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

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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.

Keywords: medical errors, complications of care, adverse drug reactions, infections, ulcers, hospital quality

JEL Classification: I11, D21, C3, H4, L3

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 each 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, increasing 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, medical procedures, and hospitals 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 a statistical 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 include 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. 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 a medical AE during the episode. [1] Van den Bemt et al. (2000) find a comparably high incidence of adverse drug events, and comment

[1] 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.

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 based on correlation and not causal analyses.

Our proposed approach informs on how likely it is to suffer an AE during one or several days in hospital for an average patient, holding all other risk factors constant. This can contribute to calculating the expected costs and benefits of days spent in hospital, of which the expected costs of AEs is one component. If expected costs are relatively high, i.e. AEs are relatively common and/or associated with high cost, it may influence hospital managers to discharge patients earlier, or transfer them to alternative care. This may be advantageous if expected cost of AEs is lower in alternative care, but other costs and benefits similar. Examples of alternative care 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, in particular lower infection rates, but they 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 statistical analysis can overcome this problem, and could be used to analyse 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. Our approach could 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).

Of course it is not the days in hospital itself, but what happens during those days that cause AEs. Ultimately, discharging patients with the objective to reducing AEs seems unsatisfactory compared to tackling the above mentioned causes of AEs. However, some types of AEs are more difficult to prevent than others, especially if they are caused by factors which cannot be changed unless under very high costs or factors which cannot be changed in

the short run. For example, a given building infrastructure may require accommodating patients in rooms with multiple beds, which increases the risk of spread of infections; an effective antibiotic to treat a particular type of infection may be unavailable temporarily. In these situations, LOS is a risk factor for AEs which can be quickly and directly influenced by the actions of hospital management.

A problem in a statistical 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 AEs. A statistical model which does not account for the potential endogeneity of LOS may generate inconsistent and biased estimates of *all* factors impacting on AEs.[2]

3. The Model

We estimate 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.

[2] Some medical studies analyse AEs per unit of time spent in hospitals, e.g. per 100 patient days, see Aranaz-Andres, J. M., C. Aibar-Remon, et al. (2008). "Incidence of adverse events related to health care in Spain: results of the Spanish National Study of Adverse Events." Journal of Epidemiology and Community Health **62**(12): 1022-1029. 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.

We specify a two-equation system model that jointly determines the probability of a patient having at least one adverse event of a certain type 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

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

where X_i is a vector of exogenous covariates including observable patient 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

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

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

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

where X_i is defined as above, 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. For comparison, we estimate (1) as univariate probit models which

assume LOS is exogenous. 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 around 200,000 episodes per year 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 the dependent and explanatory 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 (see *Table 3).* They are comparably rare events. *Adverse drug reactions,* and *wound* and *nosocomial infections* are based on external 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 'mild liver disease' and 'severe liver disease' respectively, we code two new categories 'liver disease' and 'cancer' which comprise both the less and the more serious conditions. 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 (see *Table 2).* 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 other 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. *Table 2* shows that half as many patients are discharged on Saturdays, Sundays and public holidays. 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).

Instrumental variable estimation is inconsistent if the instruments Z_i and 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 e_{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 e_{1i} may be correlated and the instruments endogenous.

Previous research investigating the relationship between day of admission and health outcomes (usually not measured by AEs but 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 medical patients (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* for both years are presented in *Table 4.* Reported are the marginal or average effects (MEs or AVEs) 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, AVEs and SEs for all other explanatory variables and the hospital dummies from the system models are presented in *Tables 5* and *6*, respectively. Coefficient estimates for the instruments from the first stage regressions for *infections* and results from F-tests of the joint significance are presented in *Table 7* (Results

for *adverse drug events* and *ulcers* are very similar).[3] Results from the UVPs for both years and estimates of ρ from the system models cannot be presented here due to space limitations.[3]

To check for endogeneity, we test whether or not there is 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, see *Table 7).* 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 (0.94) 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 for both years, and in addition March, September, October and November for 05/06 only, 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 (see *Table 4).* The MEs and AVEs are evaluated at the mean of all regressors (discussed 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%) (Due to the

[3] available on the corresponding author's website.

nonlinear nature of the models, MEs and AVEs may vary slightly according to where along the distribution of LOS they are evaluated). MEs, AVEs 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 MEs of LOS), but may want to compare treatment programs with LOS differences greater than one day. As an example, an episode with total LOS of 4 days (3 nights) implies a total risk of suffering an adverse drug event of 0.8% (1.3%), infection of 4.8% (4.8%), and ulcer of 0.4% (0.8%). An episode with LOS of 8 days (7 nights) implies a total risk of an adverse drug event of 1.9% (3.0%), infection of 11.1% (11.2%), and ulcer of 1.0% (1.9%), 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 5.8% (5.0%), infections by 4.5% (3.8%), and has no effect on ulcers *(Table 5).* 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 again 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. Focusing on the comorbidities with highest prevalence in our sample, congestive heart failure increases risk of adverse drug events by 0.8% (0.7%), infections by 4.1% (3.3%), and does not affect ulcers, in comparison to not suffering this comorbidity and holding all other factors constant. Chronic obstructive pulmonary disease decreases risk of adverse drug events by 0.6% (04/05 only) and ulcers by 0.1% (0.3%), which are counterintuitive results, but increases risk of infections by 1.2% (1.7%). Diabetes increases risk of adverse drug reactions by 1.1% (0.6%), infections by 1.0% (only in 05/06) and ulcers by 0.2% (0.6%), whereas diabetes complications do not increase risk of any AE. Cancer increases risk of adverse drug events by 2.0 (1.5%), infections by 2.7% (1.2%), and decreases risk of ulcers by -0.2% (only in 05/06).

Comparably high AVEs are observed for hemiplegia/paraplegia, and aids. Hemiplegia/paraplegia decreases (surprisingly) risk of adverse drug events by -1.3% (-1.2%),

increases risk of infections by 3.0% (3.2%), and ulcers by 1.7% (2.0%). AIDS increases risk of adverse drug events by 8.0% (5.1%) and infections by 18.3% (21%). To summarize the impact of comorbidities, the top two risk factors for adverse drug events are AIDS and rheumatoid disease, maybe because patients with these comorbidities receive comparably drug-intensive therapies. Top risk factors for infections are AIDS and cerebrovascular events, and for ulcers are hemiplegia or paraplegia, which is not surprising considering that ulcers are much more likely to occur in immobile patients. The MEs and AVEs 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.

Average 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 (see *Table 6).* AVEs for the hospitals vary from -1.5% to 9.6% (-0.6% to 12.4%) for adverse drug events, -1.6 to 5.8% (-0.6% to 9.4%) for infections, and -0.5% to 1.5% (-0.5% to 2.2%) for ulcers. This implies that some patients experienced a much higher or lower risk of AEs 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 AE 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 (or in the community), which may lead to above average rates of AEs in that hospital. It is possible that the relatively large AVEs may be due to systematic differences in reporting AEs across hospitals.

This study has several limitations. LOS enters the models as a linear continuous variable. Thus, we assume that the effect of increasing the hospital stay by one day is the same irrespective of how long the patient has already stayed in hospital, and any nonlinearity is attributable to the model specification. It is a relatively strong assumption that increasing the hospital stay from (say) 2 to 3 days leads to the same increase in risk than increasing the hospital stay from (say) 13 to 14 days. We estimate UPVs with the squared values of LOS as additional regressors to check for nonlinearity, and coefficient estimates are very small but significant, which may indicate nonlinearity.[3] Future research could explore alternative models specifications with LOS as a nonlinear variable, or the use of 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. 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.

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 need to limit the objective of our paper on estimating the impact of LOS on the incidence of AEs.

7. Conclusions

We use a statistical model to estimate the incidence of three types of medical AEs as a function of patient risk factors, hospital effects, and LOS using administrative hospital data. Our research complements previous research efforts, which are mainly qualitative because they rely on retrospective patient record reviews by medical experts. Our particular contribution is to provide structural estimates of the impact of LOS on the incidence of AE,

accounting for the possibility that LOS is endogenous with a structural equation model and additional instruments for LOS. We find that 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 factors 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 informed discharge and care decisions.

Our results provide managers with an estimate of the expected risk 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 risk of AE is of course not the only factor which should influence discharge decisions. However, considering the relatively large expected costs of AE, it seems timely that they are factored into discharge and treatment decisions in a quantitative way. Our statistical model of AEs can contribute to providing such quantitative evidence, and offers important additional information to the qualitative research efforts on incidence and risk factors of AE. It proposes an alternative to randomized controlled trials for comparing treatments with different discharge policies, which are not well equipped to deal with endogeneity, and are more expensive. 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 of dependent and explanatory variables

	2004/5		2005/6	
	Mean	**SD**	**Mean**	**SD**
total observations	198,854		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
non-elective	0.745	0.436	0.747	0.435
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 (ami)	0.036	0.186	0.038	0.191
congestive heart failure (chf)	0.080	0.272	0.079	0.270
peripheral vascular disease (pvd)	0.016	0.127	0.017	0.130
cerebrovascular event (cevd)	0.049	0.216	0.049	0.216
dementia	0.036	0.186	0.035	0.185
chronic obstructive pulmonary disease (copd)	0.080	0.272	0.079	0.269
rheumatoid disease (rheuma)	0.006	0.074	0.006	0.076
peptic ulcer (pud)	0.002	0.049	0.002	0.046
liver disease*	0.010	0.098	0.010	0.102
diabetes	0.073	0.260	0.068	0.252
diabetes complications (diab comp)	0.109	0.312	0.120	0.325
hemiplegia or paraplegia (hp papl)	0.028	0.166	0.029	0.166
renal disease	0.065	0.246	0.069	0.254
cancer^	0.082	0.273	0.082	0.274
aids	0.001	0.038	0.002	0.040

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* includes patients with severe liver disease
^ includes patients with metastatic cancer

Table 2: Summary statistics of the instruments

	2004/5		2005/6	
	Mean	**SD**	**Mean**	**SD**
Days of discharge				
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
Weekend (Saturday or Sunday)[+ #]	0.190	0.393	0.198	0.398
Months of discharge				
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

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* also discharges on days after a public holiday

^ also discharges on days before a public holiday

[+] also discharges on public holidays, on Mondays before a holiday falling on a Tuesday, and Fridays after a holiday falling on a Thursday

[#] differences in holidays across regional and metropolitan Victoria are considered

Table 3: ICD10-AM adverse events codes

Adverse drug reactions	
Y400-Y599	Drugs causing adverse effects in therapeutic use
Y630-Y639	Failure in dosage during medical care
Y601-Y603	Cut during infusion, dialysis or injection
Y621-Y623	Failure of sterile precautions during infusion, dialysis or injection
Y640-Y649	Contaminated medical or biological substance administered
Y650	Mismatched blood
Y651	Wrong fluid in infusion
T881	Rash following immunization
T886	Anaphylactic shock due to adverse effect of correct drug or medicament properly
T887	Unspecified adverse effect of drug or medicament
Infections	
Wound infections	
T814	Infection following a procedure, not elsewhere classified or post operative
T793	Post-traumatic wound infection, not elsewhere classified
T826-T827 , T835-T836 , T845-T847, T857	Infection and inflammatory reaction due to prosthetic devices, implants and grafts
T802	Infections following infusion, transfusion and therapeutic injection
T880	Infection following immunization
Y95	Nosocomial condition
Urinary tract infections	
N390	UTI
Pneumonia and lower respiratory tract infections	
J120-J189	Pneumonia
J200-J22	Lower respiratory tract infection
Sepsis	
A400-A419	Streptococcal and other septicaemia
R578	Endotoxic shock
T811	Shock during or resulting from a procedure, not elsewhere classified
Pressure ulcers	
L89	Decubitus ulcer

Table 4: Summary of results from system and univariate probit models

		Adverse drug events		Infections		Ulcers	
		ME* of LOS	SE	ME* of LOS	SE	ME* of LOS	SE
2004/5	UVP	.00195	.00008	.00685	.00016	.00049	.00002
	System model	.00248	.00118	.01449	.00236	.00271	.00102
	Test of exogeneity (rho = 0) Prob > chi2	0.6456		0.0010		0.0001	
2005/6	UVP	.00184	.00008	.00723	.00016	.00048	.00002
	System model	.00427	.00125	.01601	.00228	.00276	.00099
	Test of exogeneity (rho = 0) Prob > chi2	0.0419		0.0001		0.0001	

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* Marginal effects are evaluated at the mean of all regressors.

Table 5: Marginal and average effects for patients' explanatory variables from the system models (structural equations)

	adverse drug events				infections				ulcers			
	2004/05		2005/06		2004/05		2005/06		2004/05		2005/06	
Prob. of AE	0.043		0.040		0.164		0.141		0.006		0.009	
variables	dy/dx^	SE	dy/dx^	SE	dy/dx^	SE	dy/dx^	SE	dy/dx^	SE	dy/dx^	SE
age	0.003	0.000	0.003	0.000	0.002	0.000	0.002	0.000	0.000	0.000	0.000	0.000
age2	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
female*	0.009	0.001	0.008	0.001	0.012	0.002	0.015	0.002	-0.001	0.000	-0.001	0.000
non-elective*	0.016	0.001	0.017	0.001	0.073	0.002	0.074	0.002	0.000	0.000	0.000	0.001
number of procedures	0.001	0.002	-0.002	0.002	-0.002	0.003	-0.004	0.003	-0.001	0.001	-0.002	0.001
severity grade 1*	-0.003	0.001	-0.007	0.001	0.077	0.003	0.062	0.003	-0.002	0.001	-0.002	0.001
severity grade 3*	-0.010	0.001	-0.009	0.001	-0.018	0.003	-0.020	0.003	0.002	0.001	0.003	0.001
discharge by death*	-0.016	0.002	-0.013	0.002	0.089	0.007	0.080	0.006	excluded[#]		0.017	0.002
ami*	-0.008	0.002	-0.007	0.002	0.004	0.005	0.019	0.004	-0.002	0.001	-0.003	0.001
chf*	0.008	0.003	0.007	0.002	0.041	0.005	0.033	0.004	-0.001	0.001	-0.001	0.001
pvd*	-0.019	0.002	-0.010	0.002	-0.067	0.005	-0.048	0.004	0.006	0.001	0.006	0.002
cevd*	-0.023	0.002	-0.018	0.002	-0.083	0.004	-0.073	0.003	-0.005	0.001	-0.007	0.001
dementia*	-0.016	0.003	-0.019	0.002	0.021	0.008	0.023	0.007	0.003	0.001	0.001	0.001
copd*	-0.006	0.002	-0.001	0.002	0.012	0.003	0.017	0.003	-0.001	0.001	-0.003	0.001
rheuma*	0.034	0.008	0.027	0.007	-0.012	0.011	0.000	0.010	0.002	0.002	0.004	0.003
pud*	0.021	0.010	0.014	0.009	-0.034	0.014	-0.049	0.012	-0.002	0.002	0.000	0.003
liver disease*	-0.004	0.003	-0.008	0.003	-0.008	0.007	-0.009	0.006	0.001	0.001	-0.003	0.001
diabetes*	0.011	0.002	0.006	0.002	0.006	0.004	0.010	0.003	0.002	0.001	0.006	0.001
diab comp*	0.001	0.001	0.002	0.001	0.004	0.003	0.003	0.002	0.000	0.000	0.000	0.001
hp papl*	-0.013	0.003	-0.012	0.003	0.030	0.008	0.032	0.007	0.017	0.003	0.020	0.003
renal disease*	0.026	0.003	0.012	0.002	0.041	0.004	0.037	0.004	0.000	0.001	-0.001	0.001
cancer*	0.020	0.002	0.015	0.002	0.027	0.004	0.012	0.004	-0.001	0.001	-0.002	0.001
aids*	0.080	0.021	0.051	0.016	0.183	0.031	0.206	0.029	excluded[$]		excluded[$]	

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* dy/dx is for a discrete change of dummy variable from 0 to 1.
^ Marginal and average effects are evaluated at the mean of all regressors.
[#] 'death' is excluded due to high degree of collinearity with other explanatory variables.
[$] there are no AIDS patients with ulcers.

Table 6: Average effects for the hospital dummies from the system models (structural equations)

	adverse drug events				infections				ulcers			
	2004/05		2005/06		2004/05		2005/06		2004/05		2005/06	
Hospital dummies	dy/dx^	SE	dy/dx^	SE	dy/dx^	SE	dy/dx^	SE	dy/dx^	SE	dy/dx^	SE
A17*	0.051	0.006	0.055	0.006	0.056	0.008	0.049	0.007	0.008	0.003	0.013	0.004
A32*	0.037	0.006	0.029	0.006	0.009	0.008	-0.006	0.007	0.001	0.002	-0.001	0.002
B01*	0.064	0.010	0.068	0.011	0.058	0.012	0.046	0.011	0.000	0.002	0.004	0.004
B03*	0.037	0.004	0.058	0.006	0.035	0.006	0.034	0.006	0.001	0.001	0.008	0.003
B05*	0.027	0.004	0.041	0.005	0.010	0.006	0.009	0.005	-0.003	0.001	-0.002	0.001
B11*	0.049	0.006	0.048	0.006	0.043	0.007	0.032	0.007	0.004	0.002	0.010	0.004
B18*	0.035	0.004	0.028	0.005	0.018	0.006	0.012	0.006	-0.002	0.001	0.000	0.001
B21*	0.000	0.003	0.016	0.004	-0.008	0.006	0.003	0.005	-0.003	0.001	-0.002	0.001
B22*	0.096	0.012	0.124	0.014	0.056	0.014	0.094	0.014	0.006	0.004	0.012	0.006
B28*	0.015	0.004	0.009	0.004	0.031	0.007	0.027	0.007	0.000	0.001	0.006	0.003
B33*	0.025	0.005	0.035	0.005	-0.007	0.006	0.019	0.007	0.001	0.001	0.004	0.002
B36*	0.006	0.006	0.017	0.007	0.034	0.010	0.015	0.009	-0.003	0.001	-0.005	0.001
B39*	0.016	0.005	0.016	0.005	0.025	0.008	0.025	0.007	0.001	0.002	0.008	0.003
B45*	-0.003	0.003	0.014	0.004	-0.012	0.006	0.010	0.006	0.001	0.001	0.006	0.003
B66*	0.055	0.016	0.040	0.008	0.049	0.020	0.049	0.010	0.015	0.008	0.020	0.007
D01*	0.005	0.005	0.011	0.005	0.009	0.008	0.005	0.007	0.001	0.002	0.007	0.003
D02*	0.007	0.004	0.004	0.004	0.011	0.007	0.002	0.006	-0.002	0.001	0.000	0.002
D05*	0.021	0.004	0.036	0.004	-0.008	0.005	-0.004	0.005	0.003	0.001	0.005	0.002
D06*	0.038	0.008	0.025	0.007	0.015	0.011	0.013	0.009	0.004	0.003	0.007	0.004
D07*	0.027	0.008	0.028	0.008	-0.008	0.011	0.012	0.011	0.007	0.004	0.004	0.004
D12*	0.027	0.005	0.022	0.005	-0.016	0.007	0.008	0.007	-0.001	0.001	-0.002	0.001
D15*	0.025	0.007	0.029	0.007	0.016	0.010	0.053	0.010	0.003	0.002	0.002	0.003
D16*	0.047	0.006	0.050	0.006	0.001	0.008	-0.003	0.007	0.004	0.002	0.003	0.002
D17*	0.061	0.010	0.068	0.011	0.011	0.011	0.022	0.011	-0.002	0.002	0.016	0.007
E04*	0.032	0.007	0.030	0.007	0.030	0.009	0.038	0.009	0.001	0.002	0.004	0.003
E18*	-0.015	0.005	-0.006	0.005	0.017	0.011	0.025	0.010	-0.001	0.002	-0.005	0.002
E22*	0.014	0.004	0.009	0.004	0.026	0.007	0.040	0.007	0.014	0.004	0.018	0.005
E44*	0.021	0.005	0.016	0.005	0.050	0.009	0.036	0.007	0.009	0.003	0.004	0.002
E58*	0.034	0.008	0.025	0.007	0.029	0.011	0.058	0.011	0.008	0.003	0.019	0.006
E59*	0.004	0.005	0.019	0.006	0.013	0.009	0.017	0.008	-0.001	0.001	0.003	0.003
E66*	0.057	0.009	0.050	0.008	0.021	0.011	0.020	0.009	0.001	0.002	0.006	0.004
G25*	0.003	0.005	-0.003	0.004	0.016	0.008	0.028	0.008	0.009	0.003	0.022	0.006
P32*	-0.002	0.005	0.003	0.005	0.020	0.009	0.019	0.008	-0.005	0.001	-0.004	0.002

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

^ Average effects are evaluated at the mean of all regressors.

Table 7: Coefficient estimates for the instruments from the system models for infections^ (first stage regressions)

	2004/05		2005/06	
Instruments	β	SE	β	SE
Days of discharge				
Tuesday	-0.088*	0.033	-0.087*	0.032
Wednesday	-0.341*	0.033	-0.401*	0.032
Thursday	-0.537*	0.033	-0.526*	0.032
Friday	-0.721*	0.032	-0.727*	0.030
Weekend (Saturday or Sunday)	-0.983*	0.031	-0.944*	0.030
Months of discharge				
February	-0.137*	0.048	-0.124*	0.046
March	-0.029	0.047	-0.188*	0.045
April	-0.040	0.047	0.030	0.046
May	-0.153*	0.047	-0.148*	0.045
June	-0.034	0.047	-0.002	0.045
July	-0.008	0.047	-0.080	0.045
August	0.104	0.047	0.009	0.045
September	-0.034	0.047	-0.108*	0.045
October	-0.024	0.047	-0.174*	0.045
November	0.022	0.047	-0.126*	0.045
December	-0.175*	0.047	-0.214*	0.045

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^ coefficient estimates from the first stage regressions are very similar for adverse drug reactions and ulcers (available on request)

* significant at 95% confidence level

coefficient estimates for additional explanatory variables in the first stage regression are not reported, but available on request.

F-tests of the joint significance of the instruments for infections (results for adverse drug reactions and ulcers are very similar, and available on request):

Days and months of discharge: F(16,198776) = 92.18 for 2004/05; F(16,206414) = 94.81 for 2005/06.

Days of discharge only: F(5,198776) = 279.64 for 2004/05 for 2004/05; F(5,206414) = 288.06 for 2005/06.

Months of discharge only: F(11,198776) = 5.55 for 2004/05; F(11,206414) = 6.85 for 2005/06.

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