Journal of Biostatistics and Epidemiology

J Biostat Epidemiol. 2022;8(4): 369-375

Original Article

The Coagulopathy-Predicting Factors in Acute Trauma Patients Using the Generalized Estimation Equations Model

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ARTICLE INFO

Received 21.04.2022
Revised 17.05.2022
Accepted 17.10.2022
Published 15.12.2022

Key words:
Coagulopathy;
Trauma;
Generalized estimation equations

ABSTRACT

Introduction: Coagulation disorder is one of the major phenomena following the trauma which can deteriorate the condition of the patients. The aim of this study is to determine some factors predicting the incidence of coagulation disorder among acute trauma patients.
Methods: The generalized estimation equations were used to determine the predictors of blood coagulation disorders in a sample of 736 people over 16 years of age with acute trauma in Shahid Rajaei Hospital in Shiraz. The response variable was converted based on PT, PTT, INR, and fibrinogen level criteria as a two-state variable (with/without coagulation disorder). In the data analysis, the correlation of the coagulation disorder was considered in the first and second stages.
Results: The prevalence of coagulation disorders (mild, moderate and severe) was 19% in two stages and coagulation disorders (moderate and severe) was 7.5%. Motor vehicle accident was the most common cause of injury.The variables of blood sugar, diastolic blood pressure, pH, and sodium had a significant effect on coagulation disorders (mild, moderate, and severe). Moreover, blood phosphorus, age, and pupillary reflex had a significant effect on coagulation disorders (moderate and severe).
Conclusion: Predictors of coagulation disorders (mild-moderate-severe) include blood sugar, diastolic blood pressure, pH, and sodium. Moreover, blood phosphorus, age, and pupil reflex are predictors of moderate and severe coagulopathy. this model that taking into account the exchangeable correlation of first- and second-stage coagulopathy had a better fit than the model ignoring this correlation.

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Introduction

Trauma is one of the most important health challenges in the world. Post-trauma coagulation dis-order (coagulopathy) is an important phenomenon that can worsen the condition of patients. Co-agulopathy refers to a condition in which the blood losses its coagulation ability or produces too many clothes (over-coagulation).[1] Coagulation disorder is common among critical patients. This disorder includes increased blood clotting time, increased levels of fibrin products, and de-creased coagulation inhibitors.[2] prolonged coagulation time can be measured by prothrombin time (PT) and partial thromboplastin time (PTT).[3] The normal PT and PTT values are less than 19 s and less than 60 s, respectively.[4] An international normalized ratio (INR) is employed to standardize these methods whose normal level is less than 1.5. These tests are commonly known as prothrombin time (PT), partial thromboplastin time (PTT), and international normalization ratio (INR). Another important component of coagulation disorders is hypofibrinogenemia which oc-curs when fibrinogen levels fall below 100.[1]

Among patients admitted to the intensive care unit, blood clotting time of 14% to 28% of patients is longer.[5] Abnormal PT and PTT increase the risk of hemorrhage. On the other hand, the presence of abnormal PT or PTT in patients is an independent mortality predictor.[6]

Early prognosis, diagnosis, and management of coagulation disorders are essential. However, numerous studies have addressed the underlying reason for coagulopathy and its predictors.[3] However, there is no unified hypothesis on the main cause of coagulation disorder and its predicting variables in the patients. Therefore, the present study is aimed to model the predictors of coagulation disorders in acute trauma patients.

In previous studies, coagulation disorder and blood factor were only used in one step of the measurement. In this study, coagulation disorder information was measured at two times (upon admission and one hour later). Therefore, due to the high correlation of two-stage information, the data have a longitudinal structure and the generalized estimation equations method can be used to model the predictors of coagulation disorders.

Methods

In this cross-sectional study, information of 736 trauma patients who were referred to Shahid Rajaei Hospital in Shiraz from summer 2015 to winter 2018 was included. Data were extracted from the hospital database. In this study, the medical records of patients who were referred to the emergency department during this period (2 years in total) were also evaluated.

The inclusion criteria were being admitted as a trauma patient with a large impact at hemorrhagic shock condition[7] and the age over 16. the insufficient information in the patients' file was con-sidered as the exclusion criteria.

The demographic data, initial vital signs, laboratory results, and two-stage coagulation factors (with one-hour interval) were collected for all the included cases. The plasma fibrinogen level of all the patients with hemorrhagic shock was explored at the time of admission. If the fibrinogen level of the patient was 100 mg/ml, he/she received 1-4 g fibrinogen concentrate. This dosage was determined according to the severity of fibrinogen drop.

The response variables were defined based on PT, PIT, INR, and fibrinogen level in the form of the two-state variable (coagulopathy/non-

coagulopathy) for both coagulation conditions of mild-moderate-severe, and moderate-severe with the help of Table 1. The disorder in any of the indi-ces of Table 1 was recognized as a coagulation disorder.[8] For the data in which all 4 indices were not measured, the presence or absence of coagulation disorder was decided based on fi-brinogen level and INR.

Table 1. Index of coagulopathy in the acute trauma patients

Index	mild	Moderate	Severe
PT	13-26	27-52	>52
PTT	40-60	61-92	>=93
INR	1.2-2	2.1-4	>4
Fib	100-150	30-100	<30

Statistical analysis

The quantitative variables were reported as mean±SD; while the qualitative ones were examined as frequency and percentage. Single-variable analysis was performed by logit function and logistic regression. The correlation of the responses in the first and second stages was deter-mined by the intercultural correlation coefficient (ICC). For the double-variable case, binary re-sponse and the coagulation in the first and second stages were used simultaneously. Depending on the response correlation in the first and second steps of measurement, generalized estimation equations were used applying an exchangeable correlation matrix.[9] To investigate the effect of treatment interventions after the first stage on the coagulation state of the second stage, the re-gression model was employed. Wgee package was employed to fit the model and gee package in R software was employed for the cases where we faced missed data.[10]

Findings

Among the 736 studied cases, 615 (84.5%) were men and 121 cases (16.5%) were women. The age range of the cases was 16-90 with the mean age of 37.92±17.96. the mean sys-tolic blood pressure upon admission was 122.85±24.89 mm-Hg while their diastolic blood pres-sure was 77.18±17.3 mm-Hg. The mean Glasgow Coma Scale (GCS) upon admission was 11.26±4.09 and the mean saturate oxygen level was 90.97±7.21. The coagulation disorder fre-quency of the patients in the first and second stages are presented in Table 2.

Table 2. frequency of coagulopathy in the acute trauma patients

stage	Coagulopathy index	sex	N(%)
first	Mild, moderate and severe	female	21 (17.4)
		male	128 (21)
		total	149 (20)
second	Mild, moderate and severe	female	21 (13.2)
		male	115 (19)
		total	131 (18)
first	moderate and severe	female	10 (8.3)
		male	48 (7.6)
		total	57 (7.7)
second	moderate and severe	female	45 (7.3)
		male	9 (7.4)
		total	54 (7.3)

he ICC between the first and second stages was 0.26 and 0.28 for the patients with mild-moderate-severe and moderate-severe coagulation disorder, respectively. The blood factors were measured in both stages and listed in Tables 3 and 4 (both quantitative and qualitative ones).

The results of Table (3) showed that in the first

stage the variables of SBP and NA and in the second stage DBP, BUN, BS, P, and PO2 were significantly different between the two groups (coagulopathy and non- coagulopathy). In qualitative variables, no significant difference was seen between the two groups in any of the stages and for any variable.

Then, using the method of generalized estimation equations, each of the predictors of moderate-severe coagulation disorders that had a prevalence of 7.5% in two stages and mild-moderate-severe coagulopathy with a prevalence of 19% in the first stage and 18% in the second stage was examined, considering the correlation between the variables. The estimation of the parameter coefficients, standard error, statistical value, and probability value are summarized in Table 5.

To model the predicting factors of the coagulation disorder (moderate-severe and mild-moderate-severe) the significant variables in Table 5 were simultaneously included in

Table 3. univariate assessment of quantitative predicted variables for coagulopathy at the first and second stage in acute trauma patients

variable	first stage			Second stage		
	(mean±SD)	(mean±SD)	OR(95%CI)	(mean±SD)	(mean±SD)	OR(95%CI)
group	coagulopa-thy	No coagulopathy		coag-ulopathy	No coag-ulopathy	
Age	36.5±18.3	38.3±17.5	0.99 (0.98,1.01)	37.9±19.03	37.8±17.5	1 (0.99,1.01)
SBP	119.5±24.8	124.6±20.7	0.989 (0.98,0.998)	119.7±28.5	124.7±21.1	0.99 (0.97,0.99)
DBP	75.2±14.3	77.8±14.2	0.99 (0.97,1)	74.6±15.5	78.3±13.2	0.98 (0.97,0.99)
BUN	16.7±6.9	16.8±12.1	0.99 (0.98,10.1)	18.3±15.9	15.9±10.5	1.01 (0.99,1.02)
BS	174.4±65.4	164.2±64.3	1.002 (1,1.01)	166.7±61	145.9±59.9	1.005 (1.002,1.007)
P	101.8±23.1	99±20.6	1.006 (0.99,1.01)	102.9±23.4	97.1±20.4	1.01 (1,1.02)
NA	141.6±3.7	140.4±38.2	1.07 (1.02,1.13)	140.9±13.3	140.2±3.9	1.05 (1,1.1)
PO2	104.1±10.6	95.9±10.1	0.998 (0.99,1.004)	146±99.7	117.8±99.5	1 (0.99,1.006)
GCS	9.93±4.83	11.37±4.01	0.97 (0.93,1.011)	9.44±4.83	11.4±4	0.92 (0.88,0.96)
RR	20.37±5.44	19.96±4.24	1.05 (1.01,1.1)	21.11±5.75	19.92±4.22	1.04 (0.99,1.09)

P-values were calculated using T- test. *p-value less than 0.05 is considered statistically significant between coagulopathy and non- coagulopathy.

Table 4. univariate assessment of qualitative predicted variables for coagulopathy at the first and second stage in acute trauma patients

variable	first stage			Second stage		
	N(%)	N(%)	OR(95%CI)	N(%)	N(%)	OR(95%CI)
group	coagulopathy	No coagulopathy		coagulopathy	No coagulopathy	
Sex(male)	128 (86)	487 (17)	0.78 (0.48,1.33)	16 (12)	500 (83)	0.66 (0.38,1.16)
History of medi-cal(yes)	39 (26)	184 (32)	0.82 (0.54,1.27)	39 (30)	184 (30)	1.09 (0.7,1.72)
Pupil(yes)	112 (75)	464 (85)	0.82 (0.44,1.54)	50 (38)	259 (43)	0.52 (0.26,1.57)

P-values were calculated using the chi-squared test. *p-value less than 0.05 is considered statistically significant between coagulopathy and non- coagulopathy.

the model. The corre-lation matrix was also considered in the exchangeable form. The results can be found in Table 6.

The ICC estimated for the moderate-severe coagulation disorder was 0.28. as can be seen in Ta-ble 6, at such a condition, phosphorous content of the blood, pupillary reflex, age, and pH can predict moderate-severe coagulopathy. For the case of mild-moderate-severe coagulopathy, the ICC was estimated 0.26. under such conditions, blood sugar, diastolic pressure, pH, and sodium can significantly affect mild-moderate-severe coagulopathy.

Table 5. Predicted factors associated with coagulopathy using univariate GEE model

	Mild, moderate, and sever		moderate and severe	
	B	P-value	B	P-value
Sex	-0.31	0.15	0.052	0.86
Age	-0.003	0.51	0.016	0.005*
Signs and symptoms				
pupil	-0.198	0.291	-0.72	0.004*
Laboratory variable				
P	0.005	0.096	0.01	0.053
SBP	-0.007	0.03*	-0.003	0.47
DBP	-0.014	0.006*	-0.01	0.13
BUN	0.008	0.126	0.145	0.02*
BS	0.002	0.003	0.003	0.005
pH	-2.87	<0.001*	-3.18	<0.001*
NA	0.044	0.008*	-0.006	0.58
PO2	0.0006	0.56	0.0006	0.62

P-values were calculated using the GEE model. *p-value less than 0.05 is considered statistically significant

Table 6. Predicted factors associated with coagulopathy using multivariate GEE model

	Mild, moderate, and severe		moderate and severe	
	B	P-value	B	P-value
Patient characteristics				
age			0.016	0.007*
Signs and symptoms				
pupil			-0.645	0.013*
Laboratory variable				
P			0.012	0.024*
DBP	-0.013	0.007*		
BUN			0.009	0.166
BS	0.003	0.001*	0.002	0.252
pH	-1.36	0.04*	-1.61	0.014*
NA	0.086	<0.001*		

As seen, DBP, BS, pH, and Na were the significant variables in the case of mild-moderate-severe coagulopathy. In the case of moderate-severe coagulopathy, age, pupil, p and pH were significant.

Discussions

Coagulopathy (coagulation disorder) is one of the most common mortality causes in the intensive care unit, which can be reduced by diagnosing the main causes and timely treatment.[11] Prompt identification of acute trauma patients with coagulopathy is essential to accelerate appropriate treatment.[12] Using the results of paraclinical tests, this study is an attempt to determine the predictors of coagulation disorders in patients with trauma admitted to Shahid Rajaei Hospital in Shiraz during 2016-2018 using the method of generalized estimation equations.

The results indicated that the prevalence of coagulation disorders (mild, moderate and severe) was 20% in the first stage and 18% in the second stage. Also, the prevalence of coagulation disorders (moderate and severe) was 7.7% in the first stage and 7% in the second stage. The interclusteral correlation index (ICC) of coagulopathy patients (mild, moderate, and severe) and (moderate and severe) between the first and second stages were 0.26 and 0.28, respectively.

The findings of this study revealed that factors such as blood phosphorus, age, pH, and pupil reflex are predictors of blood coagulation disorders (moderate and severe). In a way that an increase in blood phosphorus, age and pH was associated with an increased chance of developing coagulopathy. Increased reflex was associated with a reduced chance of developing coagulation disorder. Moreover, blood sugar, diastolic blood pressure, pH and sodium had a significant effect on the incidence of coagulation disorders (mild, moderate and severe), so that increasing blood sugar, sodium and pH enhanced the chance of coagulopathy. Incremented diastolic blood pressure declined the chances of coagulation disorders. Kashefi et al. 2017 also observed a significant relationship between the coagulopathy severity and the extent of acidosis. Since the severity of acidosis can be determined by variables such as pH, HCO3 and Paco2, so there is a significant relationship between these variables and coagulopathy severity.[8] In both studies, pH was identified as a factor influencing coagulation disorder.

In the study by Paydar et al. in 2018, factors such as blood pH and sex were associated with fibrinogen levels below 100.[7] In the present study, pH was identified as an effective factor in coagulation disorders (moderate and severe) as well as (mild, moderate and severe. As decremented fibrinogen level is one of the causes of coagulation disorder and Paydar et al. examined fibrinogen levels below 100, thus these two studies are similar.

In the present, age was not recognized as an influential variable, but Kimura and Kimura 2014 identified the patient's age and prehospital fluid therapy as predictors of fibrinogen levels.[13] One reason for the difference in the results of the mentioned studies with the present research could be the inequality of the studied variables and the statistical method. in the mentioned studies, the effective factors on the fibrinogen reduction were examined in one stage but in the present study, the effective parameters were evaluated in two stages.

One of the limitations of the present study was that we were not able to accurately assess all the factors, and factors such as the underlying disease and the drugs used may have affected the results of our experiments that were not examined.

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