A structural equation model of adverse events and length of stay in hospitals

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Katharina Hauck[1], Xueyan Zhao

Department of Econometrics and Business Statistics, Monash University, Victoria, Australia.

[1] corresponding author, E-mail: katharina.hauck@buseco.monash.edu.au,
website: http://sites.google.com/site/katharinadianahauck/

Abstract

Adverse events in hospitals cause significant morbidity and mortality, and considerable effort has been invested into analysing their incidence and preventability. An unresolved issue in models of medical adverse events is potential endogeneity of length of stay (LOS): whilst the probability of suffering a medical adverse event during the episode is likely to increase as a patient stays longer, there are a range of unobservable patient and hospital factors affecting both the occurrence of adverse events and LOS, such as unobserved patient complexity and hospital management. Therefore, statistical models of adverse events which do not account for the potential endogeneity of LOS may generate biased estimates.

Our objective is to examine the effects of risk factors on the incidence of adverse events using structural equation models and accounting for endogeneity of LOS. We estimate separate models for three of the most common and serious types of medical adverse events: adverse drug reactions, hospital acquired infections, and pressure ulcers. We use episode level administrative hospital data from public hospitals in the state of Victoria, Australia, for the years 2004/05 and 2005/06 with detailed information on patients, in particular medical complexity and adverse events suffered during admission. We use days and months of discharge as instruments for LOS. Our research helps assessing the costs and benefits of additional days spent in hospital. For example, it can contribute to identifying the ideal time of discharge of patients, or inform whether 'hospital at home' programs reduce rates of hospital acquired infections.

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1. Introduction

Adverse events during hospital admission affect nearly one out of 10 patients (de Vries, Ramrattan et al. 2008). An adverse event (AE) can be defined as an unintended injury or complication resulting in prolonged hospital stay, disability at the time of discharge or death and caused by healthcare management rather than by the patient's underlying disease process (Thomas, Studdert et al. 2000). AEs are now widely agreed to be a serious problem. They are suspected of killing more people than motor vehicle accidents, breast cancer, or AIDS in a year, and total costs of preventable AEs have been estimated between $17 billion and $29 billion for the USA (Kohn, Corrigan et al. 2000). Thus, prevention of AEs promises significant societal benefits, and over the last two decades, considerable research effort has been invested to analyse the incidence of AEs, understand why they occur and how they could be prevented (for a systematic review see de Vries, Ramrattan et al. 2008).

Commonly identified causes of AEs are medical or diagnostic errors, technical failures, poor hospital procedures, or poor communication between medical staff (Neale and Woloshynowych 2003). Major risk factors for AEs are patient characteristics, with sicker and older patients more likely to suffer AEs. In recent years, efforts to prevent AEs have shifted from the person approach—blaming individuals for errors—to the 'systems approach' (Dankelman and Grimbergen 2005). The systems approach assumes that people will make mistakes, and that the system (hospital) that surrounds them should provide a safety net for these mistakes. The systems approach aims to reduce the complexity of providing medical care, by -for example- standardization of procedures and medical equipment, checklists, quality testing of equipment, and staff training.

Analysis of the causes and risk factors of AEs is important to help prevent them. It allows targeting efforts to patients and medical procedures most at risk. To date, causes and risk factors for AEs have mostly been identified by qualitative research (Michel, Quenon et al. 2004). Usually, a team of medical experts analyse patient records retrospectively to judge whether an AE has occurred, and what the reason may have been. Due to the subjective nature of this process, record reviews are said to have only modest reliability in identifying the incidence and causes of AEs (Localio, Weaver et al. 1996; Walshe 1998). An additional, and perhaps more serious, shortcoming of record reviews is that they use small and non-random samples of hospitals and patients. For example, of the studies reviewed by de Vries, Ramrattan, et al (2008), about half collect data from only one or two hospitals. Because the

reviewed patients and hospitals may have particular characteristics not present in other patients and hospitals in a health system, it is problematic to generalize results from record reviews. They should be supplemented with quantitative research based on random samples (or even the population) of patients and hospitals to inform an evidence based system level approach for prevention of AEs in all hospitals.

In this paper, we use an econometric analysis of administrative hospital data to establish the relationship between the incidence and risk factors of three of the most common and serious types of medical adverse events: adverse drug reactions, hospital acquired infections, and pressure ulcers. Those complications are relatively common, create considerable morbidity and mortality, and a large percentage of them are considered preventable under optimal care (Lazarou, Pomeranz et al. 1998; Neale and Woloshynowych 2003; Unruh 2003; Aranaz-Andres, Aibar-Remon et al. 2008). We model AEs as a function of patient risk factors, hospital characteristics, and length of stay in hospital (LOS). An important feature of our analysis is that we focus on LOS as a risk factor for AE, and that we estimate a two-equation system model allowing for the potential endogeneity of LOS. As detailed in the next section, there is a policy motivation for estimating the marginal impact of LOS on AE, and the correlation via common unobservable patient, specialty and hospital factors needs to be accounted for in this estimation. While our approach does not allow the depth of analysis provided by record reviews, it has the advantage that results can be generalized, and that it is relatively inexpensive. Most importantly, and unlike a qualitative research approach, a statistical analysis can generate and test quantitative estimates of the impact of particular risk factors and inform on their relative importance -conditional on all others.

2. Length of Stay as an Endogenous Risk Factor of Adverse Events

There is only limited evidence on the quantitative impact of one of the most important risk factors for suffering adverse events: Length of Stay. Intuitively, each additional day in hospital increases the probability of suffering an AE during the episode. Van den Bemt et al. (2000) find a comparably high incidence of adverse drug events, and comment that may be due to the fact that “the length of hospitalization in this study was relatively long, so there may have been simply more time for adverse drug events to occur”. Weingart et al. (2000) comment that “the characteristics of patients may be less important than the duration of care in explaining adverse events”. Bates et al. (1999) find that adverse drug events increase with

LOS, and Andrews et al. (1997) estimate that each additional day in hospital increases the probability of suffering an AE by 6%, although these estimates seem to be derived from correlation and not causal analyses. LOS is only a potential risk factor for medical adverse events which occur during ward care, such as adverse drug events and hospital acquired infections. Most operation-related adverse events, such as surgical errors or bleeding, are likely to occur at the beginning of the episode, and are thus unaffected by LOS.

A quantitative estimate of the impact of LOS informs on how likely it is to suffer an AE during a day in hospital for an average patient, holding all other risk factors constant. This is important information, because LOS may be one of the few risk factors which can be directly influenced by the actions of hospital management. If AEs are relatively common and associated with high cost, a quantitative estimate of the impact of LOS on their occurrence may influence hospital managers to discharge patients earlier, or transfer them to alternative care. Of course it is not the days in hospital itself, but what happens during those days that cause AEs. Ultimately, discharging patients just to avoid AEs seems a less satisfactory solution than tackling the above mentioned hospital-related causes of AEs. However, for AEs which are caused by factors which cannot be changed unless under very high costs – such as a given building infrastructure-, or by factors which cannot be changed in the short run, reducing LOS in hospital is a pragmatic and possibly the only viable option to help prevent AEs.

A statistical estimate of the marginal impact of LOS on AE can inform on the expected cost of days spent in hospital, of which the expected cost of AEs is one component. Besides informing on the costs of days in hospital at the margin, it can also be used to incorporate the expected costs of AEs into the design of optimal treatment protocols (including recommended LOS) for different conditions (Fine, Medsger et al. 1997; Howard, Evans et al. 1999). Estimates of the cost of AE also allow comparing treatment programs which substitute days in hospital with days at alternative care providers, or at home. Examples of such programs are ‘early discharge’ and ‘hospital at home’ programs which are piloted in many countries, usually for patients with chronic or terminal conditions (Leff 2009). Many of these programs are associated with greater patient satisfaction and lower AE rates, but have longer overall LOS (Graham, Keldermans et al. 1991; Leff, Burton et al. 2005; Shepperd, Doll et al. 2009). If treatment programs differ with respect to LOS *and* AE rates, it is difficult to use Randomized Controlled Trials to assess the impact of such programs on AEs. This is because patients cannot be randomized on the risk factor LOS if it is associated

with the treatment. Our proposed econometric analysis can overcome this problem, and inform whether and by how much 'early discharge' and 'hospital at home' programs reduce infection rates, controlling both for differences in LOS and other risk factors.

A problem in an econometric model of medical adverse events is potential endogeneity of LOS. It is very likely that there are a range of unobservable hospital and patient factors affecting both the occurrence of AEs and LOS. Examples are unobserved hospital management, patient complexity, and risks associated with particular medical procedures. Well managed hospitals may be more successful in implementing safety procedures to prevent AEs, but also better at planning bed occupancy to reduce overall LOS. This would imply that 'good management' decreases LOS and rates of AEs. On the other hand, hospitals may have very high occupancy rates, resulting in shorter LOS, high demands on staff and greater likelihood of AEs, leading to an inverse relation between LOS and AEs. Unobserved patient complexity is likely to increase both LOS and the likelihood of AEs. This implies that the error terms embodying effects of common unobservable factors on both LOS and AE are correlated and LOS is endogenous in the analysis of AE. Models of adverse events which do not account for the potential endogeneity of LOS may generate inconsistent and biased estimates of *all* factors impacting on AEs. Some more recent studies in the medical literature estimate the probability of experiencing AEs per unit of time spent in hospitals, e.g. per 100 patient days (Aranaz-Andres, Aibar-Remon et al. 2008). This approach solves the problem of endogeneity by creating a ratio of the two endogenous variables, but does not provide a structural estimate of the impact of LOS on the probability of AEs.

Unlike the impact of LOS on AEs, the reverse of the relationship, the impact of AEs on LOS, has been studied relatively extensively, because LOS is used as a proxy of costs in models which measure the resource implications of AEs (Zhan and Miller 2003; Graves, Birrell et al. 2005; Graves, Weinhold et al. 2007; Nuckols, Paddock et al. 2008). Results vary greatly by study and type of AE, but overall, there is evidence that most types of AEs are associated with longer LOS. This demonstrates that there is the strong intuition that LOS is endogenous in models of AEs, and AEs endogenous in models of LOS, i.e. that AEs and LOS are simulatenously determined. Ideally, LOS and AEs should be modelled jointly, for example, in a simultaneous equation model. However, this would require instruments for both LOS and AEs. As instruments for AEs are not available in our dataset, we limit the objective of our paper on estimating the impact of LOS on the incidence of AEs. This is achieved by estimating a system model consisting of a structural equation for AE and a reduced form

equation for LOS, with additional instruments for the reduced form equation. We use the day of the week and the month of the year a patient was discharged as extra instruments for LOS. As discussed in Section 5, there is evidence that these are associated with LOS, but not AEs, thus making them relevant and exogenous instruments.

3. The Model

We specify a two-equation system model that jointly determines the probability of a patient having at least one adverse event during a hospital episode and the length of hospital stay for that episode. Let AE^* ($AE^* \in (-\infty, +\infty)$ be a latent variable that is proportional to the propensity of having adverse events and is determined by

$$AE_i^* = X_i\beta_1 + H_i\delta_1 + \alpha(LOS_i) + e_{1i}, \tag{1}$$

where X_i is a vector of exogenous covariates of observable patient and episode characteristics for episode i, $H_i = (H_{ki}, ..., H_{K-1,i})$ is a vector of fixed effect hospital dummy variables, with $H_{ki} = 1$ $(k=1,...,K)$ if episode i took place in hospital k and $H_{ki} = 0$ otherwise, LOS_i is the length of stay of episode i, β_1, δ_1 and α are coefficients to be estimated, and e_{1i} is the error term representing effects of unobservable patient and hospital factors for episode i $(i = 1,..., N)$. The latent variable AE^* is unobservable and is mapped to the observable binary variable AE via

$$AE_i = \begin{cases} 1 & \text{if } AE_i^* > 0 \text{ (for having at least one adverse event)} \\ 0 & \text{if } AE_i^* \le 0 \text{ (otherwise).} \end{cases} \tag{2}$$

The length of stay variable LOS_i in (1) is given by a reduced form equation

$$LOS_i = X_i\beta_2 + H_i\delta_2 + Z_i\gamma + e_{2i}, \tag{3}$$

where Z_i is a vector of additional instruments, β_2, δ_2 and γ are unknown coefficients, and e_{2i} is the error term. Assume that the two error terms (e_{1i}, e_{2i}) $(i = 1,..., N)$ are independent and identically distributed across all N episodes and jointly follow a bivariate normal distribution with $\sigma_{11} = 1$ for identification, σ_{22} as the variance of e_{2i}, and ρ as the correlation coefficient for the two error terms.

Equations (1)-(3) define a system model consisting of a mixture of a Probit equation and a regression equation that jointly determines the probability of adverse events and the length of stay during a hospital episode. When $\rho \neq 0$, the correlation between the common unobservable factors of the same episode, including unobservable patient, specialty and hospital characteristics, that affect both AE_i and LOS_i is quantified, and the structural effect of LOS_i on AE_i (i.e. α) in equation (1) can be estimated allowing for the endogeneity of LOS_i. We estimate the system model separately for three types of AEs: adverse drug events, infections, and ulcers. The models are estimated using the maximum likelihood estimator and Stata 10 (2007).

4. Data and Specification of Variables

We use the Victorian Admitted Episodes Data (VAED) for public hospitals in the state of Victoria, Australia, for two years 2004/05 and 2005/06 (Department of Human Services 2007). The VAED are administrative hospital data of high quality as hospitals have a financial incentive to generate detailed records of all their patients because they receive the largest part of their budget via casemix funding. Our sample consists of 198,851 (2004/05) and 206,489 (2005/06) episodes in medical Diagnosis-related Groups, which are defined on basis of patients' diagnoses, procedures undertaken and other patient information (Department of Health 2005). Each episode starts with a patient's admission to a hospital department and ends with discharge from that department. We exclude maternity episodes, patients under 18 years of age, dialysis, radiology, chemotherapy, and rehabilitation episodes, and all episodes in specialty hospitals. We exclude true daycases, but not daycases which are transferred on to another department or hospital. We exclude all surgical episodes (as explained in section 5). We drop high outliers with respect to LOS, following the approach proposed by Tukey (1977).

Table 1 provides summary statistics of all variables. The dependent variables *adverse drug reactions, infections* and *ulcers* are binary variables indicating whether a patient suffered one or several of the respective AE during an episode. Definitions are based on patient diagnoses codes, and are available from the corresponding authors' website.[1] They are comparably rare events. *Adverse drug reactions,* and *wound* and *nosocomial infections* are based on external

[1] http://sites.google.com/site/katharinadianahauck/.

cause and specific injury codes, which by definition imply an AE (Jackson, Duckett et al. 2006). The codes for *sepsis* and *ulcers* follow the definition of patient safety indicators by the US Agency for Healthcare Research and Quality (2007; Quan, Drosler et al. 2009). Infections also comprise *urinary tract infections, pneumonia,* and *respiratory tract infections,* because they are usually considered complications of hospital care (Ehsani, Jackson et al. 2006). We do include patients who are coded with an AE as primary diagnosis and who may have acquired the condition before admission, for example, in another department of the same hospital, another hospital or physician's practice. It has been estimated that this affects about 14.9% of all adverse events (de Vries, Ramrattan et al. 2008). This implies that we cannot attribute the AE to the treating hospital, but this is not objective of our study.

LOS is a continuous variable measured as days of stay. Other explanatory variables mostly characterize medical complexity of the patient, and episode characteristics. The variables *severity1, severity2, severity3* are medical complexity grades based on patients' diagnoses and procedures undertaken (Department of Health 2005). We further adjust for patients' medical complexity by including 17 comorbidities as defined in the Charlson index as separate dummy variables, to allow for their differing impact on AEs (Charlson, Pompei et al. 1987; Stagg 2006). The Charlson index reflects the cumulative increase in likelihood of one-year mortality due to the severity of the effect of comorbidities. Because of high degree of correlation between 'cancer' and 'metastatic cancer', and 'liver disease' and 'severe liver disease' respectively, we include only the more serious condition for patients suffering both. AEs may not be independent occurrences in one hospital; for example, infections may spread across patients, faulty medical equipment may be used on several patients, hospital management affects implementation and execution of safety procedures, or –in rare cases- incompetence of medical staff may lead to AEs in several patients. To control for such hospital specific effects, we include separate dummy variables for all 33 hospitals with more than 1500 medical admissions in at least one year, with all smaller hospitals as reference category.

5. The Instruments

Instruments for LOS are dummy variables indicating the day of the week and month of the year the patient is discharged. Discharges on Saturdays, Sundays or public holidays are coded as weekend discharges, discharges the day before a public holiday are coded as Friday

discharges, and discharges the day after a public holiday are coded as Monday discharges. The Mondays before a holiday falling on a Tuesday, and the Fridays after a holiday falling on a Thursday are also coded as holidays, because such long weekends could be reflected in hospital discharge policy. We consider differences in holidays across regional and metropolitan Victoria.

For the instruments to be relevant, LOS_i and the instruments Z_i need to be correlated in the reduced form equation, after partialling out X_i. There is evidence that hospital operational processes and differences in staffing levels between weekdays and weekends lead to differences in LOS depending on the day of the week a patient is discharged (Schmidt, Taeger et al. 2003; Fonarow, Abraham et al. 2008; Wong, Wu et al. 2009). Towards the end of the week, discharge rates are higher, early discharge more likely, and consequently LOS lower. This may be explained by the attempt of hospital administrators to relieve pressure on reduced staffing levels at weekends. On weekends, on the hand, patients ready to be discharged may be held over until Monday due to lack of senior staff authorized to take discharge decisions. This could explain observed lower discharge rates on weekends, higher discharge rates on Mondays, and consequently longer LOS for patients discharged on Mondays. A second set of instruments is provided by month of discharge. LOS is likely to be affected by variations in staffing levels across the year and the impact of holiday periods in some months, such as Christmas and Easter. LOS may be lower in December due to the impending holiday, and higher in January –which is the summer holiday period in Victoria- due to increased staff absences and patients kept in hospital for observation. Also, seasonal variations in illness prevalence may impact on LOS. Studies on the impact of month of admission (which is highly correlated with month of discharge) on LOS show considerable seasonal variability, with shortest LOS in July (equivalent to Victorian summer) and December (Schmidt, Taeger et al. 2003), and month of admission a significant predictor of LOS (Stoskopf and Horn 1992).

IV estimation is inconsistent if the instruments Z_i and the error e_{1i} are correlated in the structural equation. This condition cannot be tested, and we need to rely on introspection to defend exogeneity of the instruments, i.e. that days and months of discharge do not influence the likelihood of suffering AEs. There is no reason to assume that day of discharge should impact on AEs, as there is an obvious time sequence, with AEs occurring during the episode and discharge at the end. However, day of *admission* may be associated with AEs, and

captured by ε_{1i} in the structural equations. If there were in addition a strong correlation between day of admission and discharge, implying a small standard deviation of LOS across the sample of patients, Z_i and ε_{1i} may be correlated and the instruments endogenous.

Previous research investigating the relationship between day of admission and health outcomes (usually measured by mortality rates) has yielded conflicting results. Higher mortality rates on weekends has been found for patients requiring emergency surgery and emergency patients presenting with a limited range of conditions, but not for other patient groups (Bell and Redelmeier 2001; Gogel, Liron et al. 2002; Arias, Taylor et al. 2004; Cram, Hillis et al. 2004; Becker 2007; Fonarow, Abraham et al. 2008; Schwierz, Augurzky et al. 2009). Dobkin (2003) shows that higher mortality rates on weekends can be explained by higher risk admissions. After controlling for this selection bias, the higher mortality for patients admitted on weekends disappears. This implies that patient complexity and not AEs are cause of poorer health outcomes on weekends. It is possible that month of treatment may be endogenous because arrival of inexperienced junior staff at the beginning of the academic year may lead to worse health outcomes in that month (the 'July phenomenon' in the USA). There is evidence for variations in outcomes for surgical (Englesbe, Pelletier et al. 2007; Haller, Myles et al. 2009) but not medical admissions (Barry and Rosenthal 2003; Finkielman, Morales et al. 2004).

Following the above evidence, and to err on the safe side and ensure that the exclusion restrictions are met, we exclude all surgical patients from our sample. Correlation between day of admission and AEs is likely to be higher for surgical than medical patients, as elective (and perhaps even emergency) surgeries are more commonly scheduled at certain days of the week, whereas admissions of medical patients are likely to be more evenly distributed across the week. In addition, treatment protocols for many surgical procedures are quite standardized, whereas this is less the case for medical admissions. This is likely to result in lower variation in LOS and thus, higher correlation between day of admission and discharge for surgical patients. We find evidence for this in our data. The standard deviation of LOS for all medical patients in Victorian hospitals in 2004/05 is nearly twice as high as for surgical patients with a similar mean, implying a smaller correlation between day of admission and discharge for medical patients. In summary, relying on current evidence and using only medical patients, we are confident that the exclusion restrictions for both sets of instruments are met.

6. Results and Discussion

Estimates of the effect of LOS on the probability of experiencing *adverse drug events, infections* and *ulcers* are presented in *Table 2.* Reported are the marginal effects (MEs) and associated standard errors (SEs) for LOS from the system models, the p-values from the exogeneity tests, and results from univariate probits (UVPs) -assuming LOS is exogenous- for comparison. MEs and SEs for all regressors from the system models and all three AEs for the year 2004/5 are presented in *Table 3.* MEs and SEs for all regressors from the system models for the year 2005/6 and from the UVPs for both years, estimates of ρ, coefficient estimates from the reduced form regressions, and F-tests of the joint significance of the instruments for both years cannot be presented here due to space limitations, but are available on the corresponding author's website.[1]

To check for endogeneity, we test whether or not there is a significant correlation, H_0: $\rho = 0$, between the pseudo error terms e_{1i} and e_{2i} in the structural and reduced from equations. This test of exogeneity is valid without assuming normality or homoskedasticity of the error e_{2i} of the reduced form equation (Rivers and Vuong 1988). Small p-values indicate that the null hypothesis of exogeneity of LOS is rejected for all but one model. The results imply that LOS is endogenous for all models and years, except in 04/05, LOS is not endogenous in the model for adverse drug events. For this model only, the UVP with LOS as exogenous regressors may be more appropriate.

The instruments in the reduced form regressions are jointly significant (F-statistics 92.18 and 94.81 for 05/06). The separate F-statistics for 'days of discharge' are much higher at 279.64 (288.06) than for 'months of discharge' at 5.55 (6.85), indicating that 'months of discharge', if they were used on their own, may be weak instruments (Staiger and Stock 1997). Coefficients estimates for 'days of discharge' are all significant and negative, decreasing gradually from -0.09 (both years) for Tuesday to -0.98 (0.95) for weekend discharges, indicating that patients discharged on Saturday or Sunday have nearly 1 day shorter LOS than patients discharged on Mondays. The only months for which coefficient estimates are significant and -0.1 or smaller in both years are February, May and December, indicating that patients discharged in those months stay at least 0.1 day shorter than patients discharged in January. Impact of month of discharge on LOS is clearly less important than day of discharge, as coefficients on months are smaller and some even not significant.

Estimates of the impact of LOS on all three types AEs and for both years are significant and positive, indicating that LOS increases the probability of experiencing AEs. The marginal effects are evaluated at the mean of all regressors (presented are results for 04/05, with results for 05/06 in brackets). Results from the system models indicate that each additional day in hospital increases the probability of suffering an adverse drug event by approximately 0.2% (0.4%), infection by 1.4% (1.6%), and ulcer by 0.3% (0.3%), evaluated at the mean. Both MEs and SEs generated by the UVPs are markedly smaller than the estimates generated by the system models. If LOS is endogenous, the differences between UVP and system models may be attributable to bias of the UVP estimates.

Hospital managers may not only be concerned with the increased risk due to one additional day in hospital (which is provided by the estimate of the marginal effects of LOS), but may want to compare treatment programs with differing LOS. As an example, if three patients who differed only in their LOS in that one stayed 2 days (=one night), the second stayed 4 days (=3 nights) and the third stayed 8 days (=7 nights), doubling LOS from 2 to 4 days increases risk of adverse drug events by 0.4% (0.7%), infections by 2.4% (2.6%), and ulcers by 0.3% (0.3%). Doubling LOS from 4 to 8 days increases risk of adverse drug events by 1.0% (1.8%), infections by 6.0% (6.7%), and ulcers by 1.3% (1.4%), for the average patient and conditional on all other observable risk factors.

To help put these numbers in perspective, other results of the model indicate that two patients who differed only in their age in that one is 40 years old and the other 60, ageing by 20 years increases the risk of adverse drug events by 3.2% (3.2%), infections by 3.8% (3.5%), and ulcers by 0.2% (0.3%). Being admitted as an emergency rather than an elective patient increases risk of adverse drug events by 1.6% (1.7%), infections by 7.3% (7.4%), and does not affect ulcers. Some patient comorbidities have considerable impact on the risk of suffering AEs, although for others effects are surprisingly small or even insignificant. AIDS is an important risk factor for adverse drug events and infections, because it increases risk of adverse drug events by 7.1% (4.9%) and infections by 16.4% (20%). Hemiplegia/paraplegia increases risk of ulcers by 1.6% (2.0%), which makes these conditions the most important patient level risk factors for ulcers in our models, which is not surprising. Congestive heart failure and cancer are important risk factors for infections. The MEs discussed here only capture the direct effects of the exogenous regressors on AEs; in addition, there may be indirect effects via LOS, which together would sum up to a total effect.

Marginal effects on the hospital dummies are relatively large, indicating that the treating hospital is as (if not more) important than LOS and patient level risk factors in explaining the probability of AEs. Marginal effects for the hospitals vary from -1.4% to 9.0% (-0.6% to 12.6%) for adverse drug events, -1.5 to 5.6% (-0.6% to 9.7%) for infections, and -0.6% to 2.6% (-0.5% to 2.2%) for ulcers. This implies, for example, that some patients in 2005/06 experienced a 13.2% higher risk of adverse drug events just because they were admitted to a particular hospital rather than another. This result should be interpreted with care, though, as the occurrence of the adverse event cannot be unambiguously attributed to the treating hospital. There is a possibility that patients are non-randomly transferred to this particular hospital after having suffered adverse drug events in other hospitals, which may lead to above average rates of adverse drug events in that hospital.

This study has several limitations, some of which we will address for the final version of this paper. LOS enters the models as a linear continuous variable. Thus, we assume that the effect of increasing the hospital stay by one day is roughly the same irrespective of how long the patient has already stayed in hospital, and any nonlinearity is attributable to the model specification. It seems unrealistic that, for example, increasing the hospital stay from 2 to 3 days leads to the same increase in risk than increasing the hospital stay from 13 to 14 days. Graphs of the association between AE and LOS -unadjusted for other factors- may indicate nonlinearity (available on the corresponding author's website).[1] In future research, we will explore alternative models specifications with LOS as a nonlinear variable. We will also explore the possibility of estimating semi- or nonparametric models which impose hardly any or no functional assumptions on LOS.

Another, related, limitation is that we do not know at what day during the episode the AE occurs, as our data do not record this. We assume that medical AEs may happen anytime during the episode, but the likelihood may not be uniformly distributed, and may also differ by type of AE. There is an argument that adverse drug events are most likely to happen at the beginning of episode, because decisions on medication regimes (and thus therapeutic errors) are most often made at the time the patient is admitted. On the other hand, errors in administration of a specified drug regime may happen anytime. Some type of infections may also be more likely to occur at the beginning of the episode, because patients could be sicker initially and thus more susceptible for infections. The likelihood of developing ulcers is strongly influenced by the length of time a patient is immobile, and thus unlikely to occur at the beginning of the episode, unless the patient is admitted with it (Agency for Healthcare

Research and Quality 2007). This may imply that the probability of developing ulcers increases exponentially with LOS. In summary, our estimate of the marginal effect of LOS on AE averages across the episode, and may over- or underestimate the risk at particular days during the episode.

7. Conclusions

We find that LOS is an important risk factor in an econometric model of AEs. LOS increases the probability of AEs at comparable magnitudes to other risk factors such as age, being an emergency patient, or suffering of significant comorbidities. However, in contrast to patient risk factors, LOS is a hospital-level risk factor which is directly amenable to the actions of hospital management; patients can be discharged earlier, and part or all of the stay in hospital can be substituted by stays at alternative care providers, or at home. This may be beneficial if it significantly lowers risk of AEs. Although it is more satisfactory to address hospital-level causal reasons for the occurrence of AEs, such as poor safety procedures, LOS may be the only factor which can be changed in the short run and under relatively low costs. Our results provide hospital managers with the quantitative evidence to take a pragmatic approach towards the reduction of AE, and make informed discharge and care decisions.

Our results provide managers with an estimate of the expected costs of AE due to an additional day in hospital, but they also allow comparing treatment programs which differ substantially with respect to AE and LOS. Expected costs of AE for the average patient episode can be obtained by multiplying our estimate of the probability of AE for an episode of mean duration with cost estimates such as the ones generated by Zhan and Miller (2003). Using their estimates of excess charges caused by infections due to medical care and ulcers (estimates for adverse drug events are not provided), our results imply that the expected costs of AE are about US $5,265 for infections and US $78 for ulcers, per episode and for the average patient. These are rough estimates of the extra health care costs due to AE, and they do not consider the costs of excess morbidity and mortality.

The expected costs of AE are of course not the only factor which should influence discharge decisions. However, considering the high costs of some types of AEs, it is timely that they are factored into discharge and treatment decisions in a quantitative way. We propose such a quantitative approach, allowing for the fact that LOS is endogenous in models of AEs. We

offer a solution to this problem by using instrumental variable methods. Our approach is an alternative to using randomized controlled trials for comparing alternative treatments, which are not well equipped to deal with endogeneity, and are more expensive. Our econometric model of adverse events offers important additional information to the qualitative research efforts on AE of the last two decades. It contributes to providing a sound evidence base for analysing incidence and risk factors of AEs, and the implementation of system level approaches for the prevention of AEs in hospitals.

Table 1: Summary statistics

	2004/5		2005/6	
	Mean	SD	Mean	SD
total observations	198,851		206,489	
Adverse events				
adverse drug reactions	0.050	0.217	0.051	0.219
infections	0.172	0.377	0.170	0.375
ulcers	0.012	0.107	0.013	0.112
Explanatory variables				
LOS	5.46	5.29	5.37	5.19
age	59.13	22.06	59.08	22.14
number of procedures	1.79	2.02	1.83	2.05
female	0.568	0.495	0.571	0.495
discharge by death	0.030	0.170	0.029	0.167
severity grade 1	0.389	0.488	0.383	0.486
severity grade 2	0.489	0.500	0.495	0.500
severity grade 3	0.122	0.327	0.122	0.328
Charlson comorbidities				
acute myocardial infarction	0.036	0.186	0.038	0.191
congestive heart failure	0.080	0.272	0.079	0.270
peripheral vascular disease	0.016	0.127	0.017	0.130
cerebrovascular event	0.049	0.216	0.049	0.216
dementia	0.036	0.186	0.035	0.185
chronic obstructive pulmonary disease	0.080	0.272	0.079	0.269
rheumatoid disease	0.006	0.074	0.006	0.076
peptic ulcer	0.002	0.049	0.002	0.046
mild liver disease	0.010	0.098	0.010	0.102
diabetes	0.073	0.260	0.068	0.252
diabetes complications	0.109	0.312	0.120	0.325
hemiplegia or paraplegia	0.028	0.166	0.029	0.166
renal disease	0.065	0.246	0.069	0.254
cancer	0.039	0.195	0.040	0.196
severe liver disease	0.006	0.079	0.007	0.081
metastatic cancer	0.041	0.199	0.042	0.201
aids	0.001	0.038	0.002	0.040
Instruments				
Monday	0.183	0.387	0.188	0.391
Tuesday	0.158	0.365	0.157	0.363
Wednesday	0.159	0.365	0.161	0.368
Thursday	0.163	0.369	0.159	0.366
Friday	0.188	0.391	0.192	0.394
Saturday or Sunday	0.190	0.393	0.198	0.398
January	0.080	0.272	0.082	0.275
February	0.076	0.265	0.076	0.266
March	0.085	0.279	0.087	0.281
April	0.082	0.275	0.078	0.268
May	0.085	0.280	0.087	0.282
June	0.084	0.278	0.083	0.276
July	0.084	0.278	0.084	0.278
August	0.085	0.279	0.087	0.282
September	0.085	0.279	0.084	0.277
October	0.085	0.279	0.084	0.278
November	0.082	0.275	0.083	0.275
December	0.085	0.278	0.084	0.278

Table 2: Results from system models and univariate probit models

		Adverse drug events		Infections		Ulcers	
		ME on LOS	SE	ME on LOS	SE	ME on LOS	SE
2004/5	UVP	.0019485	.00008	.0068466	.00016	.0004873	.00002
	System model	.0024853	.00118	.0144874	.00236	.0027127	.00102
	Test of exogeneity (rho = 0) Prob > chi2	0.6456		0.0010		0.0001	
2005/6	UVP	.0018378	.00008	.0072315	.00016	.0004801	.00002
	System model	.004266	.00125	.0160082	.00228	.0027565	.00099
	Test of exogeneity (rho = 0) Prob > chi2	0.0419		0.0001		0.0001	

Table 3: Marginal effects and standard errors for the structural equations from the system models, patient and episode risk factors, 2004/5

	Adverse drug events		Infections		Ulcers	
Predicted Prob.	.03843257		.14269246		.00838357	
variable	dy/dx	Std. Err.	dy/dx	Std. Err.	dy/dx	Std. Err.
los	0.002485	0.00118	0.014487	0.00236	0.002713	0.00102
age	0.002639	0.00014	0.002114	0.00026	0.000106	0.00007
age2	-1.64E-05	0.00E+00	4.06E-06	0.00E+00	1.06E-06	0.00E+00
female*	0.008572	0.00085	0.010813	0.00164	-0.00092	0.00045
nonelect*	0.015945	0.00104	0.073119	0.00196	-0.00027	0.00055
numberop	0.000618	0.00156	-0.00204	0.00314	-0.00216	0.0011
severity 1*	-0.00256	0.00136	0.07023	0.00284	-0.00349	0.00113
severity 3*	-0.00898	0.00128	-0.01548	0.00279	0.002508	0.00069
death*	-0.01397	0.00191	0.085237	0.00627	0.015384	0.00177
ami*	-0.00726	0.00188	0.002633	0.00425	-0.00306	0.00089
chf*	0.00758	0.00233	0.037494	0.0047	-0.00239	0.0011
pvd*	-0.01761	0.00217	-0.06001	0.00449	0.005544	0.00153
cevd*	-0.02125	0.00162	-0.07458	0.00338	-0.00605	0.0011
dementia*	-0.01462	0.00256	0.01888	0.00738	0.000414	0.00146
copd*	-0.00547	0.00148	0.010436	0.00309	-0.00231	0.00086
rheuma*	0.0312	0.00729	-0.01094	0.00981	0.001557	0.00243
pud*	0.019385	0.00924	-0.03074	0.01294	-0.00319	0.00225
mild_ld*	0.002619	0.0042	0.001241	0.00817	-0.00303	0.00176
diab*	0.01022	0.00189	0.005253	0.00326	0.001573	0.00072
diab_comp*	0.000626	0.0013	0.00394	0.0026	0.000391	0.00059
hp_papl*	-0.01145	0.00295	0.026728	0.00775	0.016232	0.0025
renal_disease*	0.023567	0.0023	0.037001	0.00392	-0.00115	0.00079
cancer*	0.023481	0.00289	0.046384	0.00506	-0.00332	0.00108
severe ld*	-0.01274	0.00372	-0.02144	0.00883	0.001309	0.00219
meta_cancer*	0.014235	0.00265	0.002743	0.00448	-0.00225	0.00096
aids*	0.070971	0.01888	0.164411	0.02962		

Table 3 (continued): Marginal effects and standard errors for the structural equations from the system models, hospital dummy variables, 2004/5

	Adverse drug events		Infections		Ulcers	
variable	dy/dx	Std. Err.	dy/dx	Std. Err.	dy/dx	Std. Err.
A17*	0.047141	0.00544	0.051524	0.00709	0.013266	0.00449
A32*	0.0343	0.00601	0.008093	0.00766	0.003298	0.00276
B01*	0.059066	0.0092	0.052354	0.01104	0.004402	0.0037
B03*	0.034318	0.00415	0.03284	0.00567	0.002895	0.00181
B05*	0.025034	0.00401	0.009485	0.00552	-0.00239	0.00092
B11*	0.045508	0.00521	0.039235	0.00662	0.007913	0.00321
B18*	0.032262	0.00408	0.017117	0.00538	-0.0022	0.00094
B21*	0.000357	0.00308	-0.00745	0.00508	-0.00428	0.00106
B22*	0.090039	0.0115	0.055752	0.01293	0.010136	0.00556
B28*	0.013739	0.00396	0.02817	0.00649	0.00173	0.0019
B33*	0.022681	0.00425	-0.00765	0.00565	0.003109	0.00218
B36*	0.005058	0.00529	0.031044	0.00956	-0.00182	0.00188
B39*	0.014432	0.00458	0.022597	0.00741	0.003931	0.00273
B45*	-0.00294	0.00306	-0.01168	0.00548	0.002968	0.00207
B66*	0.050971	0.01457	0.044989	0.01868	0.025688	0.01224
D01*	0.00457	0.00416	0.008468	0.00711	0.002534	0.00239
D02*	0.00632	0.00386	0.009687	0.00633	-0.00186	0.00132
D05*	0.019508	0.0035	-0.00716	0.00476	0.004882	0.00206
D06*	0.035504	0.00749	0.014325	0.00969	0.007342	0.00428
D07*	0.024638	0.00773	-0.00703	0.01015	0.012791	0.00562
D12*	0.025009	0.0049	-0.01481	0.00621	-0.00028	0.00164
D15*	0.023273	0.00613	0.014424	0.00874	0.005203	0.00324
D16*	0.042871	0.00583	0.000189	0.00687	0.005035	0.0025
D17*	0.05603	0.00928	0.01074	0.0104	-0.00159	0.0025
E04*	0.029311	0.00621	0.02794	0.00855	0.001192	0.00223
E18*	-0.01382	0.00458	0.015814	0.0101	-0.00116	0.00226
E22*	0.013077	0.00403	0.023348	0.00668	0.020854	0.00605
E44*	0.019132	0.00492	0.045378	0.00788	0.014035	0.00448
E58*	0.031185	0.0071	0.027746	0.0099	0.012841	0.00505
E59*	0.003883	0.00451	0.011748	0.0079	0.000129	0.00211
E66*	0.052432	0.00809	0.019735	0.00974	0.003523	0.00331
G25*	0.002936	0.00438	0.014458	0.00751	0.012841	0.00405
P32*	-0.00209	0.00452	0.018212	0.00829	-0.00628	0.00165

(*) dy/dx is for a discrete change of dummy variable from 0 to 1

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