https://doi.org/10.1590/0004-282X20190057

ARTICLE

Expressions of plasma cystatin C, D-dimer and hypersensitive C-reactive protein in patients with intracranial progressive hemorrhagic injury after craniocerebral injury, and their clinical significance

Expressões da cistatina C plasmática, dímero D e proteína C reativa hipersensível em pacientes com lesão hemorrágica progressiva intracraniana após trauma crânio-encefálico e seus significados clínicos

Qibin PENG[1,2], Jiannong ZHAO[2], Pengcheng WANG[2], Chuixue HUANG[2], Baozhi CHEN[2] , Jian SONG[1], Guozheng XU[1]

ABSTRACT

Objective: To investigate the expressions of plasma cystatin C (Cys-C), D-dimer (D-D) and hypersensitive C-reactive protein (hs-CRP) in patients with intracranial progressive hemorrhagic injury (IPHI) after craniocerebral injury, and their clinical significance. **Methods:** Forty-two IPHI patients and 20 healthy participants (control) were enrolled. The severity and outcome of IPHI were determined according to the Glasgow Coma Scale and Glasgow Outcome Scale, and the plasma Cys-C, hs-CRP and D-D levels were measured. **Results:** The plasma Cys-C, D-D and hs-CRP levels in the IPHI group were significantly higher than those in the control group ($p < 0.01$). There were significant differences of plasma Cys-C, D-D and hs-CRP levels among different IPHI patients according to the Glasgow Coma Scale and according to the Glasgow Outcome Scale (all $p < 0.05$). In the IPHI patients, the plasma Cys-C, D-D and hs-CRP levels were positively correlated with each other ($p < 0.001$). **Conclusion:** The increase of plasma Cys-C, D-D and hs-CRP levels may be involved in IPHI after craniocerebral injury. The early detection of these indexes may help to understand the severity and outcome of IPHI.

Keywords: Cystatin C; C-reactive protein; hemorrhagic; craniocerebral injury.

RESUMO

Objetivo: Investigar as expressões da cistatina C plasmática (Cys-C), dímero-D (D-D) e proteína C-reativa hipersensível (hs-CRP) em pacientes com lesão hemorrágica progressiva intracraniana (IPHI) após lesão craniocerebral e seus significados clínicos. **Métodos:** Quarenta e dois pacientes com IPHI e 20 indivíduos saudáveis (controle) foram incluídos. A gravidade e o resultado do IPHI foram determinados de acordo com a Escala de Coma de Glasgow (GCS) e Escala de Resultados de Glasgow (GOS), e os níveis plasmáticos Cys-C, hs-CRP e D-D foram detectados. **Resultados:** Os níveis plasmáticos de Cys-C, D-D e hs-CRP no grupo IPHI foram significativamente maiores do que no grupo controle ($P < 0,01$). Houve diferença significativa entre os níveis plasmáticos de Cys-C, D-D e hs-CRP entre os diferentes pacientes com IPHI de acordo com a GCS e entre os diferentes pacientes com IPHI de acordo com o GOS, respectivamente (todos $P < 0,05$). Em pacientes com IPHI, os níveis plasmáticos de Cys-C, D-D e hs-CRP foram positivamente correlacionados entre si ($P < 0,001$). **Conclusão:** O aumento dos níveis plasmáticos de Cys-C, D-D e hs-CRP pode estar envolvido no IPHI após trauma crânio-encefálico. A detecção precoce desses índices pode ajudar a entender a gravidade e o resultado do IPHI.

Palavras-chave: Cistalina C; proteína C-reativa; hemorrágica; lesão craniocerebral.

[1]Department of Neurosurgery, Wuhan School of Clinical Medicine, Southern Medical University, Wuhan, China;

[2]Department of Neurosurgery, Hainan Provincial People's Hospital, Haikou, China.

Guozheng Xu https://orcid.org/0000-0002-9005-6408

Correspondence: Guozheng Xu; Department of Neurosurgery, Wuhan School of Clinical Medicine, Southern Medical University. 627 Wuluo Road, Wuhan 430070, China; E-mail: guozhengxu1@126.com

Conflict of interest: There is no conflict of interest to declare.

Received 05 June 2018; Received in final form 04 December 2018; Accepted 20 January 2019.

With the development of transportation and construction industries, the incidence, disability rate and mortality from craniocerebral injury are increasing year by year[1,2]. A craniocerebral injury is often complicated by various hemorrhagic disorders. An intracranial progressive hemorrhagic injury (IPHI) is an intracranial hemorrhage after craniocerebral injury. It refers to a hemorrhagic focus that is more severe than the primary bleeding site or new bleeding site confirmed by imaging or surgical examination[3]. An IPHI is one of the most common complications of craniocerebral injury[4,5]. Cystatin C (Cys-C) exists in all body fluids and is involved in the damage and repair of neuronal tissues in the brain[6]. D-dimer (D-D) is a specific degradation product of fibrin monomer by fibrinolysis. It has high sensitivity and reliability for the fibrinolysis function[7]. Hypersensitive C-reactive protein (hs-CRP) can effectively and accurately respond to the low-level inflammation reaction, and is one of the most important predictors of cardiovascular risk[8]. This study investigated the expressions of plasma Cys-C, D-D and hs-CRP in patients with IPHI after craniocerebral injury, and analyzed their significances for the severity and outcome of IPHI. The objective was to provide a basis for the diagnosis and treatment of IPHI.

METHODS

Participants

Forty-two IPHI patients treated in the Department of Neurosurgery, Wuhan General Hospital of Guangzhou Military Region from July 2012 to January 2016 were enrolled in this study. In the same period, 20 healthy participants undergoing a physical examination in our hospital were selected as controls. This study was conducted in accordance with the Declaration of Helsinki, and was approved by the ethics committee of Wuhan General Hospital of Guangzhou Military Region. Written informed consent was obtained from all participants or their family members.

Inclusion and exclusion criteria

Inclusion criteria were as follows: i) the patients were confirmed as having craniocerebral injury combined with IPHI by craniocerebral computed tomography (CT) (i.e. there was a new hematoma shown in the second CT compared with the first CT, or the volume of the existing hematoma shown in the second CT had increased significantly (≥ 25%) compared with the first CT[5,9]); ii) there was no severe injury of other tissues; iii) there was no damage in the hematological system; iv) there was no history of infectious diseases within three months prior to the craniocerebral injury. The exclusion criteria were as follows: i) concomitant severe heart, liver or kidney disease; ii) a history of mental illness; iii) presence of other chronic diseases; iv) the patients had a single craniocerebral injury or single IPHI.

Determination of degree of coma level and outcome of IPHI patients

The coma level of IPHI patients was determined according to the Glasgow Coma Scale as follows: 15 points = normal; 13-14 points = mild coma; 9-12 points = moderate coma; 3-8 points = severe coma. The outcome of IPHI patients was determined according to the Glasgow Outcome Scale as follows: 5 points = excellent outcome; 4 points = good outcome; 1-3 points = poor outcome.

Detection of plasma Cys-C, D-D and hs-CRP levels

The fasting peripheral venous blood (5 ml) was taken from the IPHI patients on the morning of the day of diagnosis of intracranial hemorrhagic injuries or at the follow-up; and was taken from the healthy participants on the morning of the day of their physical examination. The plasma Cys-C and hs-CRP levels were detected using particle enhanced transmitted immunoturbidimetry[10,11]. The plasma D-D level was detected using emulsion immunoturbidimetry[12]. The procedures were performed in accordance with the kit manufacturer's instructions (Sigma-Aldrich Corp., MO, USA).

Statistical analysis

All statistical analyses were carried out using SPSS20.0 software (SPSS Inc., Chicago, IL, USA). The enumeration data were presented as number and rate, and were compared using the χ^2 test. The measurement data were presented as mean ± standard deviation. The comparison between two groups was performed using the *t*-test, and comparison among three groups was performed using one-way analysis of variance with the least significant difference *post-hoc* test. The correlation of continuous variables was investigated using Pearson's correlation analysis. Values of $p < 0.05$ and $p < 0.01$ were considered as statistically significant and highly statistically significant, respectively.

RESULTS

General characteristics of participants in two groups

Of the 42 IPHI patients, there were 23 (54.76%) males and 19 (45.24%) females. The age of patients was 8-64 years, with a mean age of 41.45 ± 8.23 years. There were 2 (4.76%) patients with a history of disease. Of the 20 healthy participants, there were 11 (43.33%) males and 9 (56.67%) females. Their ages were 10-69 years, with a mean age of 38.05 ± 9.21 years. There was 1 (5.00%) individual with a history of disease. There were no significant differences in age, gender or history of disease between the two groups ($p > 0.05$) (Table 1).

Classification of IPHI patients

Of the 42 IPHI patients, there were 10 (23.81%) injuries due to a high fall, 10 (23.81%) injuries due to sport impact, and 22

(52.38%) injuries due to a motor vehicle collision. According to the Glasgow Coma Scale, there were 10 (23.81%) mild coma, 22 (52.38%) moderate coma and 10 (23.81%) patients in a severe coma. According to the Glasgow Outcome Scale, there were 11 (26.19%) patients with an excellent outcome, 21 (50.00%) patients with a good outcome and 10 (23.81%) patients with a poor outcome.

Comparison of plasma Cys-C, D-D and hs-CRP levels between IPHI and control groups

As shown in Table 2, the plasma Cys-C, D-D and hs-CRP levels in IPHI group were 1.48 ± 0.17 mg/L, 5.34 ± 1.35 mg/L and 30.02 ± 8.18 mg/L, respectively, which were significantly higher than 1.01 ± 0.16 mg/L, 1.37 ± 0.33 mg/L and 3.93 ± 0.87 mg/L in the control group, respectively ($p < 0.01$).

Comparison of plasma Cys-C, D-D and hs-CRP levels among IPHI patients with different coma levels

Table 3 shows that the plasma Cys-C, D-D and hs-CRP levels in IPHI patients with a mild coma were 1.37 ± 0.13 mg/L, 4.63 ± 1.14 mg/L and 23.94 ± 9.21 mg/L, respectively; levels in IPHI patients with a moderate coma were 1.47 ± 0.18 mg/L, 5.30 ± 1.30 mg/L and 29.94 ± 7.34 mg/L, respectively; and those for IPHI patients with a severe coma were 1.60 ± 0.15 mg/L, 6.13 ± 1.34 and 36.27 ± 2.92 mg/L, respectively. There was a significant difference of each index among the three subgroups ($p < 0.05$). In addition, the *post-hoc* comparison showed that the plasma Cys-C and hs-CRP levels in the severe coma subgroup were significantly higher than those in the mild coma and moderate coma subgroups, respectively ($p < 0.05$), and the plasma D-D level in the severe coma subgroup was significantly higher than that in the mild coma subgroup ($p < 0.05$).

Comparison of plasma Cys-C, D-D and hs-CRP levels among IPHI patients with different outcomes

As shown in Table 4, the plasma Cys-C, D-D and hs-CRP levels in IPHI patients with an excellent outcome were 1.39 ± 0.15 mg/L, 4.63 ± 1.11 mg/L and 27.23 ± 8.16 mg/L, respectively; those in IPHI patients with a good outcome were 1.47 ± 0.17 mg/L, 5.23 ± 1.34 mg/L and 28.85 ± 8.56 mg/L, respectively; and those in IPHI patients with a poor outcome were 1.58 ± 0.16 mg/L, 6.33 ± 1.07 mg/L and 35.54 ± 4.65 mg/L, respectively. There was a significant difference of each index among the three subgroups ($p < 0.05$). The *post-hoc* comparison showed that the plasma Cys-C level in the poor outcome subgroup was significantly higher than that in the excellent outcome subgroup ($p < 0.05$); and the plasma D-D and hs-CRP levels in the poor outcome subgroup were significantly higher than those in the excellent and good outcome subgroups, respectively ($p < 0.05$).

Correlation of plasma Cys-C, D-D and hs-CRP levels in IPHI patients

Pearson's correlation analysis showed that, in IPHI patients, the plasma Cys-C and D-D levels; Cys-C and hs-CRP levels; and D-D and hs-CRP levels were positively correlated, respectively (Cys-C with D-D: $r = 0.835$, $p < 0.001$; Cys-C with hs-CRP: $r = 0.836$, $p < 0.001$; D-D with hs-CRP: $r = 0.652$, $p < 0.001$) (Table 5).

DISCUSSION

Intracranial progressive hemorrhagic injury is one of the major causes of disability and death in patients with craniocerebral injury. It can lead to aggravation of the patient's condition and has a close relationship with the prognosis of the patient. Therefore, the early and accurate diagnosis of IPHI may help to evaluate the risk to patients and formulate an

Table 1. General characteristics of participants in the two groups.

Parameter	IPHI group n = 42	Control group n = 20	t/χ^2	p-value
Age (years)	41.45 ± 8.23	38.05 ± 9.21	14.633	0.1486
Gender [male, n (%)]	23 (54.76)	11 (43.33)	0.0003	0.9859
History of disease [n (%)]	2 (4.76)	1 (5.00)	0.0017	0.9674

IPHI: intracranial progressive hemorrhagic injury.

Table 2. Comparison of plasma Cys-C, D-D and hs-CRP levels between the IPHI and control groups (mean ± SD).

Group	Cys-C (mg/L)	D-D (mg/L)	hs-CRP (mg/L)
IPHI	1.48 ± 0.17	5.34 ± 1.35	30.02 ± 8.18
Control	1.01 ± 0.16	1.37 ± 0.33	3.93 ± 0.87
t-test	10.365	12.917	14.214
p-value	< 0.001	< 0.001	< 0.001

IPHI: intracranial progressive hemorrhagic injury; Cys-C: cystatin C; D-D: D-dimer; hs-CRP: hypersensitive C-reactive protein.

Table 3. Comparison of plasma Cys-C, D-D and hs-CRP levels among the IPHI patients with different coma levels.

Subgroup	n	Cys-C (mg/L)	D-D (mg/L)	hs-CRP (mg/L)
Mild coma	10	1.37 ± 0.13	4.63 ± 1.14	23.94 ± 9.21
Moderate coma	22	1.47 ± 0.18	5.30 ± 1.30	29.94 ± 7.34
Severe coma	10	1.60 ± 0.15[ab]	6.13 ± 1.34[a]	36.27 ± 2.92[ab]
F		5.303	3.518	7.469
p		0.009	0.039	0.002

[a]$p < 0.05$ compared with mild group; [b]$p < 0.05$ compared with moderate group. IPHI: intracranial progressive hemorrhagic injury; Cys-C: cystatin C; D-D: D-dimer; hs-CRP: hypersensitive C-reactive protein.

Table 4. Comparison of plasma Cys-C, D-D and hs-CRP levels among IPHI patients with different outcomes.

Subgroup	n	Cys-C (mg/L)	D-D (mg/L)	hs-CRP (mg/L)
Excellent outcome	11	1.39 ± 0.15	4.63 ± 1.11	27.23 ± 8.16
Good outcome	21	1.47 ± 0.17	5.23 ± 1.34	28.85 ± 8.56
Poor outcome	10	1.58 ± 0.16[a]	6.33 ± 1.07[ab]	35.54 ± 4.65[ab]
F		3.622	5.153	3.513
p		0.036	0.010	0.040

[a]p < 0.05 compared with mild group;[b]p < 0.05 compared with moderate group. IPHI: intracranial progressive hemorrhagic injury; Cys-C: cystatin C; D-D: D-dimer; hs-CRP: hypersensitive C-reactive protein.

Table 5. Correlation of plasma Cys-C, D-D and hs-CRP levels in IPHI patients.

Index	Cys-C		D-D		hs-CRP	
	r	p	r	p	r	p
Cys-C	-	-	0.835	< 0.001	0.836	< 0.001
D-D	0.835	< 0.001	-	-	0.652	< 0.001
hs-CRP	0.836	< 0.001	0.652	< 0.001	-	-

IPHI: intracranial progressive hemorrhagic injury; Cys-C: cystatin C; D-D: D-dimer; hs-CRP: hypersensitive C-reactive protein; *r*: Pearson's correlation.

individualized treatment scheme. The specific mechanisms of IPHI are unclear. There are several controversial theories including the systemic hypoxia theory[13], vascular dysregulation theory[14], coagulation disorder theory[15] and protection mechanism theory[5]. This study investigated the expressions of plasma Cys-C, D-D and hs-CRP in patients with IPHI after craniocerebral injury and their significance for the severity and outcome of IPHI, so as to provide a reference for the clinical prediction of IPHI.

Cystatin C, also known as the cysteine protease inhibitor C, is a kind of alkaline secretory protein with a relatively small molecular weight. The main function of Cys-C is to combine the cysteine proteases and inhibit their activities, especially for the cathepsin in lysosome, thus adjusting the intracellular and extracellular protein hydrolysis level[16]. Cystatin C is one of the known widely-distributed cathepsin inhibitors. It can strongly inhibit cathepsin B, H, K, L and S in human lysozyme, and regulate the degree of proteolysis in cells[17]. Cystatin C participates in and regulates many physiological and pathological processes including cell proliferation, inflammatory response, antiviral reaction, anti-bacterial reaction, tumor metastasis and bone matrix reabsorption[18]. It has been found that the increase of Cys-C concentration has a strong independent correlation with secondary cardiovascular events.[19] The results of this study showed that the plasma Cys-C level in IPHI patients was significantly higher than in the control group ($p < 0.01$). With the aggravation of the degree of coma and worsening of outcome, the plasma Cys-C level had increased. This suggests that the plasma Cys-C level may be related to the severity and outcome of IPHI.

The D-D is a specific fibrinolytic marker, and its level is significantly increased in early-stage acute craniocerebral injury. Brain trauma patients with a high D-D level often have a poor prognosis[20]. The increase of D-D concentration indicates the coagulation dysfunction combined with hyperfibrinolysis. In this condition, the body is in a bleeding state, and the cranial CT shows enlargement and progress of the intracranial hematoma. Therefore, the higher D-D concentration indicates a more serious bleeding tendency and greater possibility of a delayed intracranial hematoma. When the D-D level is higher than a normal concentration, an IPHI will occur more easily[21]. The results of this study showed that the plasma D-D level in IPHI patients was significantly higher than in the control group ($p < 0.01$), and it increased with the aggravation of the degree of coma and worsening of the outcome of IPHI. This indicates that the D-D is involved in the occurrence and development of IPHI.

The Hs-CRP is currently one of the most valuable acute-phase reaction proteins. The increase of the hs-CRP level indicates the occurrence of inflammatory events[22]. The Hs-CRP is an important sign of inflammation, infection, tissue injury, necrosis and malignant tumor. It plays an increasingly important role in the diagnosis and prediction of coronary heart disease, cerebral infarction and peripheral vascular embolism, and it is even considered the gold standard for the risk assessment of cardiovascular and cerebrovascular diseases[23]. It has been found that the detection of plasma hs-CRP levels could predict the occurrence and progress of IPHI, which has great significance for the prognosis of patients[24]. In this study, the plasma hs-CRP level in IPHI patients was significantly higher than that in the control group ($p < 0.01$), and it also increased with the worsening of the coma level and of the outcome of IPHI. This indicates that hs-CRP is also an important indicator for IPHI.

There are certain correlations between plasma Cys-C, D-D and hs-CRP in the body. Dai et al.[25] found that, in patients with nephrotic syndrome, the plasma Cys-C level was positively correlated with the plasma D-D level ($p < 0.05$). Zhang

et al.[26] found that the plasma Cys-C and hs-CRP levels were positively correlated in acute cerebral infarction patients complicated by multiple organ dysfunction syndrome ($p < 0.05$). In the study by Meng et al.[27], the plasma D-D level was positively correlated with the plasma hs-CRP level in patients with cerebral infarction ($p < 0.05$). The results of the present study showed that, in IPHI patients, the plasma Cys-C, D-D and hs-CRP levels were positively correlated with each other ($p < 0.001$). This is consistent with the above results.

In conclusion, the increases of plasma Cys-C, D-D and hs-CRP levels may be involved in the occurrence and development of IPHI after craniocerebral injury. The early detection of these indexes may have important significance in the diagnosis of IPHI after craniocerebral injury. This may encourage doctors to formulate and implement individualized treatment schemes in a timely manner. This study still has some limitations. Firstly, the sample size of this study was relatively small, which may lead to a bias in the selected population. In future studies, the sample size should be enlarged to obtain more convincing results. Secondly, multiple factors are related to the elevation of plasma Cys-C, D-D and hs-CRP levels, which may affect the results. In future studies, other factors related to the elevation of these makers should be investigated.

References

1. Thomas AG, Hegde SV, Dineen RA, Jaspan T. Patterns of accidental craniocerebral injury occurring in early childhood. Arch Dis Child. 2013;98(10):787-92. https://doi.org/10.1136/archdischild-2013-304267
2. Liu S, Liu YX, Wang C. The clinical characteristics and therapy of syndrome of craniocerebral-cervical vertebral injury. Chin J Traumatol. 2005 Jun;8(3):183-5.
3. Vedantam A, Yamal JM, Rubin ML, Robertson CS, Gopinath SP. Progressive hemorrhagic injury after severe traumatic brain injury: effect of hemoglobin transfusion thresholds. J Neurosurg. 2016;125(5):1229-34. https://10.3171/2015.11.JNS151515
4. Kirchhoff C, Buhmann S, Braunstein V, Leidel BA, Vogel T, Kreimeier U, et al. Cerebrospinal s100-B: a potential marker for progressive intracranial hemorrhage in patients with severe traumatic brain injury. Eur J Med Res. 2008 Nov;13(11):511-6.
5. Oertel M, Kelly DF, McArthur D, Boscardin WJ, Glenn TC, Lee JH, et al. Progressive hemorrhage after head trauma: predictors and consequences of the evolving injury. J Neurosurg. 2002;96(1):109-16. https://10.3171/jns.2002.96.1.0109
6. Nagai A, Ryu JK, Terashima M, Tanigawa Y, Wakabayashi K, McLarnon JG, et al. Neuronal cell death induced by cystatin C in vivo and in cultured human CNS neurons is inhibited with cathepsin B. Brain Res. 2005;1066(1):120-8. https://10.1016/j.brainres.2005.10.063
7. Dindo D, Breitenstein S, Hahnloser D, Seifert B, Yakarisik S, Asmis LM, et al. Kinetics of D-dimer after general surgery. Blood Coagul Fibrinolysi. 2009;20(5):347-52. https://10.1097/MBC.0b013e32832a5fe6
8. Saito M, Ishimitsu T, Minami J, Ono H, Ohrui M, Matsuoka H. Relations of plasma high-sensitivity C-reactive protein to traditional cardiovascular risk factors. Atherosclerosis. 2003 Mar;167(1):73-9. https://doi.org/10.1016/S0021-9150(02)00380-5
9. Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, et al. The ABCs of measuring intracerebral hemorrhage volumes. Stroke. 1996; 27(8):1304-5. https://doi.org/10.1161/01.STR.27.8.1304
10. Koçak H, Oner-Iyidoğan Y, Gürdöl F, Koçak T, Esin D. The relation between serum MDA and cystatin C levels in chronic spinal cord injury patients. Clin Biochem. 2005;38(11):1034-7. https://10.1016/j.clinbiochem.2005.08.005
11. Sişman AR, Küme T, Taş G, Akan P, Tuncel P. Comparison and evaluation of two C-reactive protein assays based on particle-enhanced immunoturbidimetry. J Clin Lab Anal. 2007;21(2):71-6. https://10.1002/jcla.20141
12. Knecht MF, Heinrich F. Clinical evaluation of an immunoturbidimetric D-dimer assay in the diagnostic procedure of deep vein thrombosis and pulmonary embolism. Thromb Res. 1997 Dec;88(5):413-7. https://doi.org/10.1016/S0049-3848(97)00276-4
13. Hossain MA, Oda T, Sameshima T, Miyao J, Yoshimura N. Evaluation of indicators of tissue hypoxia during progressive hemorrhage and blood retransfusion. In Vivo. 1997 Jan-Feb;11(1):39-44.
14. Harris AK, Ergul A, Kozak A, Machado LS, Johnson MH, Fagan SC. Effect of neutrophil depletion on gelatinase expression, edema formation and hemorrhagic transformation after focal ischemic stroke. BMC Neurosci. 2005;6(1):49. https://10.1186/1471-2202-6-49
15. Folkerson LE, Sloan D, Cotton BA, Holcomb JB, Tomasek JS, Wade CE. Predicting progressive hemorrhagic injury from isolated traumatic brain injury and coagulation. Surgery. 2015;158(3):655-61. https://doi.org/10.1016/j.surg.2015.02.029
16. Bengtsson E, To F, Håkansson K, Grubb A, Brånén L, Nilsson J, et al. Lack of the cysteine protease inhibitor cystatin C promotes atherosclerosis in apolipoprotein E-deficient mice. Arterioscler Thromb Vasc Biol. 2005;25(10):2151-6. https://10.1161/01.ATV.0000179600.34086.7d
17. Kos J, Stabuc B, Schweiger A, Krasovec M, Cimerman N, Kopitar-Jerala N, et al. Cathepsins B, H, and L and their inhibitors stefin A and cystatin C in sera of melanoma patients. Clin Cancer Res. 1997 Oct;3(10):1815-22.
18. Reed CH. Diagnostic applications of cystatin C. Br J Biomed Sci. 2000;57(4):323-9.
19. Ni L, Lü J, Hou LB, Yan JT, Fan Q, Hui R, et al. Cystatin C, associated with hemorrhagic and ischemic stroke, is a strong predictor of the risk of cardiovascular events and death in Chinese. Stroke. 2007;38(12):3287-8. https://10.1161/STROKEAHA.107.489625
20. Bredbacka S, Edner G. Soluble fibrin and D-dimer as detectors of hypercoagulability in patients with isolated brain trauma. J Neurosurg Anesthesiol. 1994 Apr;6(2):75-82. https://doi.org/10.1097/00008506-199404000-00002
21. Kuo JR, Lin KC, Lu CL, Lin HJ, Wang CC, Chang CH. Correlation of a high D-dimer level with poor outcome in traumatic intracranial hemorrhage. Eur J Neurol. 2007;14(10):1073-8. https://10.1111/j.1468-1331.2007.01908.x
22. Kallergis EM, Manios EG, Kanoupakis EM, Mavrakis HE, Kolyvaki SG, Lyrarakis GM, et al. The role of the post-cardioversion time course of hs-CRP levels in clarifying the relationship between inflammation and persistence of atrial fibrillation. Heart. 2008;94(94):200-4. https://https://doi.org/10.1136/hrt.2006.108688
23. Levinson SS. Brief review and critical examination of the use of hs-CRP for cardiac risk assessment with the conclusion that it is premature to use this test. Clin Chim Acta. 2005;356(1):1-8. https://https://doi.org/10.1016/j.cccn.2004.12.021

24. Li T. [The study of correlation between hs-CRP and severity of intracranial hemorrhage]. China Modern Doctor. 2015;53(1):72-4.Chinese.

25. Dai HY, Wang HL, Li Y. [Clinical significance of combined detection of D-dimer and Cys-C in nephrotic syndrome]. Chongqing Med. 2017;46(4):896-8. Chinese.

26. Zhang T, Chen ZB, Wang T, Chen R. [Changes of Cys-C in acute cerebral infarction leading to systemic inflammatory response syndrome which causes multiple organ dysfunction syndrome]. J Apoplexy Nerv Dis. 2014;31(8):713-6. Chinese.

27. Meng XH, Chen B, Kuang TJ, Dong M. [Clinical significance of the concentration of D-Dimer,hs-CRP and NO in serum of patients with cerebral infarction].Chin J Lab Diagn. 2006;10(2):334-6. Chinese.