Prediction and Identification of Covariates of Intra-cerebral Hemorrhage

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Abstract: The authors investigate the effects of clinical covariates upon the outcome of Intra-cerebral Hemorrhage (ICH) patients by applying a discriminate model of logistic regression.

About 985 patients's data with ICH have been collected using the International classification of diseases; ninth revision codes are also included. Diagnostic codes (434 for stroke and 431 for ICH) were used to identify patients and confirmed by neuro-imaging of the patients using CT scan and MRI.

A univariate analysis of 88 covariates was undertaken and 46 of them reached statistical significance at an acceptable level of $p \leq 0.05$. The multivariable analysis exhibited a significant negative relationship between ICH and hypertension. The improvement among ICH patients having hypertension was found to be 0.5 with the p=0.001, ARR=0.5, 95% C.I. 0.3 – 0.8. The development among ICH patients using antihypertensive medicine was 1.3 with p = 0.021, ARR=1.3, 95% C.I. 1.0 – 1.6. Thus present study manifested that ICH has strong relationship with use of antihypertensive medicine. The rate of perfection in the patients physiological conditions using antihypertensive medicine at the time of discharge was 2.9 times acquiring p < 0.001, ARR=2.9, 95% C.I. 2.7 – 3.2 as compared to those who could not use antihypertensive medicine. The change in ARR from 1.3 to 2.9 times depict that the exercise of antihypertensive medicine and ICH outcome are positively associated. The fluctuations in ARR of hypertensive range of systolic blood pressure (SBP) also indicate that the blood pressure range and ICH outcome are negatively correlated. The neurological symptomoatology, indistinct speech and double vision are important factors of proposed models. Moreover, a clear decrease was found in mental status from normal to coma in most suitable model.

Surgery is an important part of recovery, and estimated that the improvement among the ICH patients, who were treated under surgical aspects, was 1.4 times with significant p-value in the best models. The complication of pneumonia during treatment of ICH subjects has highly significant showing negative correlation with the given outcome variable.

The current model has 89.3% area under the curve with sensitivity (82.6%), specificity (81.3%) and p-value (0.308). This indicates that the constructed model bestows the well performance of the ICH outcome and the model is considered as excellent.

Keywords: Intracerebral Hemorrhage, clinical covariates, multivariable analysis, logistic regression, Hosmer-Lemeshow test, discriminate model, sensitivity and specificity.

INTRODUCTION

Human since his arrival on the earth has continuously encountered different risk factors affecting almost every facet of his life. It is therefore mandatory to rightly estimate these factors to secure the resources of life. There are many ways to estimate these risk factors; however one most applicable way to handle these issues is to utilize the statistical tools. The one identified technique is the application of modeling on the given set of variables.

In the present study, multiple clinical variables were collected from a group of patients suffering from ICH[1]. ICH is a clinical condition / disorder that have important association with many common health risk factors, such as hypertension, diabetes mellitus etc. A systematic statistical analysis is required to find out actual clinical variables that affect adversely on clinical outcome of ICH.

During the literature search it was noted that many crucial risk factors such as hypertension, smoking, level of blood pressure etc., were involved in the

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[1]Rupture of blood vessel which causes Intracerebral Hemorrhage.

E-ISSN: 1929-6029/15

development of ICH (Qureshi *et al*., 2001 [12]; Fewel *et al*., 2003 [13]). These risk factors can be classified as most or relatively less important. There are several defined criteria present that identify various variables related to ICH. Different statistical analyses were applied to find out important risk factors that have different optimistic and pessimistic aspects (Daverat *et al*., 1991 [6]; Willmot *et al*., 2004 [7]; Woo *et al*., 2004 [10]). It is mandatory for the statistical method to exactly grasp most important and practical clinical variables, so that clinical research could focus on the key clinical variables that positively affect the outcomes of the treatment.

The data of present study is mainly qualitative type; that includes categorical outcome and mixed covariates. In the past multiple methods were used to analyze this type of data that include logistics, probit and log-linear approaches. During the statistical analysis of present data (ICH) categorical response variable was treated differently than the usual continuous response variables by using the logistic regression model.

The rate of occurrence of Intracerebral Hemorrhage (ICH) is 10-20 in one million populations. It is noted that people aged more than 55 years to be at the maximum risk (Siddiqui *et al*., 2013 [8]; Wasay *et al*., 2010 [9]; Woo *et al*., 2004 [10]). Intracerebral Hemorrhage is a major issue in third world countries and also in the USA and UK. Regrettably it is estimated that mortality of ICH is expected to become double by the year 2050. The unidentified reason is increase in aging population as well as changing in racial demographics (Park *et al*., 1998 [11]; Qureshi *et al*., 2001 [12]; Fewel *et al*., 2003 [13]).

Stroke is the third leading cause of death and the first leading cause of disability (Fewel *et al*., 2003 [13]; Woo *et al*., 2004 [10]). Spontaneous Intracerebral Hemorrhage accounts the 10 to 15% of all strokes (Takahashi *et al*., 2006 [14]). Approximately 50% of all deaths occur within the first 48 hours. The survival rate in Intracerebral Hemorrhage is only 38% in one year (Qureshi *et al*., 2001 [12]; Fewel *et al*., 2003 [13]; Nassisi, 2005 [15]).

MATERIALS AND METHODS

Materials

In this paper we have collected 985 patients data including both female and male with Intracerebral Hemorrhage (ICH) from one of the largest hospital of Karachi. Patients were identified through medical records at the hospital using the International classification of diseases, using ninth revision coding system. Diagnostic codes (434 for stroke and 431 for ICH) were utilized to identify patients of different sex. The diagnosis of ICH was confirmed by neuro-imaging in these patients.

Methods

In order to analyze this disease we first assessed the univariate correlation between the outcome variable with single covariate using Chi- square test and logistic regression analysis. All variables included in the tests with p-value less than 0.25 on given analysis were then diagnosed. A stepwise procedure was used to choose the variable with a value of $p<0.25$ as the followed the specific criteria to obtain the best multivariable model. We have constructed various models securing possible combinations of parameters that were significant accordingly.

The association between the various causal variables connected with each other biologically was also found. These variables such as age, hypertension, antihypertensive, SBP, mass effect, surgery, received oxygen and pneumonia, having significant p-values, were included odd ratios that could be changed but were not strongly associated with each other because of p-value > 0.05. After developing main effect model, a relationship was tried to seek out with the interactions that were biologically meaningful.

Hosmer-Lemeshow test statistics was used to evaluate the goodness of fit for logistic model. It is frequently used in risk prediction models; particularly during the assessment of human disease models. (Hosmer and Lemeshow, 1980 [16]; Lemeshow, 1982 [17]; Hosmer and Lemeshow, 1989 [18]; Cessie *et al*., 1991 [19]; Hosmer, 1997 [20]; Collett, 2003 [21]; Chuang *et al*., 2009 [22]).

The discrimination of the fitted model is determined by the measurement of the area under the receiver operating characteristic (ROC) curve and indicates the cutoff that can predict the best outcome. In current study sensitivity and specificity analyses are based on binary classification of actual outcome and predictive probabilities of the constructed models.

ANALYSIS AND RESULT

The results obtained from this analysis, manifests that p-value was found to be less than 0.25 as in the criteria of univariate model or otherwise thought to be biologically meaningful (Bendel and Afifi, 1977 [23]; Hosmer and Lemeshow, 1989 & 2000 [18]; Sauerbrei, 1999 [24]; Caberlotto and Hurd, 2001 [25]) also were entered into multivariable aspects using forward stepwise logistic approach, likelihood ratio test for the model selection. We also could have two continuous variables which were considered for age and length of stay. Analyzing the associations of the two variables with outcome, it has been found that the age seems to be insignificant. However of its nature as biologically important included in model.

In this examination of the disease, the following processes of including, deleting, refitting with different combinations of important variables and their biological interactions were obtained using multiple logistic methodology. One of the best fitted multiple logistic models is as follows:

Table 1: Multiple Logistic Regression Estimates of Covariates of Fitted Model, Showing Relative Risk (RR) and Adjusted Relative Risk (ARR) with 95% Confidence Interval and p-value for the Outcome Variable of ICH

Independent Factors Include in the Model	Field Name	RR(95% C.I.)	ARR(95% C.I.)	p-value
AGE	AGE	1.0(0.99.1.0)	1.0(0.99, 1.0)	0.06
Hypertension	htn	1.12(0.95, 1.27)	0.5(0.3, 0.8)	0.001
Coagulopathy	coag	0.5(0.3, 0.8)	0.5(0.2, 0.9)	0.022
Antihypertansive	mahtn	1.3(1.1, 1.4)	1.3(1.0, 1.6)	0.021
Slurred Speech	slusp	1.2(1, 1.3)	0.7(0.5, 1.0)	0.023
Double Vision	dbvis	0.95(0.6, 1.3)	0.4(0.2, 1.0)	0.04
Mental Status(Normal)				0.001
Sleepy	mssl1	0.9(0.7, 1.0)	1.0(0.9, 1.1)	
Confused	msco2	0.9(0.7, 1.0)	0.8(0.5, 1.0)	
Poorly Responsive	mspr3	0.7(0.3, 0.8)	1.0(0.7, 1.1)	
Unresponsive	msur4	0.5(0.3, 0.7)	0.7(0.5, 0.9)	
Coma	msco5	0.3(0.1, 0.3)	0.7(0.3, 0.9)	
Normal(90-140)				0.004
Mild.hypo.(< 90)	lsbp1	0.2(0.2, 0.4)	0.6(0.4, 0.9)	
Mild.htn.(141-160)	lsbp2	1(0.9, 1.1)	1.0(0.8, 1.2)	
Mod.htn.(161-200)	lsbp3	0.7(0.4, 0.9)	0.7(0.4, 1.0)	
Sev.htn.(> 200)	lsbp4	0.6(0.2, 1.0)	0.6(0.2, 1.3)	
Normal(Motor)	mtnor	1.2(1.05, 1.34)	1.1(0.8, 1.4)	0.417
Rt.monoparesis	mtrmp	1.6(0.9, 1.7)	1.6(0.8, 1.7)	0.064
Rt.basal Ganglia	lorbg	0.96(0.85, 1.1)	1.0(0.7, 1.1)	0.56
Putamen	loput	1.08(0.9, 1.2)	1.3(1.0, 1.5)	0.048
Pons	lopon	0.85(0.6, 1.1)	0.9(0.5, 1.3)	0.679
Cerebellum	locer	1.4(1.1, 1.6)	1.5(1.1, 1.7)	0.014
Frontal Lobe	lofrl	0.9(0.7, 1.1)	1.2(0.8, 1.5)	0.384
Parietal Lobe	lopal	1.04(0.9, 1.2)	1.1(0.8, 1.3)	0.324
Midline Shift	memidsh	0.6(0.4, 0.6)	0.9(0.5, 1.2)	0.421
Intraventricular Blood	meintb	0.7(0.5, 0.8)	1.2(0.9, 1.4)	0.183
Hydrocephalus	mehydr	0.5(0.4, 0.7)	0.9(0.5, 1.2)	0.402
Normal	menorm	0.6(0.5, 0.7)	0.7(0.5, 1.0)	0.023
White Blood Cells $4x10^3$ to 10^4 /cc, normal)				0.11
<$4x10^3$ /cc, leukopenia)	wbclp1	0.6(0.3, 1.0)	0.4(0.2, 1.0)	
>10^4 /cc, leukocytosis)	wbclc2	0.8(0.7, 0.9)	1.0(0.9, 1.2)	
IVABX	reivab	0.7(0.5, 0.8)	0.9(0.6, 1.2)	0.561
Oxygen	reoxyg	0.5(0.4, 0.6)	0.9(0.5, 1.1)	0.296
Surgery	surger	1.2(0.9, 1.3)	1.4(1.1, 1.6)	0.015
Pneumonia				0.001
Present	pnem1	0.5(0.3, 0.6)	0.6(0.3, 0.8)	
Don't know	pnem2	0.8(0.7, 0.9)	0.8(0.6, 1.0)	
Antihypertansive	dmant	2.9(2.7, 3.0)	2.9(2.7, 3.2)	< 0.001
ASA	dmasa	1.5(1.2, 1.6)	1.3(0.8, 1.6)	0.127

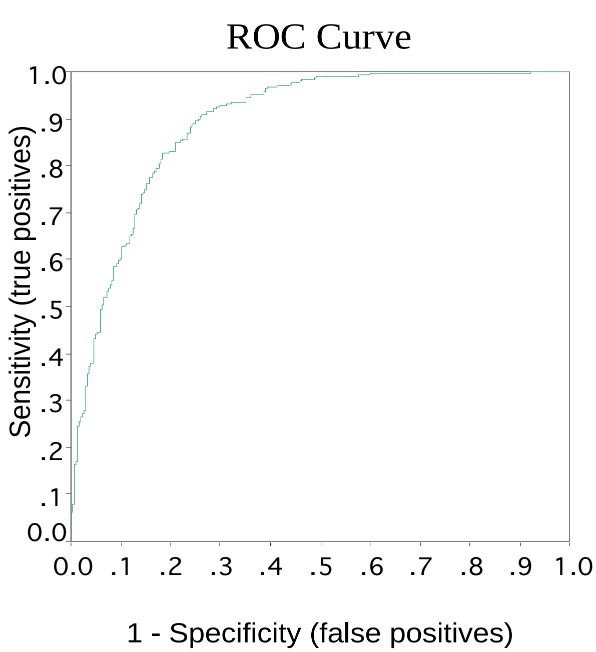
-2 log likelihood = 631.974.

g(x): 1.6-0.01(age)-1.1(htn) -1.3(coag)+ 0.6(mahtn)-0.6(slusp) -1.8(dbvis)+ 0.12(mssl1)- 0.65(msco2) -0.1(mspr3) -0.96(msur4) -1.12(msco5) – 1.1(lsbp1) + 0.05(lsbp2)-0.98(lsbp3)-1.19(lsbp4)+ 0.2(mtnor) + 2.04(mtrmp) -0.15(lorbg) +0.67(loput)- 0.23(lopon) +1.4(locer) + 0.42(lofrl) + 0.3(lopal)-0.3(memidsh) + 0.5(meintb)- 0.33(mehydr)- 1.0(menorm)-1.5(wbclp1) + 0.1(wbclc2)-0.2(reivab)-0.4(reoxyg)+ 1.1(surger)-1.3(pnem1)- 0.6(pnem2) +2.5(dmant) + 0.8(dmasa)

The parametric inequality of the model was determined by measuring the accuracy, sensitivity, specificity and area under the receiver operating characteristic (ROC) curve (Table **2**).

Table 2: Sensitivity and Specificity Analysis with 95% C.I. of Best Fitted Multiple Logistic Regression Model

Cutoff Value	0.566
Area under ROC curves (95% C.I.)	0.893 (0.870, 0.916)
Sensitivity (95% C.I.)	0.826 (0.787, 0.859)
Specificity (95% C.I)	0.813 (0.766, 0.852)
Positive Predictive Value (95% C.I.)	0.856 (0.819, 0.887)
Negative Predictive Value (95% C.I.)	0.776 (0.728, 0.817)



DISCUSSION

It has been revealed that the univariate approach inferred the observations with their results as in fact narrated that out of 88 covariates 46 were found to be significant according to p-value < 0.05.

Over all analyses illustrate that 84.8 % subjects were found to have hypertension as major risk factor explained by computations. This includes that hypertensive subjects 1.12 times as compared to non hypertensive patients indicating (95% C.I.: 0.95 – 1.27) for outcome. On the contrary to this the multivariable technique using multiple logistic regressions exhibited a significant negative relationship between ICH and hypertension. The upgrading among ICH patients having hypertension was 0.5 securing p = 0.001, ARR=0.5, 95% C.I. 0.3 – 0.8 as compared to non hypertensive's model parameters.

The present investigations as reported in this paper under the heading of multivariable analysis were in accordance to the results of a previous work carried out by Ariesen *et al*. 2003 [26]. Other studies were carried out by Brott *et al*., 1986 [27]; Juvela *et al*., 1995 [28]; Dandapani *et al*., 1995 [29]; Thrift *et al*., 1998 [30]; Broderick *et al*., 1999 [31]; Woo *et al*., 2004 [10]; Kim *et al*., 2005 [32]; Sturgeon *et al*., 2007 [33] and Chuang *et al*., 2009 [22] manifested a clear relationship between hypertension and ICH. The results of present study strictly judge the scientific evaluation of direct relation of hypertension with ICH.

In this paper data sets showed that 65.6 % subjects were using antihypertensive medicine. The current approach of this analysis exhibited a significant relationship between ICH and antihypertensive medicine conditionally if these data sets were utilized for other model parameters (Table **1**). The up-gradation of the parametric values in the ICH patients using antihypertensive medicine was 1.3 (p = 0.021, ARR=1.3, 95% C.I. 1.0 – 1.6) as compared to those unavailability of antihypertensive medicine. It has been reported by Thrift *et al*. (1998) [30], that the use of antihypertensive medicine decreased the risk of ICH due to hypertension. Thus results of our study displayed that ICH has strong relationship with use of antihypertensive medicine and it can be hypothesized that the use of antihypertensive medicine reduces the risk factor of possible occurrence of ICH due to hypertension. Our overall result of this investigation obviously presented that 84.8 % ICH patients have a risk factor of hypertension, 65.6 % ICH patients take antihypertensive medicine while 31.9 % do not take any medicine. So it has been concluded that improvement in ICH patients, the enhanced hypertension was recorded 0.5 times (ARR=0.5) as compared to undeveloped hypertension. Moreover, the time of discharge, 56 % subjects were found using antihypertensive medicine. Multivariable approach illustrated relationship between ICH and antihypertensive medicine. The improvement among ICH patients using antihypertensive medicine at the time of discharge as consequence from multiple logistic model was evaluated 2.9 times ($p < 0.001$, ARR=2.9, 95% C.I. 2.7 – 3.2). Thus the modulation in adjusted relative risk (ARR) as recorded from 1.3 to 2.9 times in antihypertensive medicine that depicts that the use of antihypertensive medicine and ICH outcome variable that are positively correlated.

As it has been observed that hypertension is a significant risk factor, the different group of level or range of blood pressure plays an important role in developing the subjects. It is important to inform that there are four groups of range of blood pressure in the present study. Two, at the time of admission after ICH, i.e., initial SBP and DBP and two, during the period of admission in hospital, i.e., lowest SBP and DBP.

The present data sets are analyzed for different range of blood pressure and it was pointed out that, in initial systolic blood pressure a large number of patients (78 %) belongs to the hypertensive blood pressure group of range (141-200 mm Hg) and 21 % patients have normal blood pressure group of range (90-140 mm Hg). Similarly in initial diastolic blood pressure group, 56 % belong to the hypertensive blood pressure group of range (>90 mm Hg) and 40.9 % patients have normal diastolic blood pressure group of range (60-90 mm Hg). In the same way during the hospitalization of patients with SBP it was found that 25 % belong to the hypertensive blood pressure group of range(141-200 mm Hg) and 64 % patients have normal blood pressure group of range (90-140 mm Hg). Similarly with reference to diastolic blood pressure during the hospitalization, 10 % of patients belong to the hypertensive blood pressure group of range (>90 mm Hg) and 62 % patients have normal diastolic blood pressure group of range (60-90 mm Hg).

The actual improvement among ICH patients belonging to hypertensive lowest systolic blood pressure group (141–160 mm Hg) was 1.0 times ($p = 0.004$, ARR=1.0, 95% C.I. 0.8 – 1.2), for the range of (161–200 mm Hg) was 0.7 times ($p = 0.004$, ARR=0.7, 95% C.I. 0.4 – 1.0) and for the range of (>200 mm Hg) was 0.6 times ($p = 0.004$, ARR=0.6, 95% C.I. 0.2 – 1.3) as compared to the normal range (90 – 140 mm Hg) of blood pressure as operated in other variables. Thus the change in adjusted relative risk (ARR) of hypertensive range of systolic blood pressure also indicates that the blood pressure range and ICH outcome variable are negatively associated.

Results of current data analysis as reported in multivariable case are in accordance to the results of previous studies. Leppala *et al*. (1999) [34] showed that the risk of ICH is increased with increasing systolic and diastolic blood pressure. Song *et al*. (2004) [35] supported the closer relationship between hemorrhagic stroke and blood pressure level. Kin *et al*. (2005) [32] indicated the risk ratio of blood pressure level and hemorrhage was associated. Hence it can be concluded that the risk of ICH is increased with increasing systolic blood pressure, as already hypothesized above in discussion of hypertension that ICH has strong relationship with hypertension.

The second and third highest frequencies of risk factor noted in this study were diabetes mellitus (24.3%) and hyperlipidemia (13.4%). As far as these two major risk factors are involved, results are quite interesting. Work done by researchers (Wong *et al*., 1999 [36]; Arboix *et al*., 2000 [37]; Ariesen *et al*., 2003 [26]; Passero *et al*., 2003 [38]; Rosand *et al*., 2004 [39]) illustrated that diabetes mellitus is not an independent risk factor for the development of ICH. However it increases mortality rate in subjects with ICH since hyperglycemia and also is reported to enhance edema and infarct size and with reduction in cerebral blood flow and cerebrovascular reserves. These manifest an indirect correlation of DM and hyperlipidemia with ICH. Sturgeon *et al*. 2007 [33] also showed that diabetes mellitus is not associated ($p > 0.05$) with ICH either in univariate and multivariate models. Arboix *et al*. (2000) [37] depicted that diabetes mellitus increases the mortality rate in subjects with ICH. The univariate and multivarible analysis of present data showed insignificant relationship between ICH and these risk factors. Diabetes mellitus and hyperlipidemia were not selected in the model as a candidate of best.

The expected assessment of coagulopathy that 3.7 % subjects to this risk factor The univariate analysis showed less clinical improvement (0.5 times) in coagulopathy subjects with ICH, as compared to non coagulopathic subjects (95% C.I.: 0.3 – 0.8) for out-come index. Multivariable analysis showed a negative significant relationship between ICH and coagulopathy when adjusted for other variables in the best fitted model. The improvement among ICH patients with coagulopathy was 0.5 times ($p = 0.02$, ARR=0.5, 95% C.I. 0.2 – 0.9) as compared to without coagulopathy when adjusted for other variables in the model.

Present Model has 89.3% area under the curve with sensitivity (82.6%), specificity (81.3%) and p-value

(0.308). This indicates that the model give the impression to fit quite well for predictive performance of the ICH outcome variable. The value of the area under the curve, sensitivity and specificity showed that the model is applicable.

CONCLUSION

The present model construction approach of multiple logistic regression suggested that ICH has strong relationship with hypertension and the use of antihypertensive medicine was found to play a pivotal role in reduction of the risk of ICH due to hypertension. They exhibited a clear up gradation as mentioned earlier (1.3 times) in patients as compared to those not using antihypertensive medicine. Likewise, the current analyses on this context clear improvement (2.9 times) among ICH patients who were using antihypertensive medicine at the time of discharge. Thus the change in adjusted relative risk from 1.3 to 2.9 times illustrate that the use of antihypertensive medicine and ICH outcome variable are positively associated. Similarly, the change in adjusted relative risk of different range of level of blood pressure showed that the blood pressure level and ICH outcome are significantly associated. Therefore, it can be tested that the risk factor of ICH is increased with the blood pressure. From other risk factors, coagulopathy was found as a negatively significant risk factor for ICH outcome in the fitted model.

Multiple logistic method revealed that neurological symptomatology, slurred speech and double vision are important factors of proposed models. Moreover, multivariable analysis discovered a clear decrease in mental status from normal to coma in applicable model. Putamen and cerebellum were positively significant with ICH outcome.

Current statistical evaluation found that the surgery is an important part of recovery of ICH patients as estimated that the improvement among the ICH patients are recorded and treated with surgery, was 1.4 times with significant p-value in best multiple logistic models. Multivariable analysis displayed that the complication of pneumonia during treatment of ICH subjects has highly significant negative correlation.

The above results are intended that the multivariable analyses using logistic regression and statistical diagnostic tools are better techniques of binary response outcomes and provide an easy interpretation and identification of the most valuable factors from the multitude factor disease data.

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Received on 15-11-2014 Accepted on 30-12-2014 Published on 27-01-2015

http://dx.doi.org/10.6000/1929-6029.2015.04.01.1