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TANAFFOS

Acute Kidney Injury in ICU Patients Following Non-Cardiac Surgery at Masih Daneshvari Hospital: Joint Modeling Application

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Background: Admission to the intensive care unit (ICU) is often complicated by early acute kidney injury (AKI). AKI is associated with high rates of mortality and morbidity. Risk factors and incidence of AKI have been notably high following non-cardiac surgery in the past decade.
The aim of this study was to determine the hazard rate of AKI, the effect of risk factors of AKI and also to assess the changes in urine output (UO) as a predictor of AKI using joint modeling in patients undergoing non-cardiac surgery.
Materials and Methods: In this retrospective cohort study, 400 non-cardiac-operated patients admitted during 3 years to the ICU of Masih Daneshvari Hospital were selected according to the consecutive sample selection method. Random mixed effect model and survival model were used to assess UO changes and the effect of UO and other risk factors on the hazard rate of AKI using joint analysis.
Results: AKI occurred in 8.8% of the Iranian non-cardiac-operated patients. Survival model showed that the risk of AKI in lower diastolic blood pressure (DBP), higher Acute Physiology and Chronic Health Evaluation II score (APACHE II score), emergency surgery, longer hospitalization and male patients was higher (P=0.001). Using joint modeling, an association was found between the risk of AKI and UO (-0.19, P=0.002).
Conclusion: Several predictors were found to be associated with AKI in the Iranian patients after non-cardiac surgery. A relationship between longitudinal and survival responses was found in this study and joint modeling caused considerable improvement in estimations compared to separate longitudinal and survival models.

Key words: Acute kidney injury, Joint models, Risk factor, Urine output, Non-cardiac surgery

INTRODUCTION

Occurrence of AKI is strongly associated with increased mortality and morbidity (1, 2). Many cohort studies have been conducted on AKI following cardiac surgery (3-7) but AKI is not limited to cardiac surgery (2). The incidence of AKI varies from 7.5% in general surgical patients to 39.8% in patients in the ICU (8). Abelha and colleagues found that the incidence of AKI after major non-cardiac surgery was 7.5% and patients who developed AKI, had higher Simplified Acute Physiology Score II (SAPS II score) and APACHE II score, longer stay in the post-anesthesia care unit (PACU) and higher hospital mortality (1, 9). Kheterpal and colleagues, using representative and large national clinical data set, found that 1.0% of patients after general surgery were complicated by AKI; also age (>=56), sex (male), diabetes mellitus (necessitating oral and insulin therapy), emergency surgery, intraperitoneal surgery, hypertension, active congestive heart failure and ascites were introduced as preoperative predictors of AKI (8).

Biteker and colleagues identified age, diabetes, revised cardiac risk index, and American Society of Anesthesiologists' physical status as independent predictors of AKI in patients undergoing non-cardiac, nonvascular surgery and the AKI incidence was reported to be 6.7%(NCS)(10).

AKI in ICU patients following non-cardiac surgery has not been described comprehensively in the Iranian patients. In this study, the effect of risk factors on UO changes as predictor of AKI and incidence of risk factors associated with AKI following non-cardiac surgery were investigated. A joint modeling of longitudinal and survival data was used to determine the effects of risk factors such as sex, age, infection, diastolic blood pressure (DBP), systolic blood pressure (SBP), emergency surgery, SAPS II score, APACHE II score, length of hospitalization and ICU stay on time to AKI following non-cardiac surgery.

MATERIALS AND METHODS

This retrospective cohort study was conducted on patients admitted to the ICU of Masih Daneshvari Hospital as a referral center during 3 years. All consecutive adult patients (N=445) who underwent non-cardiac surgical procedure in Masih Daneshvari Hospital, from October 2010 to October 2012 were evaluated. Patients' demographic characteristics, laboratory data and the reason for ICU admission were recorded in constructed forms during the ICU admission. Some non-cardiac surgeries included in this study were tracheal stenosis, resection and anastomosis of the trachea, lobectomy, pneumonectomy and trauma.

Patients older than 18 years admitted to the ICU were included in this study. Written informed consent was obtained from all patients before entry into the study. Patients who underwent more than one surgical procedure during hospitalization (n=26) were excluded. An additional exclusion criterion was preoperative renal failure requiring dialysis (n=19). Overall, 400 patients were included in the study. After surgery, patients were admitted to the ICU and followed from the day of ICU admission until ICU discharge or death. UO and other physiological variables were repeatedly measured every two hours during the first 8 hours of admission in the ICU. Patients' demographics, laboratory data, the reason for ICU admission, length of hospitalization and ICU stay were recorded in prepared forms during the ICU admission. Main survival endpoint was the time of occurrence of AKI after non-cardiac surgery. Patients were followed since ICU admission until AKI occurrence. The dosage of dopa, dobutamine, epinephrine, nor-epinephrine and vasopressin was scaled based on individual patient characteristics and comorbid conditions. Blood pressure was measured twice with a 10-minute interval and patients sat for at least five minutes before the measurement. We used AKIN criteria for AKI definition, which was defined as a reduction in urine volume to 0.5 ml/kg per hour for more than 6 hours.

Statistical analysis

A joint modeling of longitudinal and survival data, proposed by Guo-Carlin, was used for data analysis in this study (9, 11-13). Guo-Carlin's method uses a Bayesian hierarchical model obtaining estimates for the parameters of interest by Markov chain Monte Carlo (MCMC) methods. The joint modeling approach links two sub-models, one for the longitudinal process and one for the event time. In this study, longitudinal and survival responses were UO and the time of occurrence of AKI (in hours), respectively in patients with non-cardiac surgery since the time of ICU admission. A mixed effect model was assumed for UO and the time to AKI was analyzed using parametric models (Weibull and exponential models), respectively according to the equations 1 and 2:

$$UO_{ij} = intercept_i + \beta_{11} age_i + \beta_{21} sex_i + \beta_{31} DBP_{ij} + \beta_{41} infection_{ij} \quad Equation1$$

and

$$\lambda_i(t) = \lambda_0(t) \exp(\gamma * intercept_i + \beta_{12} APACHE_i + \beta_{22} sex_i + \beta_{32} DBP_i + \beta_{42} hospital\_stay_i + \beta_{52} emergency\_surgery_i + \beta_{62} UO_i) \quad Equation.2$$

Where i =1… 400, the number of patients and j for each i, equals to j=1,2,3,4 . $\lambda_i(t)$ is hazard of AKI for patient i at time t. We assessed the association of UO with AKI data for the first time by γ.

Free software Open Bugs 3.2.2 (http://www.mrc-bsu.cam.ac.uk) was used for data analysis and estimation of unknown parameters. Deviance information criterion (DIC) was used for model selection.

RESULTS

To summarize, the mean age was 43.6 years, 39.8% were women and AKI developed in 8.8% (35 of 400). The characteristics of some variables, which were used in the modeling, are reported in Table 1. Figure 1 shows the observed longitudinal measures of UO plotted against time for the patients included in the analysis. UO decreased from the onset of study to the fourth hour, and after that increased again .The survival estimates of patients are shown in Figure 2. Decreasing survival curve of patients means the increasing risk of AKI over time. The circles on the line of survival function in Figure 1 denote that AKI for some patients did not occur because the study was ended or due to the death of patients. The total number of UO longitudinal measurements was 1540 and the average of measurements was 3.85 per patient. The amount of UO decreased over time. Table 2 compares the results of joint analysis for the effect estimation of some covariates on two responses. DBP, sex, emergency surgery and APACHE II score had significant effects on the hazard of AKI. The association parameter (γ) that described the strength of association between values of UO and risk of AKI, was estimated to be -0.19 with 95% confidence interval (-0.29,-0.10) and indicated that UO and the risk of AKI were negatively correlated.

Table1: Demographic and laboratory characteristics of patients

variable	total (n=400)		Non-AKI (n=365)		AKI (n=35)	
	mean ± SE	N(%)	mean ±SE	N(%)	mean ± SE	N(%)
Urine						
2hour	1813.5±1176.9		1836.5±1170.1		1593.1±1234.5	
4 hour	722.6±542.5		738.7±636.5		558.2±548.6	
6 hour	738.7±620.4		754.5±638.4		635.1±488.9	
8 hour	1100±901.5		1150±801.5		800±601.5	
hospital length of stay (days)	19.3±1.6		18.1±10.6		28.7±17.1	
ICU length of stay (days)	6.9±1.2		6.0±5.2		17.1±12.4	
Age, year	43.59±12.8		42.2±10.8		58.2±19.8	
SAPS II score	26.4±17.5		24.6±16.2		45.1±21.4	
APHACHE II score	9.0±7.0		8.1±6.3		17.9±8.3	
Diastolic Blood Pressure	73.4±17.5		69.6±14.7		70.4±18.4	
Systolic Blood Pressure	122.9±24.3		119.0±20.5		124.4±28.4	
emergency surgery,yes		31(7.8)		27(7.4)		4(11.4)
cardiac disease, yes		35(8.5)		27(7.4)		8(22.9)
Sex, Female		159(39.8)		146(40.0)		13(37.1)
Infection, yes		27(6.6)		21(5.7)		6(17.7)

Continuous variables are presented as the mean ± SE.

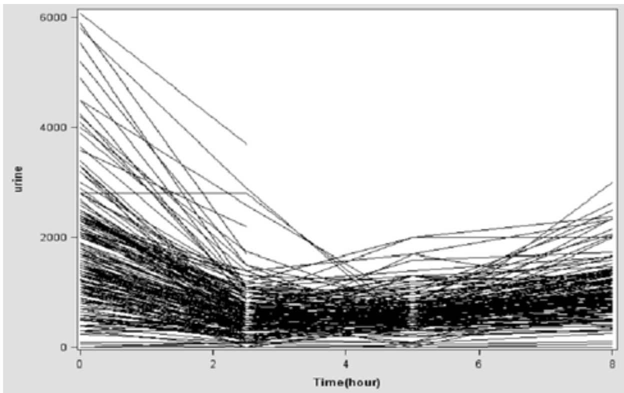

Figure1.Observed trajectories of UO

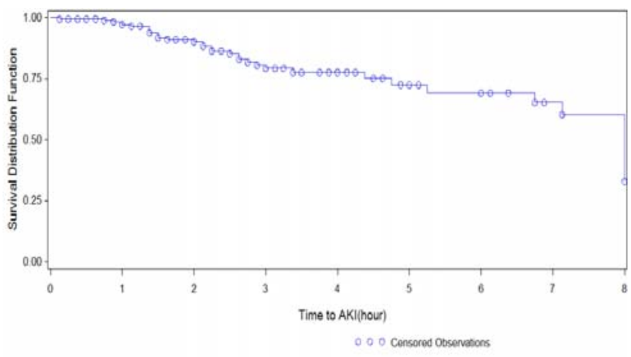

Figure2. Survival estimate of patients

Table 2.The estimated effects of risk factors associated with UO and AKI in ICU data using joint analysis

Sub-model	Parameter	β(SE)
Longitudinal(UO)		
	Age(β_{11})	1.5(1.1)
	Sex(β_{21})	-25.72 (28.6)
	DBP(β_{31})	3.6*(1.8)
	Infection(β_{41})	-180.8*(106.00)
Survival(AKI)		
	APACHE II score(β_{12})	0.43*(0.21)
	Sex(β_{22})	-0.64*(0.39)
	Diastolic Blood Pressure(β_{32})	-0.21*(0.08)
	Hospital length of stay(β_{42})	0.71* (0.62)
	emergency surgery(β_{52})	0.61* (0.42)
	UO(β_{62})	-0.09*(0.04)
Association parameter	Association(γ)	-0.19*(0.34)

*Significance of the effect at significance level of 5%.

The HR is exp(0. 61) =1.8 for patients with emergency surgery with respect to non-emergency surgery, which means that patients without emergency surgery, had a better average survival. Males had a worse survival (higher risk of AKI following non-cardiac surgery) than females and the differences were significant, because HR of AKI following non-cardiac surgery in males to females was exp (0.64)=1.9. APACHE II score was another significant predictor for AKI following non-cardiac surgery, so that for a one-unit increase in APACHE II score, the HR of AKI following non-cardiac surgery increased by 53% because HR=exp(1.43)=1.53. Also, HR of AKI in lower DBP was significant. In the longitudinal sub-model, it was shown that the decrease of UO occurred more frequently in infected patients and also in low DBP, significantly.

DISCUSSION

This study focused on the HR of AKI in the Iranian patients who underwent non-cardiac surgery in Masih Daneshvari Hospital, Tehran, Iran.

AKI developed in 8.8%(35 of 400) of patients. Many studies have developed models to predict AKI, but statistical modeling of the risk factors associated with the variation of UO in ICU patients, has been described less commonly compared to AKI and also there was no numeric quantity for association of UO and risk of AKI (16); but in this study, change of UO over time as a preferable biomarker of AKI was studied simultaneously with the HR of AKI. Our results showed that UO had a significant effect on the hazard of AKI similar to many previous studies (15-18). According to the results of the mixed model of joint analysis, a decrease in UO occurred more frequently in infected patients and also in low DBP, significantly (P<0.05). Low DBP (HR=1.2, P=0.03) and higher hospital length of stay (HR=2.0) had significant effects on the risk of AKI after non-cardiac surgery. Similar results were obtained by other researchers (3, 5, 6, 17, 18). Murray studied AKI following non-cardiac surgery and found that 87 (7.5%) developed AKI. Age, emergency surgery and ischemic heart disease were reported as preoperative predictors of AKI during the postoperative period (9). The aim of this study was finding a relationship between the time of AKI following non-cardiac surgery and UO by an association parameter, using joint modeling. Joint modeling takes into account the inter dependence of two types of survival and longitudinal responses. After using joint modeling, our findings showed a negative significant association between the risk of AKI following non-cardiac surgery and UO in patients (-0.19,P=0.04) and showed the suitable selection of joint modeling for this study.

Many other factors are associated with an increased risk of AKI but their effects will be highly dependent on the specific nature of the population (19). When using joint modeling, a reduction in the standard error of estimates occurs, thus more accurate parameter estimates and valid inference concerning the effect of covariates on the survival and longitudinal outcomes can be obtained (11,14, 20).

We recommend definite prevention programs in the ICU target patients with traditional risks of AKI such as older age, sex, blood pressure and system scoring. Also, use of joint modeling is recommended to investigate the incidence of AKI for different types of surgeries in future studies.

Nonetheless, this study makes a substantial contribution to the effort to define risk factors for AKI after non-cardiac surgery. Ideally, such works must be extended to multicenter registries. The strengths of this study were estimation of association of AKI and UO using joint modeling for the first time and large sample size.

CONCLUSIONS

A relationship between longitudinal and survival responses was found in this study and joint modeling caused considerable improvement in estimations compared to separate longitudinal and survival models.

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Conflict of interest

There is no conflict of interest to declare.

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