

# The Potentially Protective Effects of Anti-Lipid, Hypoglycemic, and Anti-Hypertensive Agents for Perioperative Mortality in Geriatric Group

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## Research Article

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## Abstract

## Background

Great efforts were made to collect information and identify risk factors in predicting post-anesthetic mortality. In this study, we use national health insurance data base, including medications, underlying comorbidities and surgical factors to assess the relationship between these factors and mortality after surgery.

## Methods

This is a retrospective, population based study. The study population who underwent general anesthesia (GA) were retrieved from the National Health Insurance Research Database in Taiwan between January 1, 2005 and December 31, 2013. We classified the study patients into 4 major comparison groups by surgical procedures, including major organ transplantation (heart, liver, lung, kidney, or pancreas), CV surgery, major neurosurgery, and others according to the diagnostic codes of the international classification of diseases, ninth revision, clinical modification (ICD-9-CM) codes. We proposed a logistic regression model with valuable variables which can significantly predicts the post-anesthesia mortality. We also designed different models for 4 subgroups according the results.

## Results

A total of 833,685 subjects were included in this study, and the most common comorbidity was hypertension. Age was an important determinant associated with post-operation mortality among different surgical types. Perioperative prescription could reduce risks of operation. The prediction model based on the preliminary training group also performed well in the validation group (AUROC=0.8753 for in-hospital mortality; AUROC= 0.8767 for 30-days mortality). A reliable predicting model can help anesthesiologists to decide the anesthesia method or monitors, as well as helping physicians to take care of their patients after operation.

## Conclusions

While GA is commonly used for the majority of the patients undergoing operations, the prediction model that we proposed from this nationwide study could identify the predictors for post-operation mortality. The potentially protective effects of anti-lipid, hypoglycemic, and anti-hypertensive agents were encouraging in geriatric preoperative group. It is expected that applying this prediction model and prescription into clinical practice could improve surgical risk stratification and further improve patient outcomes.

## Trial registration

The protocol of this study was approved by the National Taiwan University Hospital Research Ethics Committee (Trial Registration 201411078RINC). Informed consent was waived by the National Taiwan University Hospital Research Ethics Committee due to the retrospective and anonymous nature of the claims data.

## Introduction

Charlson comorbidity index which was introduced since 1987 and updated in 2011 consists twelve comorbidities rather than the original seventeen ones had showed a good ability to discriminate outcome in hospital mortality after surgery. [1] The newly developed preoperative score to predict postoperative mortality (POSPOM) used ICD 10th revision codes showed good calibration and excellent discrimination for in-hospital mortality in the development and validation cohort. [2] The above studies strive to establish a new objective evaluation tool to include individual's comorbidities and surgery types to predict post-anesthetic mortality.

In previous studies, elderly patients underwent an increasing number of operations, and usually developed more postoperative complications with poorer outcomes. [3, 4] The Multidimensional Frailty Score based on comprehensive geriatric assessments demonstrates the importance of geriatric functional independence and predicts postoperative mortality risk and postoperative complication well. [5] Another previous study using age, sex, type of surgery of geriatric patients to match death and survival groups in Taiwan health insurance data suggested that the leading comorbidity associated with 30-day post-anesthetic mortality in geriatric patients were chronic renal disease, acute myocardial infarction, and intracranial hemorrhage. [6]

Great efforts were made to collect existing information and identify risk factors to predict post-anesthetic mortality which is not a common event for general population. Therefore, it is difficult to draw the association of disease and death with limited sample size. In this study, we aimed to investigate the independent predictors of the mortality following surgeries under general anesthesia (GA) by analyzing the National Health Insurance (NHI) Database in Taiwan which several studies have been published by using the reimbursement claims data from [7, 8], aiming to stratify independent risk predictors and develop a model to estimate the probability of post-anesthetic mortality and to validate it with another set of database. We proposed a logistic regression model with 22 variables which predicts the post-anesthesia mortality. We also designed different model for 4 subgroups according the results.

## Methods

## Data source

A single-payer and compulsory NHI program was launched by the Taiwanese government in 1995. The Taiwan NHI database includes complete hospital admissions, prescriptions, surgery or procedures, disease, and vital status for 99% of the country's population (nearly 23 million Taiwanese). Enrollment rate had been achieved 99% since 2010. The current analyses linked several large computerized claims data sets with the National Death Registry through the use of birth dates and civil identification numbers unique to each beneficiary. The protocol of this study was approved by the National Taiwan University Hospital Research Ethics Committee (Trial Registration 201411078RINC). Informed consent was waived due to the retrospective and anonymous nature of the claims data. All analyses were performed in accordance with relevant guidelines and regulations.

## Study population

We identified patients receiving first GA from the claims database for the preliminary group (the training set) from the one million sampling out of the 21 million population from January 1, 2005 to December 31, 2011 and validation analysis from the whole population database between January 1, 2012 and December 31, 2013. Subjects were excluded in case of 1) age less than 20 years, 2) anesthesia in outpatient department, 3) no surgical procedure, 4) operation of cardiovascular (CV) and neurosurgical at the same time, and 5) uncertain sex.

Demographic data were recorded regarding age, gender, surgery time, hospital level, comorbidities, pharmacy prescriptions, outpatient visits, emergency room visits, and hospitalization details. ASA classification was not included in NHI database. In-hospital mortality and 30-day mortality were retrieved from the index date (date of anesthesia) to the death date, which was recorded in the NHI death dataset coding for vital status and cause of death. A total of 91,016 patients was identified as the preliminary group (the training set) by using the algorithm from the one million sampling out of the 21 million population from 2005 to 2011 and 590,763 patients from the whole population database from 2012 to 2013 as the validation group (Figure 1).

## Covariate ascertainment and adjustment

Inpatient and outpatient diagnosis files and prescription data during the 12-month period before the index date were used to ascertain patients' past history. We classified the study patients into 4 major comparison groups by surgical procedures, including 1) major organ transplantation (heart, liver, lung, kidney, or pancreas), 2) cardiovascular (CV) surgery, 3) major neurosurgery, and 4) others according to the diagnostic codes of the international classification of diseases, ninth revision, clinical modification (ICD-9-CM) codes (eTable 1 in the supplement), the surgical time with anesthesia and the underlying comorbidity were also defined (eTable 2 and eTable 3 in the supplement). Because the disease categorization was complex, we aggregated codes into disease groups to resemble clinical usage and this process was conducted by three clinicians. The prescription data were used to ascertain patients' medical history (eTable 4 in the supplement).

## Outcome ascertainment and follow-up

The primary outcome were the in-hospital mortality and the secondary outcomes were the death within 30 days following from the index date.

## Statistical analyses

Baseline characteristics, comorbidities, medication use, and resource utilization with medical cost were summarized and analyzed. Participants were further stratified according to sex (men and women) and age. The age-specific estimates were calculated for groups aged < 65 years, 65-74 years, and  $\geq$  75 years. Categorical variables were compared with  $\chi^2$  test (or Fisher's exact test) and continuous variables with Student's *t* test.

The analyses were adjusted for sex, age, surgery time, hospital level (medical center or not). Factors associated with mortality was calculated and odds ratio (OR), 95% confidence interval (CI), and *p* value were reported. The prediction model was established according to the result of logistic regression model with forward selection of covariates and formulated as coefficient of each risk factor Receiver operating characteristic curve (ROC) analysis was used with optimal cut-off generated from the largest sensitivity and specificity summation for the prediction model of mortality after operation and with discriminations of area under ROC (AUROC) and its 95% CI in clinical stratification. The accuracy of prediction model built from the preliminary group was re-evaluated in the validation group.

All statistical analyses were performed with SAS 9.2 (SAS Institute, Cary, NC). Two-tailed *p* values less than 0.05 were regarded as statistically significant.

## Results

After excluding subjects who did not meet study criteria, a total of 91,016 patients received GA were included into the preliminary group for initial model training, and 590,763 patients were selected as the validation group for further analysis (Figure 1). The baseline characteristics of the preliminary group was presented in Table 1.

Table 1  
Baseline characteristic of preliminary group

		<b>All (n=91016)</b>	<b>Major organ transplantation (n=136)</b>	<b>CV (n=2060)</b>	<b>Neurosurgery (n=4851)</b>	<b>Others (n=83969)</b>
		(%)	(%)	(%)	(%)	(%)
Mean age, years (SD)		52.0 (17.2)	49.6 (9.6)	62.8 (14.6)	56.9 (17.7)	51.5 (17.1)
Age	<65	67187 (73.8)	134 (98.5)	1032 (50.1)	3033 (62.5)	62988 (75.0)
	65-74	12977 (14.3)	2 (1.5)	534 (25.9)	884 (18.2)	11557 (13.8)
	75+	10852 (11.9)	0	494 (24.0)	934 (19.3)	9424 (11.2)
Gender	Female	49359 (54.2)	44 (32.4)	697 (33.8)	1829 (37.7)	46789 (55.7)
	Male	41657 (45.8)	92 (67.6)	1363 (66.2)	3022 (62.3)	37180 (44.3)
Surgery time	Within 2 hours	44155 (48.5)	0	142 (6.9)	1535 (31.6)	42478 (50.6)
	2-2.5 hr	12014 (13.2)	0	49 (2.4)	601 (12.4)	11364 (13.5)
	2.5-3 hr	9301 (10.2)	3 (2.2)	53 (2.6)	512 (10.6)	8733 (10.4)
	3-3.5 hr	6268 (6.9)	10 (7.4)	65 (3.2)	382 (7.9)	5811 (6.9)
	3.5-4 hr	4869 (5.3)	10 (7.4)	99 (4.8)	354 (7.3)	4406 (5.2)
	Over 4hr	14409 (15.8)	113 (83.1)	1652 (80.2)	1467 (30.2)	11177 (13.3)
Hospital level	center	44702 (49.1)	124 (91.2)	1413 (68.6)	2577 (53.1)	40588 (48.3)
	others	46314 (50.9)	12 (8.8)	647 (31.4)	2274 (46.9)	43381 (51.7)
Comorbidity:						
	Congestive heart failure	3769 (4.1)	33 (24.3)	637 (30.9)	242 (5.0)	2857 (3.4)
	Cardiac arrhythmias	4650 (5.1)	13 (9.6)	440 (21.4)	300 (6.2)	3897 (4.6)
	Valvular disease	2552 (2.8)	10 (7.4)	489 (23.7)	124 (2.6)	1929 (2.3)
	Pulmonary circulation disorders	217 (0.2)	6 (4.4)	43 (2.1)	11 (0.2)	157 (0.2)
	Peripheral vascular disorders	1871 (2.1)	2 (1.5)	250 (12.1)	125 (2.6)	1494 (1.8)
	Hypertension	22440 (24.7)	49 (36.0)	1096 (53.2)	1556 (32.1)	19739 (23.5)
	Paralysis	958 (1.1)	0	31 (1.5)	122 (2.5)	805 (1.0)
	Other neurological disorders	2106 (2.3)	5 (3.7)	52 (2.5)	372 (7.7)	1677 (2.0)
	Chronic pulmonary disease	10502 (11.5)	18 (13.2)	470 (22.8)	591 (12.2)	9423(11.2)
	Diabetes	11717 (12.9)	30 (22.1)	629 (30.5)	699 (14.4)	10359 (12.3)
	Hypothyroidism	2123 (2.3)	0	26 (1.3)	61 (1.3)	2036 (2.4)
	Renal failure	3487 (3.8)	60 (44.1)	231 (11.2)	201 (4.1)	2995 (3.6)
	Liver disease	4175 (4.6)	47 (34.6)	84 (4.1)	194 (4.0)	3850 (4.6)
	Peptic ulcer disease excluding bleeding	12071 (13.3)	31 (22.8)	322 (15.6)	509 (10.5)	11209 (13.3)
	AIDS/HIV	41 (0.0)	0	0	6 (0.1)	35 (0.0)
	Lymphoma	221 (0.2)	0	6 (0.3)	24 (0.5)	191 (0.2)
	Metastatic cancer	908 (1.0)	0	24 (1.2)	85 (1.8)	799 (1.0)

Cardiovascular (CV), angiotensin-converting-enzyme inhibitor (ACE inhibitors), standard deviation (SD)

	All (n=91016)	Major organ transplantation (n=136)	CV (n=2060)	Neurosurgery (n=4851)	Others (n=83969)
Solid tumor without metastasis	10389 (11.4)	26 (19.1)	151 (7.3)	350 (7.2)	9862 (11.7)
Rheumatoid arthritis/ collagen vascular diseases	3895 (4.3)	5 (3.7)	91 (4.4)	187 (3.9)	3612 (4.3)
Coagulopathy	406 (0.4)	15 (11.0)	21 (1.0)	27 (0.6)	343 (0.4)
Obesity	505 (0.6)	0	7 (0.3)	21 (0.4)	477 (0.6)
Weight loss	699 (0.8)	0	18 (0.9)	44 (0.9)	637 (0.8)
Fluid and electrolyte disorders	2135 (2.3)	9 (6.6)	98 (4.8)	160 (3.3)	1868 (2.2)
Blood loss anemia	877 (1.0)	0	14 (0.7)	16 (0.3)	847 (1.0)
Deficiency anemia	2074 (2.3)	8 (5.9)	42 (2.0)	56 (1.2)	1968 (2.3)
Alcohol abuse	1306 (1.4)	11 (8.1)	18 (0.9)	136 (2.8)	1141 (1.4)
Drug abuse	197 (0.2)	0	6 (0.3)	14 (0.3)	177 (0.2)
Psychoses	949 (1.0)	0	16 (0.8)	92 (1.9)	841 (1.0)
Depression	4021 (4.4)	5 (3.7)	66 (3.2)	297 (6.1)	3653 (4.4)
Medication use:					
Biguanides	7679 (8.4)	16 (11.8)	407 (19.8)	468 (9.6)	6788 (8.1)
Sulfonylurea	7968 (8.8)	19 (14.0)	453 (22.0)	485 (10.0)	7011 (8.3)
Alpha-glucosidase inhibitors	1855 (2.0)	6 (4.4)	132 (6.4)	108 (2.2)	1609 (1.9)
Thiazolidinediones	1885 (2.1)	8 (5.9)	110 (5.3)	107 (2.2)	1660 (2.0)
Glinides	1414 (1.6)	7 (5.1)	105 (5.1)	95 (2.0)	1207 (1.4)
Any oral anti-diabetic agents	10510 (11.5)	28 (20.6)	564 (27.4)	630 (13.0)	9288 (11.1)
Fast-acting insulins	2938 (3.2)	24 (17.6)	245 (11.9)	189 (3.9)	2480 (3.0)
ACE inhibitors	7989 (8.8)	20 (14.7)	710 (34.5)	567 (11.7)	6692 (8.0)
Angiotensin receptor blockers	8027 (8.8)	40 (29.4)	647 (31.4)	533 (11.0)	6807 (8.1)
Alpha-blockers	3243 (3.6)	12 (8.8)	184 (8.9)	249 (5.1)	2798 (3.3)
Beta-blockers	18087 (19.9)	68 (50.0)	1122 (54.5)	1166 (24.0)	15731 (18.7)
Calcium channel blockers	20624 (22.7)	50 (36.8)	1124 (54.6)	1465 (30.2)	17985 (21.4)
Diuretics	13659 (15.0)	81 (59.6)	1010 (49.0)	868 (17.9)	11700 (13.9)
Other anti-hypertensive agents	721 (0.8)	14 (10.3)	81 (3.9)	41 (0.8)	585 (0.7)
Statins	7929 (8.7)	21 (15.4)	637 (30.9)	421 (8.7)	6850 (8.2)
Fibrates	2879 (3.2)	2 (1.5)	156 (7.6)	176 (3.6)	2545 (3.0)
Digitalis glycoside	1497 (1.6)	20 (14.7)	330 (16.0)	92 (1.9)	1055 (1.3)
Anti-arrhythmics class I and III	1902 (2.1)	18 (13.2)	227 (11.0)	145 (3.0)	1512 (1.8)
Mean no. of different prescription drugs (SD)	23.3 (17.2)	34.0 (19.0)	32.6 (20.8)	22.7 (18.2)	23.1 (17.0)
Mean no. of cardiovascular-related medications (SD)	1.6 (2.7)	4.9 (4.2)	6.0 (4.6)	2.0 (2.8)	1.5 (2.5)
Mean no. of outpatient visit (SD)	25.9 (22.4)	37.4 (19.8)	32.4 (25.7)	24.9 (24.1)	25.8 (22.2)
Mean no. of emergency room visit (SD)	0.7 (2.1)	2.1 (5.8)	1.3 (2.1)	0.9 (2.7)	0.7 (2.0)
Mean no. of hospitalization (SD)	0.3 (0.9)	1.6 (1.7)	0.9 (1.3)	0.4 (1.0)	0.3 (0.9)
Mean days of hospitalization (SD)	2.5 (11.3)	15.4 (23.8)	6.1 (13.0)	3.5 (13.1)	2.4 (11.1)

Cardiovascular (CV), angiotensin-converting-enzyme inhibitor (ACE inhibitors), standard deviation (SD)

		All (n=91016)	Major organ transplantation (n=136)	CV (n=2060)	Neurosurgery (n=4851)	Others (n=83969)
Mean follow-up days (SD)		29.8 (1.9)	29.4 (2.8)	29.0 (4.7)	28.6 (5.4)	29.9 (1.3)
Mean person-year follow-up (SD)		0.0795 (0.0051)	0.0785 (0.0074)	0.0773 (0.0125)	0.0764 (0.0143)	0.0798 (0.0035)
Sum of person-year follow-up		7239.48	10.68	159.17	370.8	6698.83
<b>Resource utilization of index hospitalization</b>						
days of hospitalization	Mean (SD)	10.7 (31.6)	41.2 (41.4)	24.9 (37.7)	28.2 (62.4)	9.3 (28.2)
	Median (Q1-Q3)	5 (3-10)	29 (15-51)	17 (11-27)	14 (7-31)	5 (3-9)
medical cost	Mean (SD)	108187 (207469.9)	1214102 (938757.1)	484404 (384955.0)	271852 (374019.7)	87711 (161571.5)
	Median (Q1-Q3)	54891 (35950-102692)	978193 (366156-1841393)	428177 (323254-495202)	171012 (80513-335195)	53636 (35027-88189)
<b>Mortality Rate</b>						
No. of death within 30 days (%)		962 (1.1)	6 (4.4)	125 (6.1)	336 (6.9)	495 (0.6)
30 days mortality rate, per 100 py	(95% CI)	12.94 (12.14-13.78)	54.71 (24.58-121.78)	76.48 (64.18-91.13)	88.25 (79.3-98.21)	7.19 (6.59-7.86)
No. of death during admission (%)		1388 (1.5)	11 (8.1)	155 (7.5)	384 (7.9)	838 (1.0)
Cardiovascular (CV), angiotensin-converting-enzyme inhibitor (ACE inhibitors), standard deviation (SD)						

Not surprisingly, antihypertensive agents were most frequently used in high-risk surgical patients, including angiotensin-converting-enzyme inhibitor, angiotensin receptor blockers, alpha-blockers, beta-blockers, calcium channel blockers, diuretics, and other anti-hypertensive agents in both groups.

Patients who underwent CV and major neurosurgical procedures had a higher crude incidence rate of death and mortality rate within 30 days (6.1 and 6.9%, separately). The medical cost was also associated with the duration of hospitalization after operation, and the patients who received major organ transplantation got the most medical resource utilization (Table 1).

In the crude analysis of factors associated with mortality in preliminary group, the major surgeries such as major organ transplantation, CV surgery, and neurosurgery, were associated with a significantly higher risk for mortality (Table 2). Among these, neurosurgery was associated with the highest risk of post-operation mortality with adjusted OR ranging from 6.94 to 10.37 (Table 2). After the stratified analysis, age also showed significant influence for determining post-operation mortality, especially in the elderly groups (Table 2).

Table 2

Factors associated with mortality in preliminary group by using logistic regression model with forward selection of covariates ( $p > 0.10$  for exclusion,  $p < 0.05$  for inclusion)

In-hospital mortality				30-days mortality			
Covariates selected	Adjusted Odds Ratio	95% CI	p-value	Covariates selected	Adjusted Odds Ratio	95% CI	p-value
Surgical types			<.0001	Surgical types			<.0001
Others	Reference			Others	Reference		
CV	4.25	3.49-5.17		CV	6.37	5.12-7.92	
Neurosurgery	6.94	6.08-7.91		Neurosurgery	10.37	8.94-12.03	
Organ transplant	5.20	2.67-10.13		Organ transplant	4.40	1.85-10.51	
Age			<.0001	Age			<.0001
<65 years	Reference			<65 years	Reference		
65-74 years	2.13	1.82-2.49		65-74 years	1.96	1.63-2.36	
>=75 years	4.49	3.90-5.16		>=75 years	3.90	3.30-4.60	
Female vs. Male	0.65	0.58-0.73	<.0001	Female vs. Male	0.71	0.62-0.82	<.0001
Hospital level (others vs. medical center)	1.13	1.01-1.27	0.0307	Hospital level (others vs. medical center)	1.38	1.20-1.57	<.0001
Peripheral vascular disorders	0.71	0.53-0.94	0.0186	Other neurological disorders	0.66	0.47-0.91	0.0102
Renal failure	1.43	1.19-1.71	0.0001	Hypertension	0.77	0.64-0.93	0.0062
Liver disease	1.25	1.01-1.54	0.0367	Renal failure	1.59	1.27-2.00	<.0001
Weight loss	1.77	1.23-2.55	0.0023	Liver disease	1.44	1.12-1.84	0.0043
Fluid and electrolyte disorders	1.42	1.15-1.75	0.0010	Coagulopathy	1.99	1.20-3.28	0.0074
Blood loss anemia	1.81	1.21-2.69	0.0036	Alcohol abuse	2.43	1.74-3.41	<.0001
Alcohol abuse	2.09	1.55-2.82	<.0001	Psychoses	1.89	1.22-2.93	0.0044
Psychoses	1.62	1.09-2.39	0.0160	Directics	1.44	1.22-1.69	<.0001
Fast-acting insulins	1.42	1.17-1.71	0.0003	Antiarrhythmics class I and III	1.45	1.11-1.89	0.0060
Diuretics	1.53	1.34-1.75	<.0001	no. of emergency room visit	1.02	1.00-1.03	0.0189
Statins	0.80	0.67-0.96	0.0133	no. of hospitalization	1.06	1.01-1.12	0.0217
Anti-arrhythmics class I and III	1.51	1.22-1.86	0.0002	no. of outpatient visit	0.99	0.99-1.00	0.0005
no. of outpatient visit	0.99	0.99-1.00	<0.0001				
no. of emergency room visit	1.01	1.00-1.03	0.0480				
no. of hospitalization	1.10	1.05-1.15	<.0001				
Cardiovascular (CV), 95% confidence interval (95% CI)							

For subgroup analysis, variables of the underlying comorbidities were almost positively related to post-operation mortality (Table 2). Unexpectedly, hypertension was not associated with increasing risk of post-operation mortality (adjusted OR: 0.77, CI: 0.64- 0.93) as other comorbidities were (Table 2).

Nevertheless, prescription with statins usage seemed to be protective for the patient accepted GA (adjusted OR: 0.8, CI: 0.67- 0.96, Table 2).

The results of factors associated with post-operation mortality for different surgery types in preliminary group were showed in Table 3 (in-hospital mortality and 30-days mortality). As different surgical types were considered, age was still a significantly determining factor associated with post-operation mortality (Table 3).

Table 3  
Factors associated with in-hospital and 30-day mortality for different surgery types in preliminary group

CV	Neurosurgery			Transplantation			Other				
<b>In-hospital mortality</b>											
Covariates selected	AOR	95% CI	Covariates selected	AOR	95% CI	Covariates selected	AOR	95% CI	Covariates selected	AOR	95% CI
Area under ROC curves	0.6652		Area under ROC curves	0.6467		Area under ROC curves	0.8418		Area under ROC curves	0.8677	
Age			Age			Others vs. medical center	8.91	1.41-56.17	Age		
<65 y/o	ref.		<65 y/o	ref.		Alpha-glucosidase inhibitors	9.45	0.68-130.6	<65 y/o	ref.	
65-74 y/o	1.49	0.97-2.28	65-74 y/o	1.22	0.92-1.62	Glinides	14.15	1.46-136.8	65-74 y/o	2.99	2.42-3.69
>=75 y/o	2.10	1.41-3.13	>=75 y/o	1.62	1.25-2.10	Fast-acting insulins	4.31	0.93-19.97	>=75 y/o	7.40	6.15-8.90
Valvular disease	0.45	0.28-0.72	Others vs. medical center	1.50	1.21-1.86	no. of outpatient visit	0.92	0.87-0.98	Female vs. Male	0.52	0.45-0.61
Hypertension	0.63	0.44-0.90	Cardiac arrhythmias	1.51	1.05-2.17				Valvular disease	1.43	1.07-1.97
Lymphoma	5.51	0.95-32.15	Diabetes, uncomplicated	1.61	1.23-2.11				Peripheral vascular disorders	0.45	0.29-0.70
Beta-blockers	0.65	0.45-0.93	Renal failure	2.27	1.54-3.34				Hypertension	0.80	0.66-0.96
Statins	0.58	0.38-0.89	AIDS/HIV	5.62	0.98-32.30				Renal failure	1.27	1.02-1.59
no. of emergency room visit	1.07	1.00-1.16	Lymphoma	3.05	1.09-8.54				Solid tumor without metastasis	0.74	0.60-0.92
no. of hospitalization	1.14	1.01-1.30	Coagulopathy	3.89	1.65-9.17				Weight loss	1.91	1.27-2.88
			Other neurological disorders	0.33	0.18-0.60				Fluid and electrolyte disorders	1.40	1.10-1.79
									Blood loss anemia	1.72	1.11-2.68
									Alcohol abuse	2.79	1.96-3.97
									Psychoses	2.38	1.52-3.72
									Thiazolidinediones	0.63	0.47-0.96
									Fast-acting insulins	1.38	1.10-1.74
									Directics	1.85	1.56-2.19
									Antiarrhythmics class I and III	1.68	1.29-2.18
									no. of outpatient visit	0.99	0.99-1.00
									no. of emergency room visit	1.02	1.01-1.03
									no. of hospitalization	1.10	1.09-1.16
<b>30-day mortality</b>											
Covariates selected	AOR	95% CI	Covariates selected	AOR	95% CI	Covariates selected	AOR	95% CI	Covariates selected	AOR	95% CI
Cardiovascular (CV), Adjusted Odds Ratio (AOR), 95% confidence interval (95% CI), Receiver operating characteristic curve (ROC)											

CV	Neurosurgery					Transplantation				Other		
Age			Age			Pulmonary circulation disorders	>999.999	-		Age		
<65 y/o	ref.		<65 y/o	ref.		Solid tumor without metastasis	>999.999	-		<65 y/o	ref.	
65-74 y/o	1.15	0.70-1.88	65-74 y/o	1.18	0.87-1.59	no. of outpatient visit	0.15	<0.0001-141.07		65-74 y/o	3.18	2.44-4.14
>=75 y/o	2.07	1.34-3.18	>=75 y/o	1.53	1.16-2.01	Hypertension, uncomplicated	>999.999	-		>=75 y/o	7.33	5.78-9.29
Valvular disease	0.39	0.22-0.69	Others vs. medical center	1.81	1.44-2.27	Antiarrhythmics class I and III	0.004	-		Female vs. Male	0.57	0.47-0.68
Hypertension	0.54	0.36-0.81	Cardiac arrhythmias	1.64	1.12-2.39					Others vs. medical center	1.23	1.02-1.48
Lymphoma	8.89	1.49-52.96	Renal failure	2.32	1.55-3.50					Valvular disease	1.75	1.23-2.50
Psychoses	4.09	1.09-15.39	Coagulopathy	4.21	1.72-10.27					Peripheral vascular disorders	0.37	0.19-0.70
Beta-blockers	0.56	0.38-0.83	Other neurological disorders	0.37	0.20-0.69					Hypertension	0.65	0.50-0.83
no. of emergency room visit	1.09	1.01-1.17								Renal failure	1.44	1.08-1.92
										Liver disease	1.38	1.01-1.87
										Solid tumor without metastasis	0.76	0.57-1.00
										Alcohol abuse	3.85	2.59-5.80
										Psychoses	2.82	1.69-4.71
										Directics	1.78	1.44-2.20
										Antiarrhythmics class I and III	1.46	1.02-2.08
										no. of outpatient visit	0.99	0.99-1.00
										no. of emergency room visit	1.02	1.00-1.03
										no. of hospitalization	1.09	1.02-1.15

Cardiovascular (CV), Adjusted Odds Ratio (AOR), 95% confidence interval (95% CI), Receiver operating characteristic curve (ROC)

For patients accepting CV surgery, the comorbidity of "valvular heart disease", or "hypertension" was not associated with increasing risk of post-operation mortality (Table 3). Medication with beta-blockers or statins usage seemed to be protective for the patients undergoing CV operation (Table 3). For the neurosurgery, age and underlying comorbidities were important covariates for the post-operation mortality (Table 3). As major organ transplantation was considered, the hospital level and the underlying comorbidities might determine the survival rate of the patients after operation. Unsurprisingly, patients accepted organ transplantation at the medical center got better outcomes (Table 3).

For the less risk surgeries, increasing age was associated with a significantly higher risk for post-operation mortality. Interesting, hypertension and prescription of thiazolidinediones (TZD) for diabetes mellitus (DM) were with decreasing post-operation mortality (Table 3) in these less risk surgeries. We also observed "valvular heart disease" was associated with increasing post-operation mortality among less risk surgeries, and that phenomenon was converse among the category of CV surgery (Table 3).

The prediction model was established according to the result of logistic regression model with forward selection of covariates and formulated as coefficient of each risk factor as e-Table 5 and e-Table 6 in the supplement showed. By applying individual's parameters into the formula, it can be used to estimate the probability of 30-day mortality and in-hospital mortality of each patient.

The ROC analysis of this prediction model was built in preliminary group initially. (Figure 2A and 2B) The optimal AUROC generated from the largest sensitivity and specificity summation for the prediction model of mortality after operation under GA was 0.8746 for predicating in-hospital mortality (Figure 2A) and 0.8698 for 30-days mortality (Figure 2B). After the prediction model was built from the preliminary group, further evaluating of the accuracy was conducted in the validation group. The prediction model based on the preliminary group also performed well in the validation group for post-operation mortality. (AUROC=0.8753 for in-hospital mortality; AUROC= 0.8767 for 30-days mortality) (Figure 2C and 2D). Validation of this prediction model demonstrated a high level of sensitivity and reliability.

## Discussion

To our knowledge, this is the first and largest nationwide study that formally integrates the individual patient's clinical information (e.g., age, comorbid disease, and medication) to estimate the postoperative mortality. We subdivided surgery into high risk surgery (organ transplantation, CV, and neurosurgery) and non-high risk surgery (others) to explore the different risk factors of 30-day and in-hospital mortality in each group. The most important factors that attributed to post-operative mortality are the selected surgery types. Some factors could increase or lower the risk of mortality in non-high risk surgery. Our prediction model built from a smaller set of study population turned out to remain high reliability when applied to the whole population.

Our results showed that age was an important determinant associated with post-operation mortality among different surgical types, also multidimensional score of elderly patients which could possibly improve the prediction was not present in our current database, perioperative prescription could reduce risks of operation. Our data presented the potentially protective effects of anti-lipid, hypoglycemic, and anti-hypertensive agents were encouraging in geriatric preoperative group. It should be part of the patient preoperative preparation as a major contributory factor to the primary causes of perioperative mortality. [9]

Hypertension was one of the most common comorbid diseases among the patients who underwent major surgery. However, hypertension was not independently associated with an increased risk of post-operation mortality. As in the previous studies, hypertension was highly prevalent in patients presenting for surgery but its impact on surgical outcome was still under debating. [10] In our study, antihypertensive agents such as beta-blockers and calcium channel blockers were the most commonly prescribed among all of the patients, especially for those in the high-risk groups. On the other hand, valvular heart disease was a major part of cardiovascular surgery. Its presence remained an increased risk for post-operation mortality when the patients underwent less risky surgeries.

Risk factors for the patients undergoing operation with GA are modifiable or non-modifiable. Regular medication usage might be important to reduce risks of adverse events after operation with GA. In our prediction model, the use of statins, TZD, and beta-blockers for patients was all related to less operative risk and better operation outcomes, indicating that an adequate control of cardiovascular risk factors [11] could decrease overall mortality. [12, 13] However, this is the first study which included medication as a parameter to predict post-anesthetic mortality. The potentially protective effects of anti-lipid, hypoglycemic, and anti-hypertensive agents were encouraging. Further survey with more complete dataset should be warranted.

The types of surgery have determined the risk of post-anesthetic mortality. The major surgeries, such as those involving heart, major vessels, brain, and transplantation, were intrinsically associated with a significantly higher risk for mortality. Among these, neurosurgery was associated with the highest risk of post-operation mortality. Besides the surgical types, the prediction model we developed also included a variety of personalized information such as age, comorbidities, medications, hospital level, and recent medical resource utilization. We might incorporate this tool into an on-site information system, with which when a new patient is to be admitted to the hospital to receive surgery under GA, the individual profile can be acquired immediately. According to the formula we established (see Appendix), individual's risk of in-hospital and 30-day mortality after general anesthesia can be estimated based on different type of surgery. Clinicians might be able to use this model as a reference to explain the risk of post-anesthetic mortality to patients and their family.

## Strengths

This is a nationwide, large-scale study which extract data from National Taiwan Insurance Database which enrolled more than 68,000 surgical cases with GA. This database is pioneer and unique in the Asian population. The prediction model included a variety of personalized information in addition to surgical types per se. In addition, the use of both a training set to develop a model and a separated validation set has ensured that the model is not only accurate but also stable. The multidimensional and comprehensive prediction model can be applied easily in a real-time clinical setting.

## Limitations

There are several limitations in our study. First, the study used a claims database in which some crucial information, such as anthropometric data, blood pressure measuring, laboratory results, is lacking. Using some surrogate variables to develop a prediction model could achieve a differential capacity as high as 88%. But it is unlikely to get even higher with current data. Second, the database lacks some information to determine the status class in the ASA classification. We were not able to examine the consistency between our prediction model and ASA classification. Third, the patients were exclusively the people in Taiwan. The generalizability to other people remains uncertain.

## Conclusions

The results of this study have not only identified the risk factors associated with different types of surgeries under general anesthesia, but also explored protective effect on adequate control of chronic disease. We established a clinically applicable prediction model from one population, and further proved its reliability and stability from the other. It is expected that applying this prediction model into clinical practice could improve surgical risk stratification and further improve patient outcomes.

## List Of Abbreviations

ASA-PS, American society of Anesthesiologists Physical Status

CV, cardiovascular

GA, general anesthesia

ICD-9 CM, international classification of diseases, ninth revision, clinical modification

NHI, national health insurance

OD, odds ratio

AUROC, area under receiver operating characteristic curve

TZD, thiazolidinediones

DM, diabetes mellitus

## Declarations

### Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the National Taiwan University Hospital (Trial Registration 201411078RINC). Informed consent was waived by the National Taiwan University Hospital Research Ethics Committee due to the retrospective and anonymous nature of the claims data. All procedures performed in this study involving human participants were in accordance with the ethical standards of the Institutional Review Board of the National Taiwan University Hospital and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

### Consent for publication

There are no conflicts of interest to report regarding this study.

### Availability of data and materials

All data generated or analyzed during this study are included in this published article as its supplementary files.

### Competing interests

There are no conflicts of interest to report regarding this study.

### Funding

None

**Authors' contributions** (This statement must exactly match on Editorial submission system and in the manuscript)

F.F.T., and S.N.C. and C.L.C wrote the main manuscript text

J.W.L and L.P.L and J.J.H. collected data and data analysis

J.W.L prepared figures 1-2.

H.M.Y coordination

All authors reviewed the manuscript.

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## Figures

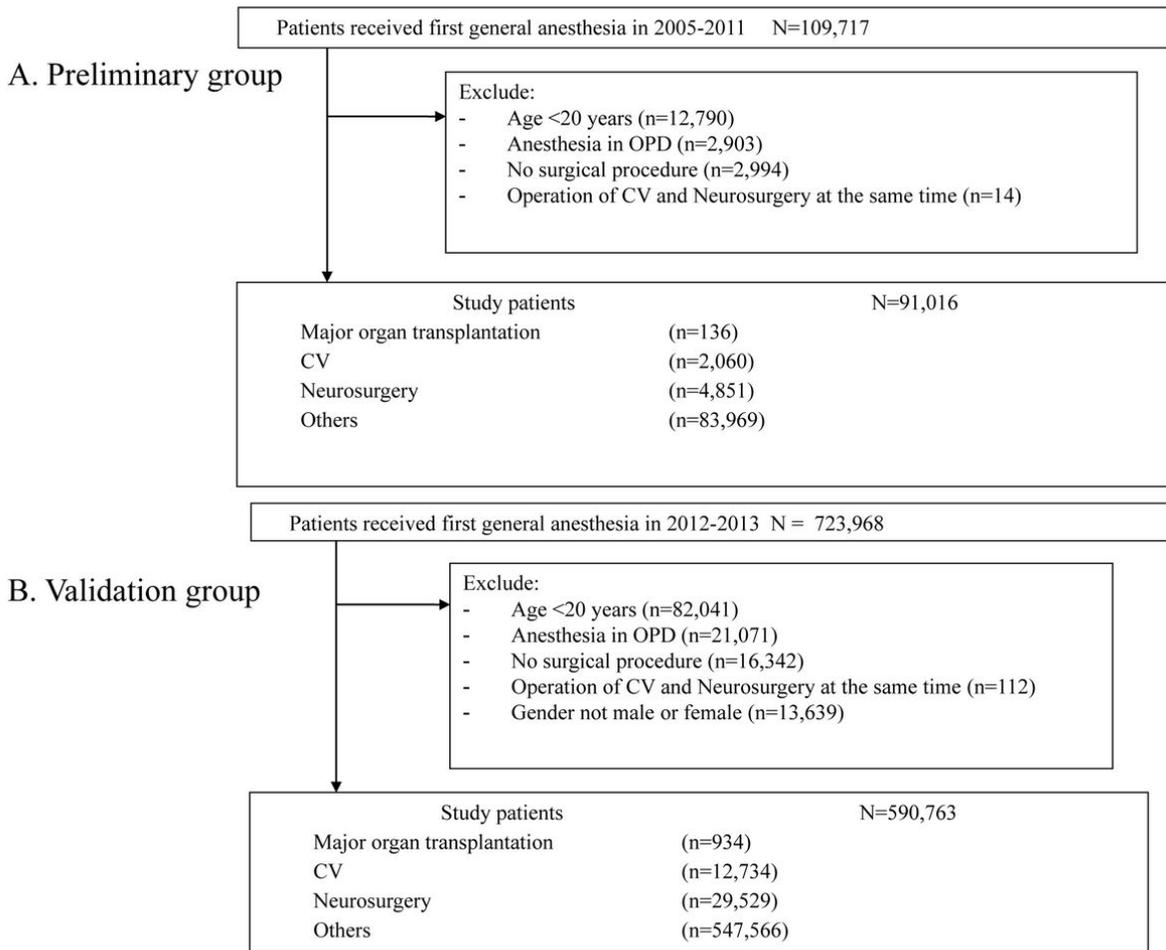
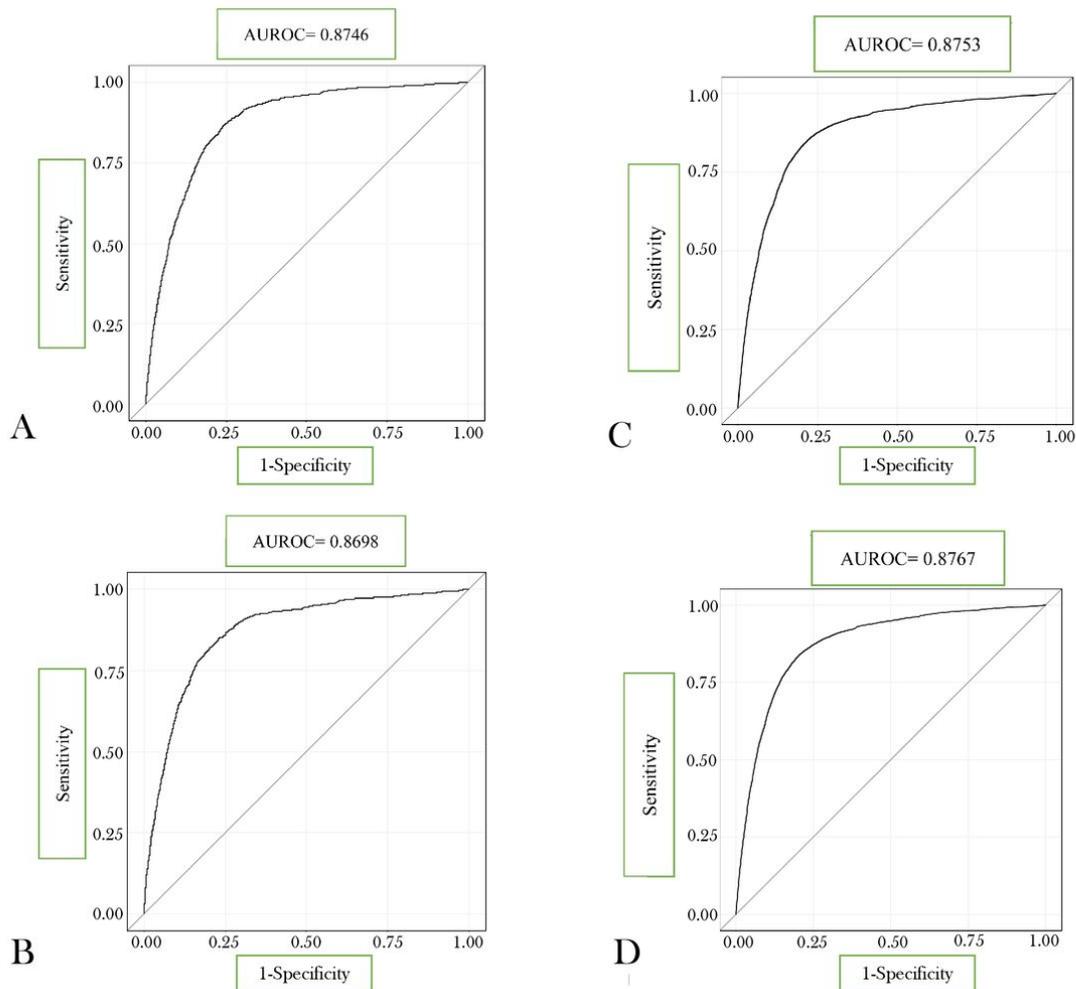


Figure 1

Study algorithm

Figure 1 Legend Preliminary (A) and validation (B) group study algorithm



**Figure 2**

**AUROC of prediction model**

Figure 2 Legend ROC curves of prediction model built for all patients in preliminary group (A) In-hospital mortality (B) 30-days mortality; in validation group (C) In-hospital mortality (D) 30-days mortality; Receiver operating characteristic curve (ROC), area under ROC (AUROC)

**Supplementary Files**

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