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Original Article

A New Classification System for Evaluating Patients with Severe Trauma Using B-type Natriuretic Peptide Levels and Estimated Glomerular Filtration Rate

Sunao Morisada*, Toyomu Ugawa, Nobuyuki Nosaka, and Yoshihito Ujike

Advanced Emergency and Critical Care Center of Okayama University Hospital, Okayama 700–8558, Japan

Current systems for the evaluation of trauma severity are tedious and difficult to apply in an actual emergency setting. We aimed to develop and assess the accuracy of a more efficient severity evaluation system, termed the Ugawa classification, using brain-type natriuretic peptide (BNP) measurement and the estimated glomerular filtration rate (eGFR). Two-hundred trauma patients were divided into 2 groups using an eGFR cut-off value of 90 ml/min/1.73 m^2 as an indicator of normal renal function and 2 additional groups according to whether the BNP values were greater or less than the age in years. This resulted in 4 subject groups with different combinations of eGFR and BNP. The mean SOFA score, injury severity scores (ISS), trauma and injury severity scores (TRISS), and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores of the groups were compared by Kruskal–Wallis test, and the mortality rate after 90 days was calculated. Significant intergroup differences were found in SOFA scores, ISS scores, and APACHE II-predicted mortality rates. Although no significant differences were found in the mortality rate after 90 days or TRISS-predicted mortality rate among the 4 groups, there was a trend toward increasing trauma severity from group 1 to 4. Thus, the Ugawa classification is as accurate as existing systems, has greater efficiency, and is user-friendly.

Key words: acute injury, Acute Physiology and Chronic Health Evaluation II, injury severity score, sequential organ failure assessment, trauma and injury severity score

The initial treatment choice for patients with severe trauma must be determined within minutes and early intervention provided accordingly. The predicted reserve respiratory capacity, circulation dynamics, and renal function during the initial acute stage are important indicators in selecting a therapeutic strategy during the acute phase. While reserve respiratory capacity is relatively easy to estimate by reviewing physiological findings during the acute treatment stage, biomonitoring, blood gas analysis, and detailed evaluation of heart and renal function are difficult.

To assist in determining the strategy for early intervention, various scoring systems for the evaluation of severity have been developed, including the injury severity score (ISS), the sequential organ failure assessment (SOFA) score, the trauma and injury severity score (TRISS), and the Acute Physiology and Chronic Health Evaluation II

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*Corresponding author. Phone:+81–86–235–7427; Fax:+81–86–235–7427
E-mail:morimorisunao@yahoo.co.jp (S. Morisada)

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(APACHE II) score. However, it is difficult to objectively evaluate the severity of injury in an actual emergency setting using these complex systems [1–3]. In addition, the continuous monitoring of respiratory status, circulation dynamics, and renal function to provide life support is also a challenge in these settings. Thus, the development of a simple yet accurate system for evaluating the severity of injury is critical to facilitate the selection of a treatment strategy.

The utility of the brain-type natriuretic peptide (BNP) value for evaluation of heart failure has been widely reported [4–15]. Because the BNP value is affected by renal function and age, renal function is evaluated and age is considered during BNP measurement [16–24]. Regarding its use in assessing injury patients, several studies have examined the utility of BNP measurement for assessing patients with sustained solitary head injury [25–28] and extensive burn injury [29, 30]. However, there have been very few studies on the utility of BNP values specifically for patients with severe trauma, including those who have sustained multiple injuries [31]. To fill this research gap, we evaluated the severity of trauma in patients with acute injury using the BNP value as an indicator of heart function and the estimated glomerular filtration rate (eGFR) as an indicator of renal function. Based on the results, we developed a new severity classification system for patients with severe trauma. We then used this system to predict the mortality rate after 90 days and compared its accuracy to that of existing severity evaluation systems.

Methods

All trauma patients (n = 208) who had been transferred to the emergency intensive care unit (EICU) of the advanced critical care center of Okayama University Hospital between March 1, 2012 and August 31, 2013 were included in this study. These 208 patients included patients who had experienced high-energy injuries, multiple injuries, extensive burn injuries, and extremity amputation. Exclusion criteria were traumatic cardiopulmonary arrest at the time of transfer (2 patients), withdrawal from treatment because of irreversible central nervous system damage (*i.e.*, brain death) (2 patients), serious extensive burns from a suicide attempt and refusal of informed consent by the family (1 patient), and age < 18 years (3 patients). Thus, the final sample consisted of 200 subjects (133 men and 67 women) with a mean age of 49.67 years (age range, 18–98 years; median: 50 years).

For each of the 200 trauma patients in the final subject group, we calculated the regression curves for BNP and age and for BNP and eGFR, and found that the BNP levels tended to increase with advancing age and decreasing eGFR ($p < 0.05$, Fig. 1A and B). This suggested that BNP is associated with both age and eGFR. The subjects were then divided into 2 groups based on a cut-off value of eGFR = 90 ml/min/1.73 m^2 as an indicator of normal renal function [32]. The subjects were also divided into 2 other groups, a BNP ≥ age and a BNP < age group, using BNP as an indicator of heart function. Then, each patient was assigned to one of the following 4 groups based on their combination of BNP and eGFR group assignments: group 1, eGFR ≥ 90 ml/min/1.73 m^2 and BNP < age; group 2, eGFR < 90 ml/min/1.73 m^2 and

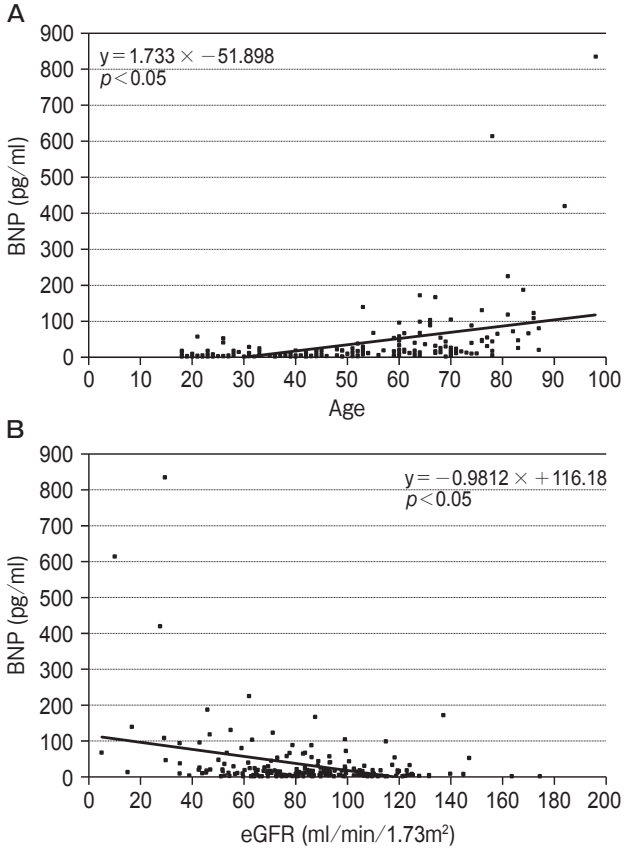

Fig. 1 Regression analysis. **A**, Regression curve for BNP and age; **B**, Regression curve for BNP and eGFR.

BNP < age; group 3, eGFR ≥ 90 ml/min/1.73 m^2 and BNP ≥ age; and group 4, eGFR < 90 ml/min/1.73 m^2 and BNP ≥ age (Table 1). We set the cutoff value for BNP based on age because a universal BNP cutoff value for injured patients is not available and BNP is known to be affected by age [21–24]. We designated this classification the Ugawa classification system. The mean SOFA score, mean ISS score, APACHE II-predicted and TRISS-predicted mortality rates of the groups were compared using the Kruskal–Wallis test for the identification of statistical differences, and the mortality rate was calculated after 90 days for each group.

Data for age, sex, disease severity, disease history and treatment progression, laboratory blood parameters, prognosis, and presence of delayed effects were extracted from the medical records and archives of our advanced critical care center and analyzed. Any personal information appearing with data extracted from the medical records was removed and replaced with a number to maintain patient privacy. Before study initiation, all patients provided signed informed consent, which was posted publicly on the hospital's announcement board and the departmental homepage on the hospital website. The Okayama University Hospital Ethical Review Board reviewed and approved the study aims and procedures.

Results

Among the 200 patients, the mortality rate after 90 days was 6.0%; the mean ISS, 18.20; the mean SOFA score, 3.09; the mean TRISS-predicted mortality rate, 17.22%; and the mean APACHE II-predicted mortality rate, 17.1%. The mean SOFA score was significantly different between the eGFR ≥ 90 ml/min/1.73 m^2 and eGFR < 90 ml/min/1.73 m^2 groups (2.51 [SE = 0.251] vs. 3.47 [SE = 0.232]; $p < 0.01$). In contrast, the difference between the groups' mortality rates was not significant (3.7% vs. 6.7%). The mean SOFA score of the BNP < age group was 2.86 [SE = 0.173] compared to 4.51 [SE = 0.604] in the BNP ≥ age group ($p < 0.01$). In contrast, the difference between the groups' mortality rates, which were 4.1% and 7.4%, respectively, was not found to be significant (Fig. 2).

These results indicate that a more serious degree of organ disorder was experienced in the eGFR < 90 ml/min/1.73m^2 group and the BNP ≥ age group. Based on these results, the patients were divided into 4 groups as shown in Table 1 (Ugawa classification).

The mortality rate was 2.67% in group 1, 8.1% in group 2, 14.3% in group 3, and 15.79% in group 4. Although no significant differences were found among the groups in the mortality rate after 90 days ($p = 0.162$), the mortality rate showed an increasing trend from groups 1 to 4. Statistical comparison of the Ugawa classification to the currently used severity assessment tools revealed that there were no significant differences in the TRISS-predicted mortality rate among the 4 groups ($p = 0.086$), but significant intergroup differences in the SOFA score ($p < 0.01$), ISS ($p < 0.01$), and APACHE II-predicted mortality rate ($p < 0.01$; Table 2).

Table 1 Ugawa classification according to BNP and eGFR values

Ugawa classification	BNP (pg/ml)	eGFR (ml/min/1.73 m^2)
1	< Patient's age	≥ 90
2	< Patient's age	< 90
3	≥ Patient's age	≥ 90
4	≥ Patient's age	< 90

BNP, brain-type natriuretic peptide; eGFR, estimated glomerular filtration rate.

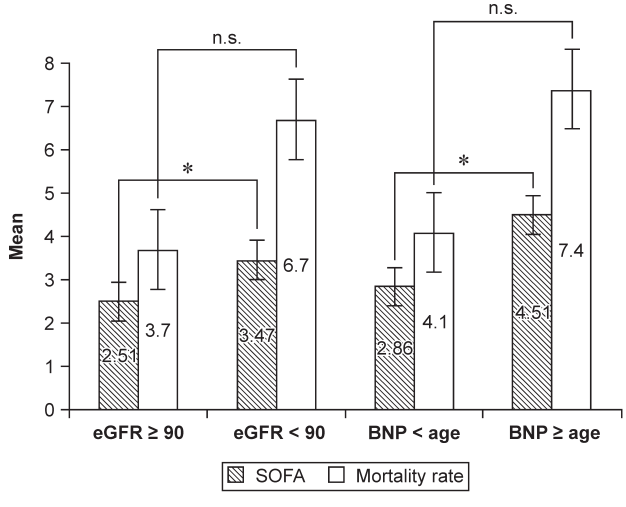

Fig. 2 Classification of SOFA score and mortality rate based on eGFR and BNP values. SOFA values indicate mean scores and mortality rates are shown in %. BNP, brain-type natriuretic peptide; eGFR, estimated glomerular filtration rate; SOFA, sequential organ failure assessment.

Table 2 Severity scores and mortality rate after 90 days

	Group 1	Group 2	Group 3	Group 4	p-value
SOFA score	2.34	3.2	3.28	5.34	<0.01
ISS	14.21	21.46	16	17.79	<0.01
APACHE II score	12.03	18.88	13.53	29.4	<0.01
TRISS score	11.83	19.48	20.1	25.34	0.086
Mortality rate after 90 days	2.67	8.1	14.3	15.79	0.162

SOFA, sequential organ failure assessment; ISS, injury severity score; APACHE II, Acute Physiology and Chronic Health Evaluation II; TRISS, trauma and injury severity score.

Discussion

Among the four groups examined in this study, all the severity scores and the mortality rate after 90 days were lowest in group 1. However, the mean ISS and TRISS-predicted mortality rate in group 1 were 14.21 and 11.83%, respectively, suggesting that the patients in this group had sustained severe injury. In group 2, the mean ISS was 21.46, which was the highest value among all the groups, and the APACHE II-predicted mortality rate was 18.88%, which was the second highest value among the groups, but the mortality rate after 90 days (8.1%) was relatively low. This finding can be attributed to the initially normal heart and renal function in patients in group 2, as well as their greater likelihood of sustaining severe trauma because of a high level of activity, resulting in a lower eGFR value due to severe trauma. In addition, because the lowest value within 24h of EICU admission—the most severe phase of patient presentation—is the value used for calculating the APACHE II-predicted mortality rate, this value was relatively high [33]. The results indicate that, compared to the ISS and APACHE II scores, Ugawa classification is a more accurate means of determining the prognosis of patients with severe trauma.

While group 3 had a mean ISS of 16.00, which was the third highest value among the 4 groups, the mortality rate after 90 days was 14.3%, which, being the second highest, was relatively high. The APACHE II-predicted mortality rate of this group was 13.53%, which was not significantly different from the actual mortality rate. In group 3, only patients with an abnormal BNP value were predicted to have low heart reserve capacity. In addition to a mean ISS of 16, which suggests a high level of damage, cardiovascular system failure occurred with treatment progression in patients with a low heart reserve capacity, resulting in a high mortality rate of 14.3%.

Comparison of groups 2 and 3 revealed that group 2 had a lower mortality rate, despite its high mean ISS score. For patients in group 2, the circulating blood volume was reduced due to hemorrhage; therefore, they had lower eGFR values. By using the Ugawa classification as an index during initial treatment, fluid resuscitation and hemostasis with aggressive infusion and blood transfusion could be initiated promptly and serve as key lifesaving measures for these patients. On the other hand, an important consideration is that patients in group 3 could have had a poor heart function from treatment initiation. Thus, in addition to early hemostasis, infusion and blood transfusion could be promptly initiated to avoid excessive water load. Prognosis would have been expected to improve with the provision of this circulatory support.

Group 4 had the highest mortality rate after 90 days as well as the highest SOFA score and both TRISS- and APACHE II-predicted mortality rates. This group had a mean ISS of 17.79, the second highest value. Review of these results indicates that patients classified into group 4 during the initial treatment experience had reduced heart and renal function from treatment initiation and had sustained fatal injury.

In this study, the SOFA score, ISS, and APACHE II-predicted mortality rate were found to differ significantly among the 4 study groups. While no significant intergroup differences were found in the mortality rate after 90 days or in the TRISS-predicted mortality rate, an increasing trend was seen from group 1 to 4. A strong correlation was observed between the Ugawa classification and TRISS-predicted mortality and mortality after 90 days, although this did not

reach statistical significance. We anticipate that future studies including a larger number of cases will reveal a significant difference. Use of the Ugawa classification to determine an appropriate therapeutic strategy accompanied by rapid and appropriate intervention may thus improve the survival rate.

In addition to accuracy, the Ugawa classification for severity evaluation offers the advantages of efficiency and simplicity compared to the other complex scoring systems, as it requires only 15 min to perform from initial blood sampling. Particularly in group 2, the Ugawa classification more accurately reflected the actual mortality rate compared to mortality-rate prediction by the APACHE II system. This finding suggests that patients in group 2 who survive after the acute trauma period can be useful for effective prognosis, which can be improved by investing in healthcare with adequate planning and improvement in the quality of care. Furthermore, the measurement and assessment of eGFR and BNP values are critical not only when designing an initial treatment strategy but also throughout the treatment. The tool also suggests that monitoring of the patient's general condition and renal and heart functions are critical for survival.

In conclusion, we developed the Ugawa classification tool for evaluating the severity of trauma using BNP and eGFR values. The tool is as accurate as the existing severity evaluation tools and has the advantages of simplicity and efficiency. Because it requires only blood sampling for severity prediction, this assessment tool would be particularly useful in outpatient clinics with limited time and resources.

References

1. Christian MD, Hawryluck L, Wax RS, Cook T, Lazar NM, Herridge MS, Muller MP, Gowans DR, Fortier W and Burkle FM: Development of a triage protocol for critical care during an influenza pandemic. CMAJ (2006) 175: 1377–1381.
2. Knaus WA, Draper EA, Wagner DP and Zimmerman JE: APACHE II: a severity of disease classification system. Crit Care Med (1985) 13: 818–829.
3. Boyd CR, Tolson MA and Copes WS: Evaluating trauma care: the TRISS Method. Trauma Score and the Injury Severity Score. J Trauma (1987) 27: 370–378.
4. Boldanova T, Noveanu M, Breidthardt T, Potocki M, Reichlin T, Taegtmeyer A, Christ M, Laule K, Stelzig C and Mueller C: Impact of history heart failure on diagnostic and prognostic value of BNP: results from the B-type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) Study. Int J Cardiol (2010) 142: 265–272.
5. McCullough PA, Hollander JE, Nowak RM, Storrow AB, Duc P, Oml and T, McCord J, Herrmann HC, Steg PG, Westheim A, Knudsen CW, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS and BNP Multinational Study Investigators: Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. Acad Emerg Med (2003) 10: 198–204.
6. Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amirnovin R, Lenert L, Clopton P, Alberto J, Hlavin P and Maisel AS: Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in urgent-care setting. J Am Coll Cardiol (2001) 37: 379–385.
7. Porapakkham P, Porapakkham P, Zimmet H, Billah B and Krum H: B-type natriuretic peptide–guided heart failure therapy: a meta-analysis. Arch Intern Med (2010) 170: 507–514.
8. Breidthardt T, Noveanu M, Cayir S, Viglino M, Laule K, Hochholzer W, Reichlin T, Potocki M, Christ M and Mueller C: The use of B-type natriuretic peptide in the management of patients with atrial fibrillation and dyspnea. Int J Cardiol (2009) 136: 193–199.
9. Noveanu M, Breidthardt T, Potocki M, Reichlin T, Twerenbold R, Uthoff H, Socrates T, Arenja N, Reiter M, Meissner J, Heinisch C, Stalder S and Mueller C: Direct comparison of serial B-type natriuretic peptide and NT-proBNP levels for prediction of short- and long-term outcome in acute decompensated heart failure. Crit Care (2011) 15: R1.
10. Nakagawa O, Ogawa Y, Itoh H, Suga S, Komatsu Y, Kishimoto I, Nishino K, Yoshimasa T and Nakao K: Rapid transcriptional activation and early mRNA turnover of BNP in cardiocyte hypertrophy. Evidence for BNP as an "emergency" cardiac hormone against ventricular overload. J Clin Invest (1995) 96: 1280–1287.
11. Maeda K, Tsutamoto T, Wada A, Hisanaga T and Kinoshita M: Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart J (1998) 135: 825–832.
12. Harrison A, Morrison LK, Krishnaswamy P, Kazanegra R, Clopton P, Dao Q, Hlavin P and Maisel AS: B-type natriuretic peptide predicts future cardiac events in patients presenting to the emergency department with dyspnea. Ann Emerg Med (2002) 39: 131–138.
13. Maisel AS, McCord J, Nowak RM, Hollander JE, Wu AHB, Duc P, Omland T, Storrow AB, Krishnaswamy P, Abraham WT, Clopton P, Steg G, Aumont MC, Westheim A, Knudsen CW, Perez A, Kamin R, Kazanegra R, Herrmann HC and McCullough PA: Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure: primary results from the Breathing not Properly (BNP) Multinational Study. N Engl J Med (2002) 347: 161–167.
14. McCullough PA, Nowak RM, McCord J, Hollander JE, Herrmann HC, Steg PG, Duc P, Westheim A, Omland T, Knudsen CW, Storrow AB, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R and Maisel AS: B-type natriuretic peptide and clinical judgment in the emergency diagnosis of heart failure: an analysis from the Breathing Not Properly (BNP) Multinational Study. Circulation (2002) 106: 416–422.
15. Pedersen EB, Pedersen HB and Jensen KT: Pulsatile secretion of atrial natriuretic peptide and brain natriuretic peptide in healthy humans. Clin SciLand (1999) 97: 201–216.
16. Bhat G, Pauwaa S, Sheffield C, Caldeira C, Weston M, Rinde-Hoffman D, Berman P and Cintron G: Elevated B-type natriuretic peptide without volume overload in a left ventricular assist device patient with a subdural hematoma. ASAIO J (2010) 56: 77–78.

17. Cataliotti A, Malatino LS, Jougasaki M, Zoccali C, Castellino P, Giacone G, Bellanuova I, Tripepi R, Seminara G, Parlongo S, Stancanelli B, Bonanno G, Fatuzzo P, Rapisarda F, Belluardo P, Signorelli SS, Heublein DM, Lainchbury JG, Leskinen HK, Bailey KR, Redfield MM and Burnett JC Jr. Circulating natriuretic peptide concentrations in patients with end-stage renal disease: role of brain natriuretic peptide as a biomarker for ventricular remodeling. Mayo Clin Proc (2001) 76: 1111–1119.
18. McCullough PA, Duc P, Omland T, McCord J, Nowak RM, Hollander JE, Herrmann HC, Steg PG, Westheim A, Knudsen CW, Storrow AB, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R and Maisel AS; Breathing Not Properly Multinational Study Investigators; B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. Am J Kidney Dis (2003) 41: 571–579.
19. Mueller C, Laule-Kilian K, Scholer A, Nusbaumer C, Zeller T, Staub D and Perruchoud AP: B-type natriuretic peptide for acute dyspnea in patients with kidney disease: Insights from a randomized comparison. Kidney Int (2005) 67: 278–284.
20. Takami Y, Horio T, Iwashima Y, Takiuchi S, Kamide K, Yoshihara F, Nakamura S, Nakahama H, Inenaga T, Kangawa K and Kawano Y; Diagnostic and prognostic value of plasma brain natriuretic peptide in non-dialysis-dependent CRF. Am J Kidney Dis (2004) 44: 420–428.
21. Wang TJ, Larson MG, Levy D, Benjamin EJ, Corey D, Leip EP and Vasan RS; Heritability and genetic linkage of plasma natriuretic peptide levels. Circulation (2003) 108: 13–16.
22. Raymond I, Groenning BA, Hildebrandt PR, Nilsson JC, Baumann M, Trawinski J and Pedersen F; The influence of age, sex and other variables on the plasma level of N-terminal pro brain natriuretic peptide in a large sample of the general population. Heart (2003) 89: 745–751.
23. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR and Burnett JC Jr; Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol (2002) 40: 976–982.
24. Tang WH, Girod JP, Lee MJ, Starling RC, Young JB, Van Lente F and Francis GS; Plasma B-type natriuretic peptide levels in ambulatory patients with established chronic symptomatic systolic heart failure. Circulation (2003) 108: 2964–2966.
25. James ML, Wang H, Venkatraman T, Song P, Lascola CD and Laskowitz DT: Brain natriuretic peptide improves long-term functional recovery after acute CNS injury in mice. J Neurotrauma (2010) 27: 217–228.
26. Zhang W, Li S, Visocchi M, Wang X and Jiang J: Clinical analysis of hyponatremia in acute craniocerebral injury. J Emerg Med (2010) 39: 151–157.
27. Lu DC, Binder DK, Chien B, Maisel A and Manley GT: Cerebral salt wasting and elevated brain natriuretic peptide levels after traumatic brain injury: 2 case reports. Surg Neurol (2008) 69: 226–269.
28. Sviri GE, Soustiel JF and Zaaroor M: Alteration in brain natriuretic peptide (BNP) plasma concentration following severe traumatic brain injury. Acta Neurochirwien (2006) 148: 529–533.
29. Lindahl AE, Stridsberg M, Sjöberg F, Ekselius L and Gerdin B: Natriuretic peptide type B in burn intensive care. J Trauma Acute Care Surg (2013) 74: 855–861.
30. de Leeuw K, Nieuwenhuis MK, Niemeijer AS, Eshuis H, Beerthuizen GI and Janssen WM: Increased B-type natriuretic peptide and decreased proteinuria might reflect decreased capillary leakage and is associated with a better outcome in patients with severe burns. Crit Care (2011) 15: R161.
31. Kia M, Cooley A, Rimmer G, MacDonald T, Barber K, Manion P, Shapiro B and Iddings D: The efficiency of B-type natriuretic peptide for early identification of blood loss in traumatic injury. Am J Surg (2006) 191: 353–357.
32. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A; and Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis (2009) 53: 982–992.
33. Knaus WA, Draper EA, Wagner DP and Zimmerman JE: APACHE II: a severity of disease classification system. Crit Care Med (1985) 13: 818–829.