually, patients are nested in hospitals on the basis of reasons that lead them to make some choices (place of residence, trust in a particular doctor, the hospital's reputation, etc), thus violating one of the basic assumptions of traditional regression analysis. In hierarchical models the random variability of data is divided into two parts: variation between different hospitalizations and between different hospitals. The hospital frailty component is interpreted as representing differences in hospital quality.

Therefore hierarchical modeling represents an appropriate statistical method for dealing with data when individual patients are clustered within hospitals [12-15, 31].

The use of the frailty model revealed a variation in risk not resulting from any of the measured covariates. One possible explanation for this variability could be the ease of access the hospital and the different services available. Due to the inexistence of a variable for measuring the accessibility, one way to incorporate this could be through the investigation of a geographical pattern in the frailty of hospitals [32, 33]. In this study, we used the catchment area but this variable was not statistically significant in the frailty model, though more investigation is needed.

Study limitations

This study, like most studies, has limitations. The DRG data cannot account for multiple admissions reducing our experimental unit to discharge episode instead of patient. It should be stressed that the information on hospital characteristics was gathered for other purposes than this study and some vital features of HIV/AIDS patients are missing, such as CD4 counts and viral charges [8, 34].

Conclusions

The use of DRG data is critical in comparing different hospitals, patients and places. Moreover, the frailty model used in this study proved to be useful for this purpose. Nonetheless, it is a strong candidate to be a very efficient tool for the state health authorities, augment by the fact of software availability. For future developments we want to construct a joint spatial survival model to investigate factors that affect HIV intra-hospital mortality and taking into account geographical factors.

This work can contribute to the debate on the evaluation of a hospital's performance on HIV treatment. Finally, local investigation of higher risk hospitals should be undertaken in order to disclose factors leading to differences in the HIV intra-mortality risk detected in this study.

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