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ABSTRACT

Objective To assess differences in acute ischaemic stroke (AIS) in-hospital mortality between referral stroke hospitals and provide evidence on the association of those differences with the overtime adoption of effective reperfusion therapies.

Design Retrospective, longitudinal observational study using administrative data for virtually all hospital admissions from 2003 to 2015.

Setting Thirty-seven referral stroke hospitals in the Spanish National Health System.

Participants Patients aged 18 years and older with a hospital episode with an admission diagnosis of AIS in any referral stroke hospital (196 099 admissions).

Main endpoints (1) Hospital variation in 30-day in-hospital mortality measured in terms of the intraclass correlation coefficient (ICC); and (2) the difference in mortality between the hospital of treatment and the trend of utilisation of reperfusion therapies (including intravenous fibrinolysis and endovascular mechanical thrombectomy) in terms of median OR (MOR).

Results Adjusted 30-day AIS in-hospital mortality decreased over the study period. Adjusted in-hospital mortality after AIS rates varied from 6.66% to 16.01% between hospitals. Beyond differences in patient characteristics, the relative contribution of the hospital of treatment was higher in the case of patients undergoing reperfusion therapies (ICC=0.031 (95% Bayesian credible interval (BCI)=0.017 to 0.057)) than in the case of those who did not (ICC=0.016 (95% BCI=0.010 to 0.026)).

Using the MOR, the difference in risk of death was as high as 46% between the hospital with the highest risk and the hospital with the lowest risk of patients undergoing reperfusion therapy (MOR 1.46 (95% BCI 1.32 to 1.68)); in patients not undergoing any reperfusion therapy, the risk was 31% higher (MOR 1.31 (95% BCI 1.24 to 1.41)).

Conclusions In the referral stroke hospitals of the Spanish National Health System, the overall adjusted in-hospital mortality decreased between 2003 and 2015. However, between-hospital variations in mortality persisted.

INTRODUCTION

In the last decade, endovascular treatment strategies for acute ischaemic stroke (AIS)

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study has covered virtually all acute ischaemic stroke admissions in referral stroke hospitals in the Spanish National Health System from 2003 to 2015.

⇒ The use of a generalised additive mixed model has yielded a robust assessment of differences in mortality across hospitals as it has allowed modelling time-dependent associations relevant to this topic of study; for example, the uneven adoption of new technologies in referral stroke hospitals, changes in the organisation of stroke care or the evolving indication patterns due to overtime changes in patients' characteristics.

⇒ Although lack of adjustment for patient severity across hospitals can be a study limitation based on the secondary use of routinely collected health data, restricting the comparison to referral stroke hospitals, likely treating similar case-mixes of patients in large numbers, helps to reduce the risk of residual confounding.

have been continuously developing, resulting in a reduction in short-term mortality and a significant increase in functional independence.¹

However, since their introduction, effective reperfusion therapies, such as intravenous fibrinolysis or endovascular mechanical thrombectomy (EMT),^{2,3} have been unevenly implemented across health systems and healthcare providers depending on adequate access to fibrinolysis drugs, lack of specialised resources (eg, stroke units, endovascular operating theatres), adequate access to urgent CT scan imaging or limited coverage of neurointerventional surgeons.^{4,5}

In Spain, the first Stroke Health Care Plan was developed in 2006⁶ by the Spanish Society of Neurology. However, the widespread adoption of reperfusion therapies within the Spanish National Health System (SNHS)

occurred in November 2008 after adopting the National Stroke Care Strategy.⁷

The National Stroke Care Strategy aimed to harmonise stroke care across autonomous communities (ACs), covering all the services to be provided to patients who had a stroke (primary and secondary prevention of stroke, care in the acute phase, rehabilitation and return to everyday life, as well as training and research). Notably, in acute care, the strategy inception the Stroke Code, which is the same for all the ACs, including clinical practice guidelines and protocols, the organisation of care pathways, and the required resources for adequate coverage and provision (telestroke programmes, stroke units, neurosonology resources, diffusion and perfusion magnetic resonance and neurovascular interventions). Instead, the Stroke Code set up a hierarchy of stroke hospitals, with a smaller group acting as referral stroke hospitals for endovascular interventions.⁸

Research on the impact of the National Stroke Care Strategy has primarily focused on monitoring healthcare processes,⁹ case studies,¹⁰ narrative descriptions of clinicians' responses within care guidance and epidemiological studies on the evolution of the health determinants of stroke.¹¹ Still, there has yet to be an assessment of variations in hospitals' outcomes in a period that has witnessed substantial policy and organisational changes in treating AIS.

This study aimed to assess differences in AIS in-hospital mortality between referral stroke hospitals and provide evidence on the association of those differences with the overtime adoption of effective reperfusion therapies.

METHODS

Design

We conducted a retrospective, longitudinal observational study using administrative data for virtually all SNHS hospital episodes between 1 January 2003 and 31 December 2015.

Population and setting

From all the hospital admissions in the study period, we first selected those episodes with an admission diagnosis of AIS (662 997 episodes). Then, we defined *referral stroke hospitals* as those capable of performing EMT confirmed through identifying EMT procedures performed in the last year of analysis (2015).

From those episodes treated in hospitals identified as referral stroke hospitals, we kept only the episodes with a stay shorter than 30 days, restricting the observation of case fatalities to those more likely to be associated with the medical intervention on stroke (ie, deaths in more extended stays are more likely associated with nosocomial infections or the underlying health status of the patient). Finally, to reduce extra-heterogeneity, which may produce an overestimation of the intraclass coefficient, we restricted the study to those referral stroke hospitals with at least 2000 ischaemic stroke episodes recorded

throughout the study period. The final study population included 196 099 episodes from 37 referral stroke hospitals (see flow chart in online supplemental figure 1).

Main endpoints

Hospital variation in 30-day in-hospital mortality measured in terms of the intraclass correlation coefficient (ICC); and (2) the difference in mortality between the hospital of treatment and the trend of utilisation of reperfusion therapies in terms of median OR (MOR).

Variables

In-hospital mortality within 30 days from admission in patients with AIS was defined following the Agency for Healthcare Research and Quality's quality indicators definition¹² (see indicator definition in online supplemental table 1), validated for the SNHS by the Atlas VPM.¹³

Eliciting the potential effect of the hospital of treatment on the risk of death, regardless of the differences in the patients attended, required risk adjustment. Patients' age, sex and the list of Elixhauser comorbidities were used in the risk adjustment following a data-driven approach, thus, retaining in the model only those comorbidities statistically associated with the outcome (significantly associated for an alpha error of 5%).^{14 15} Finally, we included time variables for each episode characterising long-term structural trends and monthly seasonality and identified special admission days, such as bank holidays or weekends.

Data sources

Episodes were extracted from the Atlas VPM dataset that collects virtually all hospital episodes discharged in the public hospitals of the SNHS.¹⁶ In addition, hospital features were collected from the National Hospital Catalogue.¹⁷ Atlas VPM reuses routine data mainly from electronic records from hospital admissions and primary care visits for the identification and selection of cases (eg, surgical procedures of interest, specific diseases, quality and safety events), the analysis of clinical attributes of the patient (eg, comorbidities, concurrent surgery), the analysis of administrative features worth to collect (eg, admission and discharge data, date of surgery) and for the identification of the place of residence (ie, primary, healthcare or area where the patient resides). In addition, Atlas VPM implies a linkage and exchange process with the 17 Departments of Health of the Spanish regions sharing a research agenda assessing unwarranted variations in medical practice and translating research outcomes into profiling and benchmarking tools meant to facilitate clinical and policy decision-making.¹⁸ Notably, as part of its data quality assurance methodology, Atlas VPM conducts regular (once a year) quality checks to, for example, reduce incompleteness, avoid overtime coding variations, correct semantic and syntactic inconsistencies in the variables, or reallocate admission episodes to the place of residence if there are changes in the geolocation of administrative areas or hospital providers.

Table 1 Background characteristics of the population hospitalised due to an acute ischaemic stroke

| | 2003 | 2006 | 2009 | 2012 | 2015 |
|--|---------------|---------------|---------------|---------------|---------------|
| In-hospital mortality (%)[*] | 12.99 | 12.19 | 11.39 | 10.75 | 10.46 |
| Number of deaths (#) | 1686 | 1647 | 1735 | 1809 | 1848 |
| Number of admissions (#) | 12 976 | 13 505 | 15 227 | 16 829 | 17 658 |
| Reperfusion therapy (%) | 0.52 | 2.49 | 7.00 | 12.10 | 15.45 |
| Age, years (SD) | 73.59 (12.17) | 73.46 (12.75) | 73.68 (13.04) | 74.27 (13.11) | 74.04 (13.44) |
| Gender, female (%) | 46.59 | 46.60 | 46.95 | 47.59 | 46.15 |
| Public holiday admission (%) | 26.88 | 27.09 | 26.98 | 27.71 | 27.44 |
| Congestive heart failure (%) | 4.09 | 4.15 | 4.55 | 5.41 | 5.41 |
| Pulmonary circulation disease (%) | 1.03 | 1.21 | 1.60 | 1.77 | 2.07 |
| Chronic obstructive pulmonary disease (%) | 9.65 | 8.34 | 8.37 | 9.30 | 9.44 |
| Renal failure (%) | 2.89 | 3.47 | 5.62 | 6.83 | 7.89 |
| Lymphoma (%) | 0.22 | 0.33 | 0.35 | 0.30 | 0.42 |
| Metastatic cancer (%) | 0.94 | 1.20 | 1.18 | 1.36 | 1.44 |
| Coagulopathy (%) | 0.62 | 0.70 | 0.72 | 1.31 | 1.26 |
| Fluid and electrolyte disorders (%) | 1.52 | 1.47 | 1.90 | 2.35 | 2.83 |
| Drug abuse | 0.28 | 0.59 | 0.72 | 0.66 | 0.83 |

*Absolute and average values every 3 years to highlight their evolution.

Bias control

Our sample includes patients who were alive at the time of admission. Although sudden death is less likely to happen in ischaemic stroke, there might have been an unknown toll of patients dying before arriving at the hospital. Should this number be relevant, this could have affected the estimation of the trend in the first years of the series when emergency care needs were likely undercovered.

Another potential source of bias could be the accuracy of our data source to capture all deaths after AIS within the hospitals in our sample. We checked conditions for in-hospital mortality for ischaemic stroke in Spain, as documented by the Organization for Economic Cooperation and Development (OECD) 2011 Health at a Glance report.¹⁹

Since coding practice has increased over the years, it is more likely to find more secondary diagnoses per episode in the last years of the series. Elixhauser comorbidities are sensitive to coding practice, and coding practice may vary across hospitals; risk adjustment may be affected, artificially smoothing down adjusted rates in those hospitals with a more intensive coding practice. We conducted a sensitivity analysis considering independent coding variables such as age and sex in the models to assess to what extent this might have misclassified hospitals.

Finally, patients can access hospital care differently because of the time distance from their location of residence to the referral hospital, which may imply a selection bias not fully corrected by using the random hospital effect included in our models. Therefore, as the time to treatment may potentially lead to the treatment decisions and the patient's prognosis, we performed sensitivity analyses considering travelling distances from the area of

residence to the nearest hospital when that information was available.

Analysis

Given the time-dependent non-linear association between our endpoint (*in-hospital mortality 30 days from admission*) and some of the predictors, and the hierarchical nature of the data, we used a generalised additive mixed model (GAMM)²⁰ with a logit link function to assess the influence of potential risk factors and other covariates on in-hospital mortality within 30 days of admission. In addition, we added smoothing functions for the covariates with continuous values such as age, months, and the interaction between the time trend and the 'reperfusion therapy' variable. We estimated the smoothing functions non-parametrically using a scatterplot smoother. Thin-plate splines and cyclic cubic splines (in the 'months' covariate) were used as basic functions, and optimal tuning parameters were selected using the cross-validation method to account for seasonality. Finally, we modelled the hospitals' effects as independent random effects adding an interaction parameter between reperfusion therapy (patient level) and the hospital of treatment. Modelling hospitals as random effects allowed us to account for the natural clustering of the ischaemic stroke episodes within each hospital, thus measuring differences among them while considering the interaction with reperfusion therapy enabled also modelling the potential differences between both groups of patients. ICC²¹ and CIs, MOR²² and Bayesian credible intervals (BCIs) were calculated to estimate the independent effect of the hospitals—beyond differences in the underlying risks of patients—on ischaemic stroke case fatalities. The ICC was calculated using

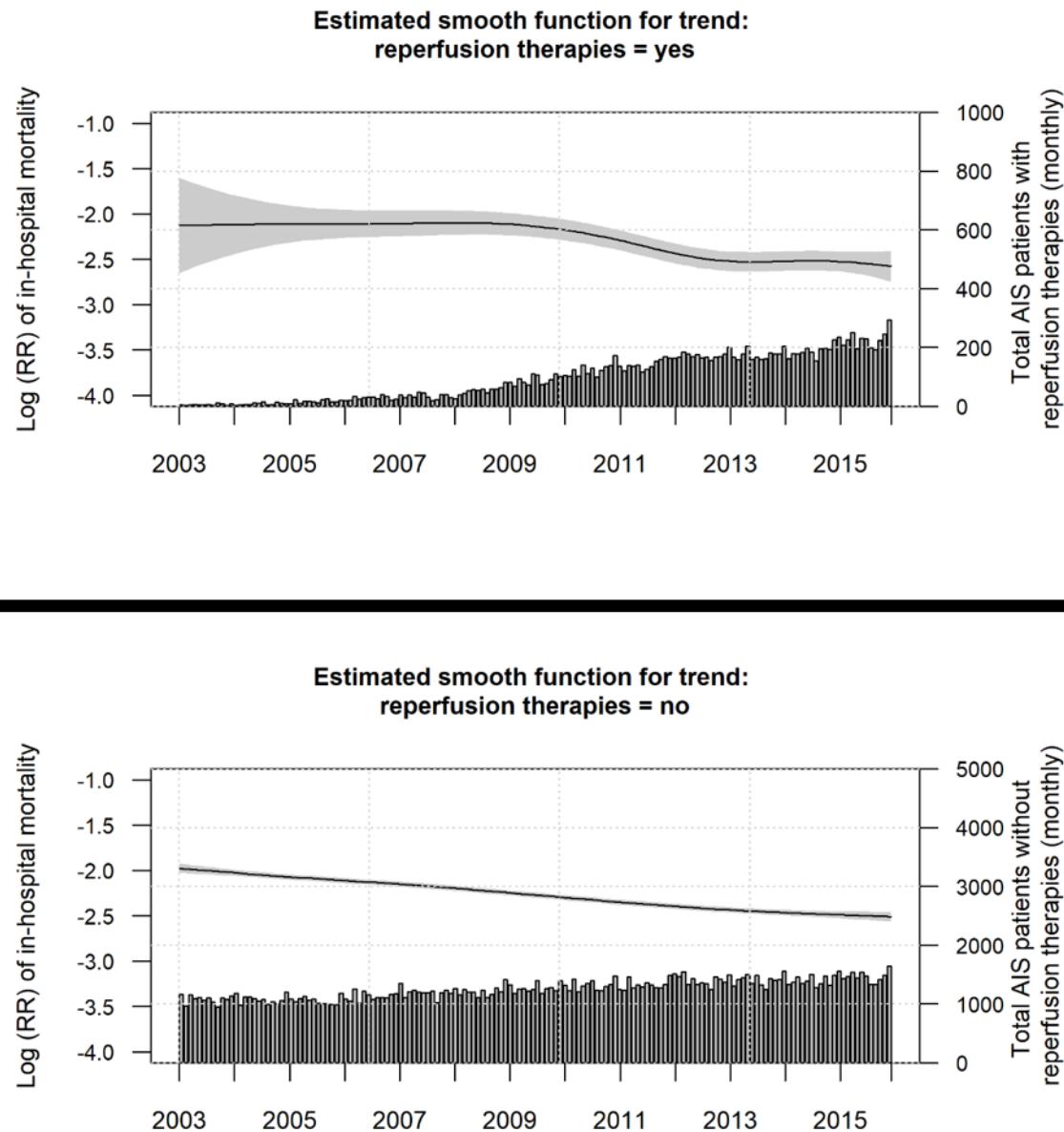


Figure 1 Fitted smooth functions for the in-hospital case fatality trend related to receiving or not reperfusion therapy. The model is fitted using thin-plate splines in the generalised additive mixed model. The main ordinate (left-side y-axis) represents the natural log of the relative risk of in-hospital case fatality due to AIS (log(RR)). The abscissa (x-axis) represents the time period variable (months). The solid line represents the relationship between log(RR) of in-hospital case fatality and the time period variable, with the shaded area representing the 95% CI. The right-side y-axis represents the evolution of the volume of patients with AIS (ie, bars) without reperfusion (above) or with reperfusion (below). AIS, acute ischaemic stroke.

the linear threshold model method, which is just a function of the area-level variance and consequently independent of the prevalence of the outcome. ICC informs of the proportion of total variation in the outcome that the hospital can explain. The MOR translates the variance attributed to the hospital into a more intuitive estimate that informs on the different relative risks for an individual if treated in a hospital with a different underlying risk of the outcome. The MOR is defined as the median value of the distribution of ORs obtained when randomly picking two patients with the same covariate values from two hospitals with a different underlying risk of an event of interest and comparing the one from the hospital with the highest risk with the one from the hospital with the

lowest risk. In simple terms, the MOR can be interpreted as the median increased odds of reporting the outcome if a similar patient (ie, receiving reperfusion therapy or not) were treated in another hospital with a higher risk.

We used t-statistics to test the individual parametric coefficients' significance and evaluated the smooth terms' significance through the effective df. We tested the approximate significance of the smooth terms using χ^2 statistics. Given the large numbers in this study, we performed all hypothesis tests using a type 1 error rate of 0.001. Finally, we considered the receiver operating characteristic curve for the estimation of the goodness of fit of the model. The decision on the final model presented in the results was taken according to the Akaike information

Table 2 Hospital-level random effects on case fatalities considering the differential use of reperfusion therapies

| | Estimate | (95% Bayesian credible interval) | |
|-------------------------------|----------|----------------------------------|--------|
| ICC (reperfusion therapy=no) | 0.0160 | 0.0100 | 0.0258 |
| ICC (reperfusion therapy=yes) | 0.0311 | 0.0167 | 0.0572 |
| MOR (reperfusion therapy=no) | 1.3089 | 1.2354 | 1.4087 |
| MOR (reperfusion therapy=yes) | 1.4589 | 1.3161 | 1.6806 |

ICC, intraclass correlation coefficient; MOR, median OR.

criteria. All statistical analyses were programmed using the R software,²³ including the *mgcv* package,²⁴ to fit the GAMM.

Patient and public involvement

None.

RESULTS

Table 1 describes the population of the study stratified for selected years. Over the period, there was a 36% increase in admissions from 12 976 to 17 658 patients with AIS. In turn, the proportion of patients who received some reperfusion therapy substantially increased from 0.52% to 15.45%. Regarding patients' profiles, the age and sex kept somewhat similar, with patients around 74 years old and 46% female, and an increased number of comorbidities registered, notably renal failure, metastatic cancers, coagulopathy and electrolytic disorders. On the contrary, the number of episodes registering lymphoma or chronic obstructive pulmonary disease (COPD) as comorbidity held over time.

The count of in-hospital mortality within 30 days of admission increased at 9.61%, from 1685 to 1848 in absolute numbers, with a decrease in in-hospital mortality rates from roughly 13% of in-hospital mortality in 2003 to 10.46% in 2015.

Patients' factors explaining differences in adjusted in-hospital mortality after AIS

Once seasonal effects were smoothed, patients who did not get any reperfusion therapy were less likely to die over the years, while those undergoing reperfusion therapy observed a steeper decrease in deaths, specifically after August 2008 (**figure 1**). Older patients were more likely to die within 30 days after admission. For instance, the OR for those patients in their 70s versus those in their 40s is 1.89 (95% CI 1.79 to 2.01). This is likewise the case for patients with metastatic cancer (OR=5.10, 95% CI 4.66 to 5.58), fluid and electrolyte disorders (OR 2.43; 95% CI 2.25 to 2.62), congestive heart failure (OR 2.30; 95% CI 2.12 to 2.42), pulmonary circulation disease (OR 1.69; 95% CI

1.54 to 1.85) and coagulopathy (OR 1.54; 95% CI 1.34 to 1.75). Other comorbidities also significantly associated with in-hospital mortality were renal failure (OR 1.38; 95% CI 1.30 to 1.46) and COPD (OR 1.18; 95% CI 1.12 to 1.23). Finally, patients admitted on a public holiday were more likely to die during their stay (OR 1.05; 95% CI 1.01 to 1.08). Finally, patients receiving reperfusion therapies had an increased mortality risk (OR 1.47; 95% CI 1.25 to 1.73). No statistically significant differences were found in the rest of the variables (see all statistically significant variables associated with the outcome in online supplemental table 2). All fitted smooth terms, including the interaction terms introduced in the model, were found as statistically significant (see online supplemental table 2).

Differences in adjusted mortality across referral stroke hospitals

Adjusted in-hospital mortality rates after AIS varied from 6.66% to 16.01% among hospitals. Beyond differences in patients' characteristics, the relative contribution of the hospital of treatment (**table 2**) was higher in the case of patients undergoing reperfusion therapies (ICC=0.031 (95% BCI=0.017 to 0.057)) than in the case of those who did not (ICC=0.016 (95% BCI=0.010 to 0.026)). Using the MOR, the difference in risk of death was as high as 46% between the hospital with the highest risk and the hospital with the lowest risk in patients undergoing reperfusion therapy (MOR 1.46 (95% BCI 1.32 to 1.68)), while in patients not undergoing any reperfusion therapy, the risk was 31% higher (MOR 1.31 (95% BCI 1.24 to 1.41)). This MOR difference between the two groups of patients was not statistically significant for a χ^2 test of differences ($\chi^2>0.13$; $p=0.7178$). **Figure 2** shows the observed variation across hospitals.

DISCUSSION

This study found a 19.5% decrease in AIS in-hospital mortality rate from 2003 to 2015, despite increasing AIS hospital admissions (36%) with more comorbidities on average.

A steep reduction in AIS in-hospital mortality was observed in 2008 (**figure 1**) in those patients receiving reperfusion therapy, concurrent with the widespread implementation of reperfusion therapies as part of the National Strategy on Stroke Care. However, this change in the trend was not observed in patients not receiving reperfusion therapy. Interestingly, after the decrease, in-hospital mortality rates in patients receiving any reperfusion therapy stagnated even though reperfusion therapies had been widely implemented across hospitals, potentially denoting a new phase in their implementation and utilisation.

These findings are consistent with the evolution of AIS hospital mortality rates in different international studies on the matter, such as the global stroke statistics at the national level,²⁵ the Global Burden of Disease Study,²⁶ or population-based studies in China,²⁷ Germany²⁸ or

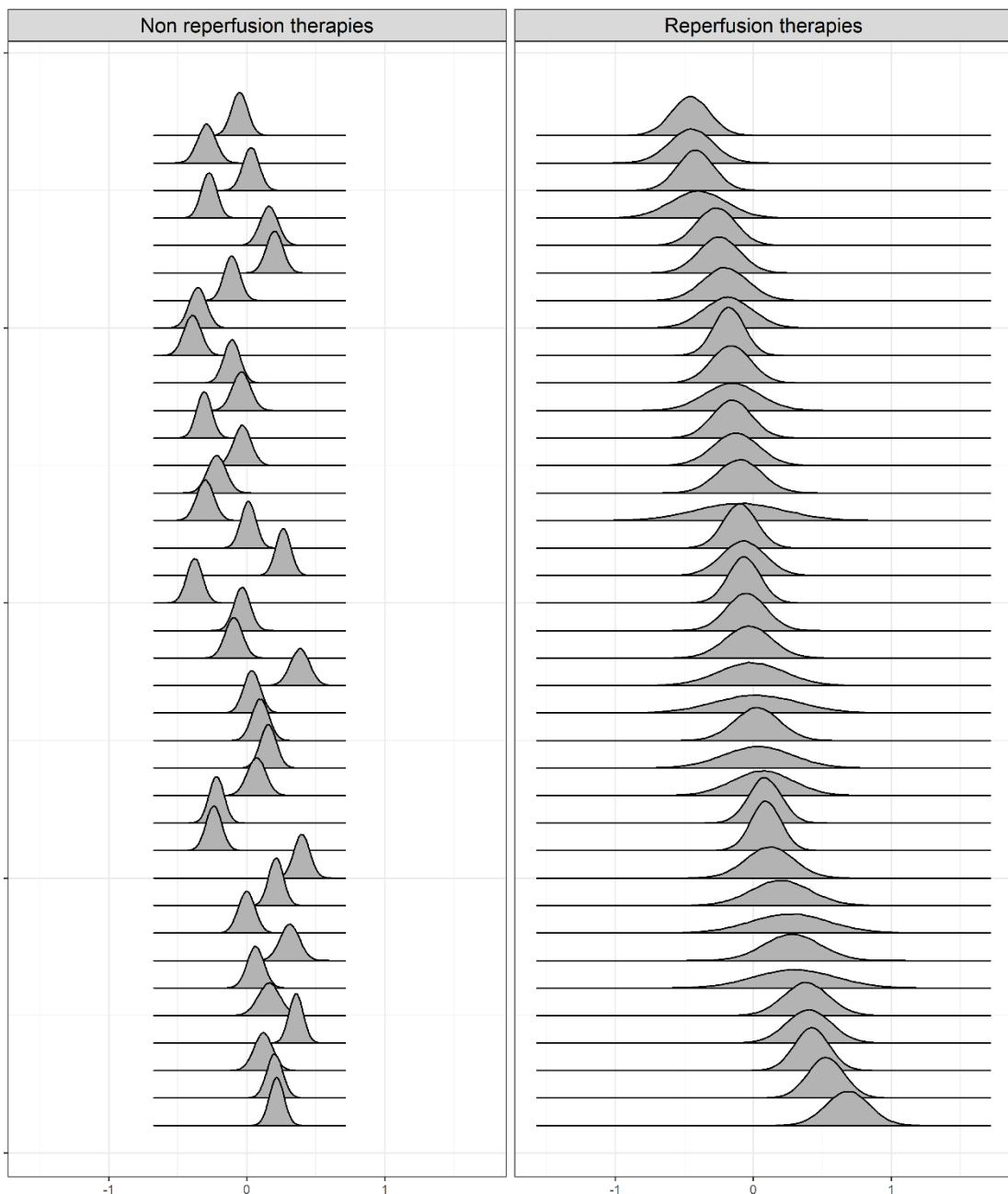


Figure 2 Hospital-level random effects: in-hospital case fatality probability density distribution with and without reperfusion therapy. The model is fitted using thin-plate splines in the generalised additive mixed model. The ordinate (y-axis) represents the referral hospitals for stroke analysed. The abscissa (x-axis) represents the normalised residuals at hospital level (or the in-hospital case fatality probability density distribution) in patients who did not undergo reperfusion therapies and in patients who received reperfusion therapies. The probability density distributions of patients who received reperfusion therapies are sorted by hospital from best to worst performance (in-hospital case fatality rate) to highlight the magnitude of the variation attributed to the hospital in those cases.

England.²⁹ In addition, prior studies on unwarranted variations in AIS in-hospital outcomes in Spain had also elicited differences in mortality rates as large as 4.7-fold after adjusting for age, sex and various comorbidities.³⁰

Regarding our main endpoint, our study shows that referral stroke hospitals explained part of the variation in adjusted in-hospital mortality after AIS after patients' differences and time effects were adjusted in both patients undergoing reperfusion therapy and those who

did not. The risk of dying was estimated to be 31% lower in the best-performing hospitals in patients not receiving reperfusion therapies and 46% lower in those patients receiving reperfusion therapies. The uneven adoption of intravenous fibrinolysis (figure 2), the early adoption of endovascular mechanical thrombectomy only in a small set of referral stroke hospitals,³¹ different learning curves influencing the performance of those more complex interventions, organisational factors that affected the

implementation of the Stroke Code (for example, the existence of Stroke Units) differentially and finally, some unobserved latent factors as uneven patterns of patients' transfers from secondary hospitals to the referral stroke hospitals may explain these differences between hospitals.

Strengths and limitations

A first caveat interpreting our results is that this study focuses on referral stroke hospitals. Thus, any generalisation of the results could be referred to those hospitals accredited to provide high-profile treatments requiring 24/7 on-call specialists. Second, our data sources are limited to registering patients dying during the hospital stay. We did not have access to the patient's status before arriving at the hospital or after being discharged alive, leading to a possible underestimation of the overall mortality. In addition, different kinds of access to treatment because of geographical barriers or distance to the referral hospital, a time-sensible treatment condition, could also lead to differences in the use of reperfusion therapies and, consequently, to higher mortality. To assess the plausibility of this bias, we re-estimated AIS in-hospital mortality rates considering the travel distance (in minutes) from the centroid of the patient's area of residence to the nearest referral stroke hospital for all patients with valid information about the area of residence from 2012 to 2015. As a result, most patients receiving reperfusion therapies (92.42%) lived at a travel distance of 60 min or less, and all, irrespective of the treatment, lived at a travel distance of 180 min or less. This model provided similar results regarding the ICC, remaining the hospital of treatment effect on mortality rates (see online supplemental figure 2A).

Third, it is unlikely that we may have failed in capturing in-hospital deaths after AIS, provided that the dataset used for this study is part of the mandatory national statistics. In addition, our figures are comparable with those documented in the 2011 OECD report¹⁹—11.0 case fatalities per 100 patients who had a stroke in the OECD report vs 11.4 case fatalities per 100 patients who had a stroke in our sample.

Additionally, Elixhauser comorbidities in the model are subject to coding practices, which may vary across hospitals, biasing the adjustment. However, the sensitivity analysis results using just age, sex and time variables showed no differences in our estimates (see online supplemental figure 2B).

All in all, the results of our study are conditioned to the information registered in the administrative records. This issue may entail a limitation, as we may not have been able to adjust for some residual differences in patients' severity across hospitals. However, limiting the comparison to those referral stroke hospitals, likely to treat similar case-mix of patients, and the large numbers in this study, may have reduced the risk of residual confounding.

The differences among referral stroke hospitals elicited in this study point towards highly relevant opportunities to reduce unwarranted variations in medical practice

and improve the provision of healthcare in conditions where effective interventions are available, for instance, by learning from best-performing hospitals.

CONCLUSION

Overall, in-hospital mortality rates within 30 days after admission decreased between 2003 and 2015, coincidentally with the widespread adoption of reperfusion therapies within referral hospitals in Spain. However, over the years, between-hospital variations in mortality persisted beyond differences in the patients treated. After its implementation, the National Strategy on Stroke Care seems to have prompted changes within the SNHS but unevenly across referral stroke hospitals covering the population in different regions.

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Contributors EB-D and FE-R worked on the conceptualisation and design. FE-R prepared the dataset. JPD implemented the analytical scripts and ran the analyses. Finally, FE-R and EB-D drafted the paper. All authors read, edited and approved the final manuscript and supplementary files.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study, observational by design, uses retrospective anonymised non-identifiable and non-traceable data, and was conducted in accordance with the amended Helsinki Declaration, the International Guidelines for Ethical Review of Epidemiological Studies, and Spanish laws on data protection and patients' rights. The study was reviewed and approved by the Research Ethics Committee of Aragon (CEICA), which waived the need for written informed consent from the participants.

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Data availability statement Data are available upon reasonable request. The data underlying this article will be shared upon reasonable request to the corresponding author.

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Correction: *Differences in acute ischaemic stroke inhospital mortality across referral stroke hospitals in Spain: a retrospective, longitudinal observational study*

Estupiñán-Romero F, Pinilla Dominguez J, BernalDelgado E, *et al.* Differences in acute ischaemic stroke inhospital mortality across referral stroke hospitals in Spain: a retrospective, longitudinal observational study. *BMJ Open* 2023;13:e068183. doi:10.1136/bmjopen-2022-068183.

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