Int J Clin Exp Med 2017;10(1):951-957
www.ijcem.com /ISSN:1940-5901/IJCEM0027088

Original Article

Application of combined test of blood, C-reactive protein, and prealbumin in the differential diagnosis of pathogens for children's upper respiratory tract infection

Yanzi Gan[1], Shaohua Tao[2], Huan Qi[3], Yinfeng Li[4]

[1]Department of Pediatrics, The First Hospital of Hohhot, Hohhot, Inner Mongolia, China; [2]Department of Pediatrics, Southern Medical University, Zhujiang Hospital, Guangzhou, Guangdong, China; [3]Department of Neonatology, The First Hospital of Hohhot, Hohhot, Inner Mongolia, China; [4]Department of Gynecology, The First Hospital of Hohhot, Hohhot, Inner Mongolia, China

Received March 2, 2016; Accepted August 17, 2016; Epub January 15, 2017; Published January 30, 2017

Abstract: Upper respiratory tract infection (URI) is a common childhood disease. Accurate determination of risk factors is of great significance for the follow-up treatment. Combinations of blood test, C-reactive protein, and prealbumin in the differential diagnosis of pathogens for children's URI were investigated in this study. 538 children with URI and 40 healthy children were included in this study. Children with URI were divided into bacterial infection group, viral infection group, and other pathogens group according to the results of blood test. C-reactive protein (CRP) and prealbumin (PA) were tested for all 578 included children. Results showed that in bacterial infection group, CRP was increased ($P < 0.05$) and PA was decreased ($P < 0.05$) compared with control. In viral infection group, CRP was decreased ($P < 0.05$), whereas PA showed no difference to control ($P > 0.05$). In other pathogens group, CRP was increased ($P < 0.05$) and PA showed no difference to control ($P > 0.05$). Combination test of blood, C-reactive protein, and prealbumin improved the specificity (72.3%) and sensitivity (95.3%) on the differential diagnosis of URI. In conclusion, combined test of blood, C-reactive protein, and prealbumin can improve the diagnosis specificity and sensitivity of URI, leading to accurate determination of pathogens of URI and providing scientific foundation for follow-up treatment.

Keywords: Blood test, C-reactive protein, prealbumin, children, upper respiratory infection

Introduction

Upper respiratory tract infection (URI) is a common childhood illness. It can happen anytime, but usually be seen in winter and spring. It can be caused by virus infection, bacterial infections or other pathogens infection such as mycoplasma infection. Determination of the pathogen is of great significance in the subsequent treatment [1-3]. Currently, in addition to symptoms and signs, the diagnosis of URI mainly relies on blood test. Diagnosis is made according to the changes in the total number of white blood cells and leukocyte ratio. However, the changes of white blood cells sometimes cannot represent URI and thereby lead to misdiagnosis. It is necessary to introduce other methods to improve the accuracy of diagnosis.

C-reactive protein (CRP) is an acute phase protein which increases in infection, inflammation, and trauma. It increases a few hours after inflammation and reaches a peak at 48 hours after inflammation, then returns to normal levels with the disappearance of risk factors and recovery of tissue function. CRP is a widely used acute phase protein that cannot be affected by radiotherapy, chemotherapy, or corticosteroids [4, 5]. Prealbumin (PA), also known as transthyretin, is another acute phase protein that decreases in infection, inflammation, and trauma. PA is the only acute phase protein that decreases [6-8]. In this study, combined test of blood, CRP, and PA was applied to 538 cases of URI to investigate the effect of combined test in the determination of pathogens of URI.

Table 1. Grouping

Group	BIG	VIG	OPIG	CG
Cases	274	143	121	40
Age	2.9±1.2	2.1±0.9	2.3±1.9	2.2±1.1
Male	101	69	71	20
Female	163	74	50	20
Total number of WBC ($\times 10^9$/L)	14.1±7.7	6.2±3.3	8.3±4.6	4~10
WBC proportion (%)	Neutrophils > 70%	Lymphocytes > 50%	Monoytes > 8%	Normal

Table 2. CRP and PA level in each group

Group	Cases	CRP result (mg/L)	PA result (mg/L)
BIG	274	42.67±13.49*	72.36±22.58*
VIG	143	6.14±3.27**	227.06±39.31***
OPIG	121	38.23±8.98*	169.33±42.4***
Control	40	5.45±1.21	190.71±27.22

*CRP and PA in VIG and OPIG, compared to control group ($P < 0.05$). **CRP in VIG, compared to control group ($P < 0.05$). ***CRP and PA in VIG and OPIG, compared to control group ($P > 0.05$).

Table 3. ROC curve parameters of combined detection of blood, CRP and PA in the diagnosis of bacterial infection

Parameters	Blood test	CRP	PA
AUC	0.924	0.862	0.813
Threshold	12.27	72	224
Sensitivity	0.821	0.762	0.7
Specificity	0.96	0.934	0.82
Positive likelihood value	28.64	12.16	3.6
Negative likelihood value	0.16	0.21	0.3

Material and methods

General information

538 children diagnosed with URI from the First Hospital of Hohhot, Hohhot, Inner Mongolia from October 2014 to September 2015 were included in this study. There were 237 males and 301 females with the mean age of 3.1±1.7 years old. All 538 cases met the diagnostic criteria for URI accordance to "Pediatrics" textbook. The patients were divided into bacterial infection group (BIG), viral infection group (VIG), and other pathogens infection group (OPIG) according to the symptoms, signs, and blood test results, i.e., the total number of white blood cells (WBC) (normal value: 8.0~10.0×10^9/L) and WBC proportion (**Table 1**). No significant differences were found in patients' height, weight, age, or body temperature ($P > 0.05$). 40 healthy outpatients (20 males and 20 females) at the same time period with an average age of 2.2±1.1 were used as controls (CG). All children were informed the research goals and methods in accordance with the requirements of the First Hospital of Hohhot, Hohhot, Inner Mongolia ethics committee.

Materials

Disposable vacuum blood collection tubes were purchased from Jiang Su Kangdian Pharmaceutical Co.; hematology analyzer (SYSMEX-800i) and its reagents, controls and standards were purchased from Japan Heath Kang; FIA8000 Immunoassay analyzers, C-reactive protein testing reagents, standards and controls, were purchased from Nanjing Jidan biological Technology Co.; prealbumin, Roche Cobas8000 automatic biochemical analyzer and reagents, standards and controls, were purchased from Roche diagnostics. Specimen collection, transport and testing were performed under ISO15189 quality requirements.

Methods

Blood test: 2 ml venous blood was collected to blood tubes containing EDTA-K2 anticoagulant for all children, mix thoroughly. SYSMEX-800i blood analyzer was used to do the blood test.

CRP testing: CRP was measured for all children admitted to hospital. 20 μl whole blood was transferred to a reaction tube containing 1 ml buffer with a micropipette and loaded to FIA8000 Immunoassay Analyzer (instrument has been completely calibrated, quality controlled within the controlled range). Results were ready in about 5 min.

Measurement of PA: PA was measured for all children admitted to hospital. 2 ml venous

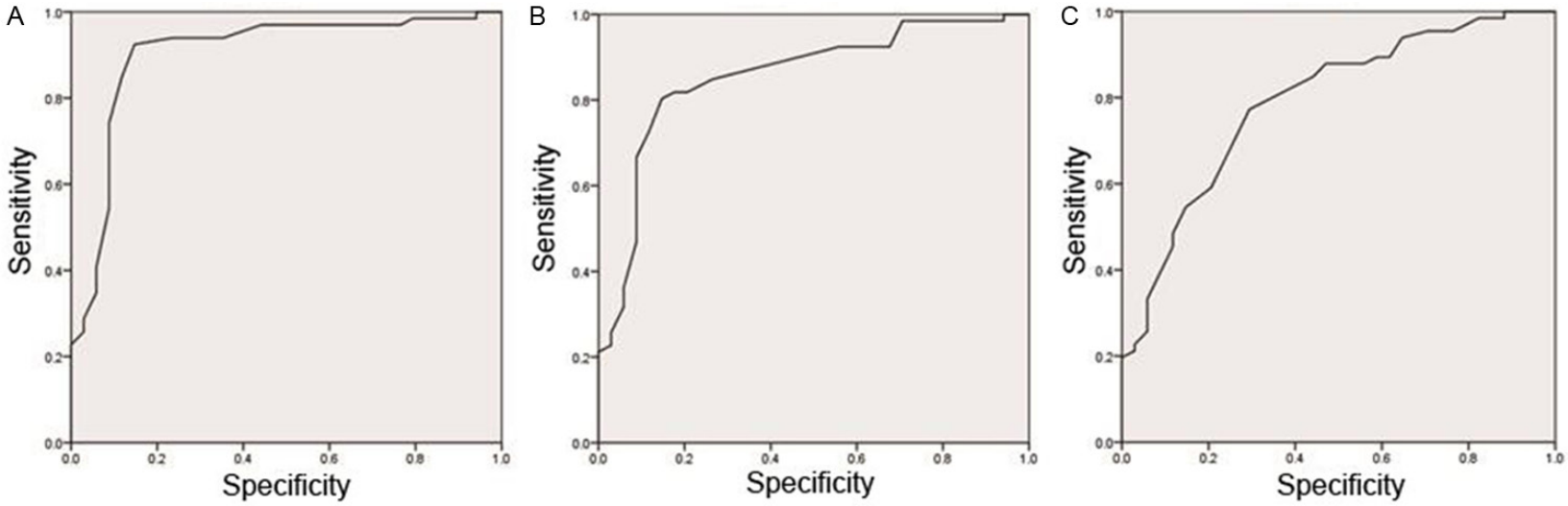

Figure 1. ROC curve for blood test, CRP and PA in the diagnosis of bacterial infection. A: Blood test, B: CRP; C: PA.

Table 4. ROC curve parameters of combined detection of blood, CRP and PA in the diagnosis of viral infection

Parameters	Blood test	CRP	PA
AUC	0.781	0.733	0.712
Threshold	8.39	11	128
Sensitivity	0.736	0.778	0.729
Specificity	0.843	0.811	0.795
Positive likelihood value	27.81	11.89	3.2
Negative likelihood value	0.12	0.32	0.36

Table 5. ROC curve parameters of combined detection of blood, CRP and PA in the differential diagnosis of viral infection and bacterial infection

Parameters	Blood test	CRP	PA
AUC	0.799	0.682	0.726
Threshold	11.3	32	163
Sensitivity	0.716	0.677	0.705
Specificity	0.825	0.72	0.689
Positive likelihood value	6.3	1.743	1.821
Negative likelihood value	0.361	0.628	0.572

blood was drawn and transferred into conventional biochemical tube without anticoagulant, centrifuged at 3000 rpm for 20 minutes. 500 μl serum was transferred to Roche cuvette and loaded into Roche Cobas8000 automatic biochemical analyzer (instrument has completed calibration, quality control within the controlled range). Normal reference range is 220~400 mg/L.

Statistical analysis

SPSS19.0 software was used for statistical analysis. One-Way ANOVA analysis was used for comparisons between groups. ROC curve was used to evaluate the effect of blood test, CRP measurement, and PA measurement on diagnosis. $P < 0.05$ represents statistically different.

Results

CRP test

Results of CRP test were shown in **Table 2** for each group. CRP in BIG was significantly higher than that in VIG (P = 0.000), but showed no significant difference when compared with that in OPIG (P = 0.280). Compared with control group, CRP in BIG and OPIV was significantly higher (P = 0.000) (P = 0.000), however, CRP in VIG showed no significant difference (P = 0.057).

PA test results

PA in BIG was significantly lower than that in VIG and OPIG (P = 0.000) (P = 0.000). Compared with control group, PA in BIG was significantly lower (P = 0.000). However, no significant difference of PA was found in VIG or OPIG when compared with that in control group (P = 0.077).

Application of combined test of blood, CRP and PA in the differential diagnosis of children URI

ROC curve parameters of combined detection of blood, CRP and PA in the diagnosis of bacterial infection were shown in **Table 3** with individual ROC curve presented in **Figure 1**. The results showed that combined detection of blood, CRP and PA had higher accuracy in the diagnosis of bacterial infection. ROC curve parameters of combined detection of blood, CRP and PA in the diagnosis of viral infection were shown in **Table 4** with individual ROC curve presented in **Figure 2**. Results showed that combined detection of blood, CRP and PA had a better effect in the diagnosis of viral infection. ROC curve parameters of combined detection of blood, CRP and PA in the differential diagnosis of bacterial infection and viral infection were shown in **Table 5** with individual ROC curve presented in **Figure 3**. The results showed that combined detection of blood, CRP and PA had some positive effects in the differential diagnosis of bacterial infection and viral infection.

Discussion

URI is a common set of general acute respiratory infectious diseases, including the common cold, viral pharyngitis, laryngitis, herpangina, pharynx conjunctival fever, and bacterial throat-tonsillitis. URI has a higher prevalence and can be seen in all years around, but more cases were seen in winter and spring [9, 10]. Because the respiratory system of children especially infants have not yet fully developed, and young children do not have fully functional immune system, so they are vulnerable to infections of bacteria, viruses and other pathogens such as mycoplasma. According to incomplete statistics, URI accounts for about 70% of hospital outpatients. Quickly detection of pathogens of

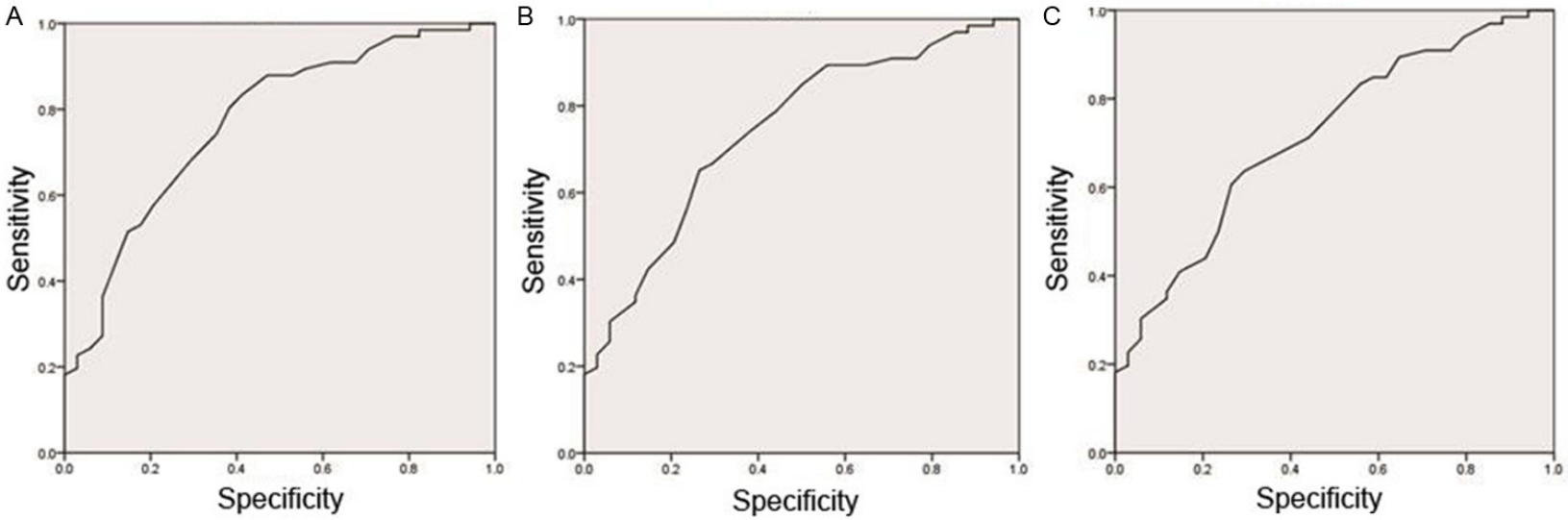

Figure 2. ROC curve for blood test, CRP and PA in the diagnosis of viral infection. A: Blood test, B: CRP; C: PA.

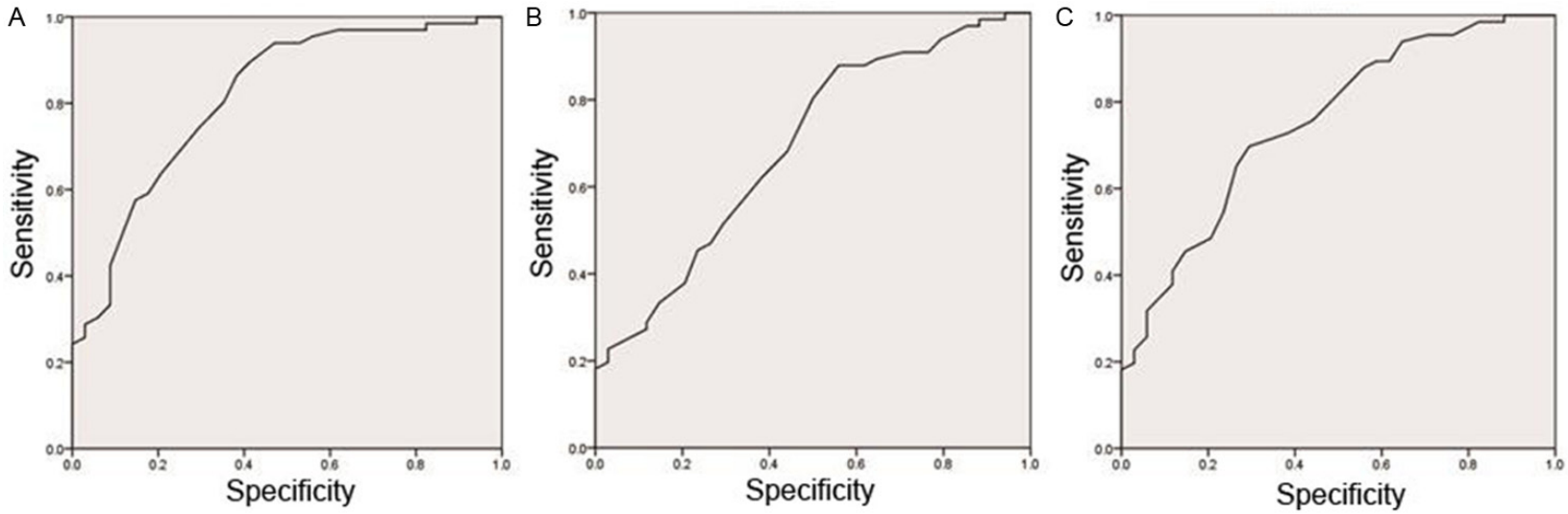

Figure 3. ROC curve for blood test, CRP and PA in the differential diagnosis of viral infection and bacterial infection. A: Blood test, B: CRP; C: PA.

URI is of great significance for follow-up treatment. Changes of numbers of leukocytes and leukocyte classification were used to determine the infection of virus, bacteria or other pathogens. However, the leukocytes are susceptible to the age, the body's immunity, mood, body activity, pain, and other factors [11], so depending on a single blood test is prone to misdiagnosis, and other tests are required to provide the basis for clinical judgment by the physician. Currently, blood test plus CRP detection was used to diagnose URI in our hospital. The total number of blood leukocytes, changes of leukocyte classification and elevation of CRP were used to determine whether URI is caused by viruses, bacteria or any other pathogens infection. Studies showed that PA is a negative acute phase protein and decreases expression in inflammation. So it is possible to check the existence of inflammation and infection through measuring the expression of PA. In this study, blood test, CRP test, and PA test were performed on 538 URI patients. The effect of combination of blood test, CRP test, and PA test on determination of pathogens of URI was investigated.

Compared with the traditional blood test, as a positive acute phase protein, CRP increases usually in 6 to 8 hours after inflammation, CRP can be increased up to several times in a short period of time, and decreased rapidly after inflammation is controlled since its half-life is only 4 to 5 hours [12, 13]. In this study, we found that, CRP was elevated in URI caused by bacterial infections and other pathogens infections, but showed no change in URI caused by virus infection. This can be used as a hint to identify whether the URI is caused by bacterial infection or viral infection or other pathogens infection.

PA is a glycoprotein synthesized in the liver and is also a negative acute phase protein [14-16]. It reduces rapidly when the body has bacterial infection, usually in 6 to 8 hours after inflammation. When the body is recovering from infection, PA gradually increases to normal level [17-20]. In this study, we found that PA decreased in URI caused by bacterial infection, but showed no significant change in URI caused by virus infection and other pathogens infection in children. Through blood test, CRP test, and PA test, we found that CRP increased and PA decreased in URI caused by bacterial infection; CRP decreased and PA did not change in URI caused by virus infection; CRP increased and PA did not change in URI caused by other pathogens. Combination of blood test, CRP test, and PA test, can improve the differential diagnosis of URI caused by bacterial infections, viral infections or other pathogens, providing the basis for diagnosis and treatment by clinical physicians.

In conclusion, this study showed that combination of blood test, CRP test and PA test can determine the types of URI pathogens, make more accurate determination of causes, and provide better treatment plans.

Acknowledgements

The National High Technology Research and Development Program (863 Program) Sub Project Funding (2014AA022304).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yinfeng Li, Department of Gynecology, The First Hospital of Hohhot, No. 150 South Second Ring Road, Yuquan District, Hohhot, Inner Mongolia, China. Tel: +86-0471-5281407; Fax: +86-0471-5281407; E-mail: wangxiaofangkl@sina.com

References

[1] Calvo C, Cuevas MT, Pozo F, Garcia-Garcia ML, Molinero M, Calderon A, Gonzalez-Esguevillas M, Perez-Sautu U and Casas I. Respiratory Infections by Enterovirus D68 in Outpatients and Inpatients Spanish Children. Pediatr Infect Dis J 2016; 35: 45-49.

[2] Onal Z, Cullu-Cokugras F, Isildak H, Kaytaz A, Kutlu T, Erkan T and Dogusoy G. Evaluation of the likelihood of reflux developing in patients with recurrent upper respiratory infections, recurrent sinusitis or recurrent otitis seen in ear-nose-throat outpatient clinics. Turk J Pediatr 2015; 57: 258-265.

[3] Blyer K and Hulton L. College students, shared decision making, and the appropriate use of antibiotics for respiratory tract infections: A systematic literature review. J Am Coll Health 2016; 64: 334-341.

[4] Bi Y, Min M, Shen W, Deng P, Du Q, Dong M and Liu Y. Prognostic value of high sensitivity C-reaction protein in non-insulin dependent diabe-

tes mellitus patients with non-alcoholic fatty liver disease. Int J Clin Exp Pathol 2015; 8: 8494-8499.
[5] Akaboshi I. Elevation of Serum Levels of High-Sensitivity Procalcitonin, C-reactive Protein, and Amyloid A in a Prepubertal Child with Mumps Orchitis. Clin Lab 2015; 61: 1795-1798.
[6] Agilli M and Ekinci S. Value of prealbumin in assessment of nutrition for critically ill patients. Turk J Med Sci 2015; 45: 991.
[7] Codullo V, Cereda E, Klersy C, Cavazzana I, Alpini C, Bonardi C, Turri A, Franceschini F, Caccialanza R, Montecucco C and Caporali R. Serum prealbumin is an independent predictor of mortality in systemic sclerosis outpatients. Rheumatology (Oxford) 2016; 55: 315-319.
[8] Li B, Liu HY, Guo SH, Sun P, Gong FM and Jia BQ. Impact of early enteral and parenteral nutrition on prealbumin and high-sensitivity C-reactive protein after gastric surgery. Genet Mol Res 2015; 14: 7130-7135.
[9] Tramuto F, Maida CM, Napoli G, Mammina C, Casuccio A, Cala C, Amodio E and Vitale F. Burden and viral aetiology of influenza-like illness and acute respiratory infection in intensive care units. Microbes Infect 2016; 18: 270-276.
[10] Hakim H, Dallas R, Zhou Y, Pei D, Cheng C, Flynn PM, Pui CH and Jeha S. Acute respiratory infections in children and adolescents with acute lymphoblastic leukemia. Cancer 2016; 122: 798-805.
[11] Pedersen HP, Haastrup EK, Helweg-Larsen J, Ifversen M and Fischer-Nielsen A. Severely elevated C-reactive protein accompanied by prolonged high fever and leukocytosis in a healthy peripheral blood stem cell donor: an atypical granulocyte-colony-stimulating factor reaction? Transfusion 2015; 55: 2771-2772.
[12] Wu J, Jin YU, Li H, Xie Z, Li J, Ao Y and Duan Z. Evaluation and significance of C-reactive protein in the clinical diagnosis of severe pneumonia. Exp Ther Med 2015; 10: 175-180.
[13] Vashist SK, Venkatesh AG, Marion Schneider E, Beaudoin C, Luppa PB and Luong JH. Bioanalytical advances in assays for C-reactive protein. Biotechnol Adv 2016; 34: 272-290.
[14] Caccialanza R, Palladini G, Klersy C, Cereda E, Bonardi C, Quarleri L, Vadacca G, Albertini R and Merlini G. Serum prealbumin: an independent marker of short-term energy intake in the presence of multiple-organ disease involvement. Nutrition 2013; 29: 580-582.
[15] Davis CJ, Sowa D, Keim KS, Kinnare K and Peterson S. The use of prealbumin and C-reactive protein for monitoring nutrition support in adult patients receiving enteral nutrition in an urban medical center. J Parenter Enteral Nutr 2012; 36: 197-204.
[16] Xie Q, Zhou Y, Xu Z, Yang Y, Kuang D, You H, Ma S, Hao C, Gu Y, Lin S and Ding F. The ratio of CRP to prealbumin levels predict mortality in patients with hospital-acquired acute kidney injury. BMC Nephrol 2011; 12: 30.
[17] Deng J, Wu Q, Liao Y, Huo D and Yang Z. Effect of statins on chronic inflammation and nutrition status in renal dialysis patients: a systematic review and meta-analysis. Nephrology (Carlton) 2012; 17: 545-551.
[18] Pellicane AJ, Millis SR, Barker KD, Temme KE, Sayyad A, Oswald MC and Roth EJ. The effect of protein and calorie intake on prealbumin, complications, length of stay, and function in the acute rehabilitation inpatient with stroke. NeuroRehabilitation 2013; 33: 367-376.
[19] Fujii T, Yajima R, Takada T, Sutoh T, Morita H, Yamaguchi S, Tsutsumi S and Kuwano H. Serum albumin and prealbumin do not predict recurrence in patients with breast cancer. Anticancer Res 2014; 34: 3775-3779.
[20] Badjatia N, Monahan A, Carpenter A, Zimmerman J, Schmidt JM, Claassen J, Connolly ES, Mayer SA, Karmally W and Seres D. Inflammation, negative nitrogen balance, and outcome after aneurysmal subarachnoid hemorrhage. Neurology 2015; 84: 680-687.