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Original Research

Expression levels of blood platelet and C-reactive protein in patients with severely pneumonic and their predictive values for efficacy

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Abstract: This paper aims to detect the expression levels of blood platelet (PLT) and C-reactive protein (CRP) in severely pneumonic patients and analyze their correlation. For this purpose, eighty-one severely pneumonic patients were retrospectively selected as an observation group and 106 healthy people as a control group. Pretreatment and post-treatment expression levels of PLT and CRP, their predictive values for efficacy, and correlation of PLT, CRP, and PSI scores in observation group after treatment were analyzed. Before treatment, the expression level of PLT in the observation group was higher than the control group ($P< 0.05$). In the observation group, the expression level of PLT after treatment was significantly lower than that before treatment ($P< 0.05$). Before treatment, the expression level of CRP in the observation group was higher than the control group ($P< 0.05$). In the observation group 1) the pretreatment PLT expression level was higher than that in the control group; 2) the post-treatment PLT expression level was significantly lower than that in the pretreatment one; 3) the pretreatment CRP expression level was higher than that in the control group; and 4) the post-treatment CRP expression level was significantly lower than the pretreatment one (All P-values< 0.05). Based upon the efficacy, the observation group was divided into an effective group and an invalid group. The post-treatment expression levels of PLT and CRP in the effective group were lower than those in the invalid group ($P< 0.05$). Based upon the ROC curve, the area under curves (AUC) of PLT, CRP, and joint detection were 0.843, 0.864, and 0.886, respectively. When the cut-off point was > 0.579, the best specificity and sensitivity were 98.44 and 70.59%, respectively. According to the Pearson test, positive correlations existed between PLT and CRP, between PLT and PSI scores, and between CRP and PSI scores. In conclusion, the expression levels of PLT and CRP in severely pneumonic patients might be used to evaluate the efficacy and conducive to detection of the disease, which have high application values in clinic.

Key words: Severe pneumonia; Blood platelet; C-reactive protein; ROC curve; Efficacy prediction.

Introduction

As an inflammatory disease of pulmonary tissue, the pneumonia has a high incidence rate through the world; most patients are children and elders (1, 2). It is estimated that developing countries have 157 million new cases annually, of which 7-13% should be hospitalized (3). 1.2-10% of the hospitalized patients have severe pneumonia being hospitalized at ICU (4). The in-hospital mortality rate is 46.51% indicating severe sepsis, multiple organ failure, and septicemia (5, 6). Severely pneumonic patients have a high mortality rate, although they can be treated by antibiotics. Nearly 12-36% of ICU patients die in a short time possibly because of more serious complications or because drug-resistant strains during antibiotic therapy result in poor efficacy (7, 8). Therefore, finding reliable biomarkers to evaluate the patients' conditions is being strongly recommended. Severe pneumonia is mainly caused by the pulmonary infection leading to severe inflammatory responses (9, 10). The Blood level of platelet (PLT) can be used as a sensitive indicator for the inflammations; for example, it has been showed that it increases with aggravation of lower respiratory tract infection in children (11) and of pulmonary tuberculosis (12). On the other hand, C-reactive protein (CRP) is an acute phase reactive protein which would be synthesized by liver cells. CRP concentration is low in the blood of healthy people, but it increases rapidly by infection and tissue damages (13). In a recent study, CRP which may be a good predictor of cardiovascular diseases is related to inflammatory responses and atherosclerosis (14). A study shows that its expression level distinguishes specific virus and bacterial infections (15). PLT and CRP have been reported to be differentially expressed in pneumonic patients, and they have certain diagnostic predictive values (16, 17). Nonetheless, few reports exist on whether the expression levels of PLT and CRP can evaluate the efficacy

on severely pneumonic patients. In the present study, we investigated the expression levels of PLT and CRP in severely pneumonic patients in order to survey their values as efficacy indicators.

Materials and Methods

Clinical data

Eighty-one severe pneumonic patients (50 male and 31 female; average age = 52.44±13.75 years old), referred to Baoji Traditional Chinese Medicine Hospital from October 2014 to August 2016, were retrospectively selected as the observation group. As the control group, 106 healthy people (61 male and 45 female; average age = 51.83±11.74 years old), examined physically simultaneously, were selected. This study was approved by the Medical Ethics Committee of the Baoji Traditional Chinese Medicine Hospital. All the patients signed agreement sheets.

Inclusion and exclusion criteria

Inclusion criteria: Patients who met the diagnostic criteria for severe pneumonia proposed in guidelines of Respiratory Society, Chinese Medical Association in 2016 (18) were included. Patients who met 1 main criterion or ≥ 3 secondary criteria were diagnosed with severe pneumonia. The main criteria were as follows: 1) patients who required tracheal intubation for mechanical ventilation therapy; 2) patients who still required vasoactive drug therapy after aggressive fluid resuscitation (AFR) for septic shock. Secondary criteria were as follows: 1) patients with a respiratory frequency ≥ 30 times/min; 2) patients with an oxygenation index ≤ 250 mmHg; 3) patients with multilobar infiltration; 4) patients with consciousness disorder and/or disorientation; 5) patients with blood urea nitrogen ≥ 7.14 mmol/L; 6) patients with a systolic blood pressure < 90 mm Hg. Patients who required AFR were included; patients who had not taken immunosuppressive drugs recently; patients who had not been prescribed by antibiotics recently; patients with complete clinical data and definite diagnosis. Exclusion criteria: complication with other pulmonary diseases; malignant tumors; severe cardiovascular and cerebrovascular diseases; inflammations in other organs; pregnancy or lactation.

Reagents and instruments

Cefodizime sodium injection (Shandong Luya Pharmaceutical Co., Ltd., SFDA Approval Number: H20010044), a CRP test kit (Shanghai Kindu Biotechnology Co., Ltd., JD-0604), a fully automatic biochemical analyzer (Beckman Coulter, Inc., dxc800), a fully automatic hematology analyzer (Beckman Coulter, Inc., dxH800).

Treatment methods

After admission, 250 mL glucose 5% plus cefodizime sodium 2 g were injected intravenously once per day for the observation group, and they were treated by bronchospasm relief, cough relief, asthma relief, phlegm elimination, infection prevention, correction of internal environment disturbance, and oxygen inhalation for 72 hours. According to patients' conditions, non-invasive positive pressure ventilation therapy might be applicate if necessary.

Detection methods

5 mL fasting venous blood was sampled in three subsequent days since admission at 7:00 am; it was poured into an anticoagulant tube and a vacuum drying tube. The tubes were centrifuged at 3,000 rpm/min over 10 minutes. The serum and plasma were stored at -80 °C. PLT was detected in the plasma by the hematology analyzer. The collected plasma was poured into a test tube filled with a diluent. The test tube was shaken to mix well; it was placed under the sampling needle, then the test was started. CRP was detected in the serum by the biochemical analyzer using immunoturbidimetry according to the kit instructions. 30 μl serum was shaken and placed into the instrument's test plate, and an empty cuvette was placed next to it.

Observational indexes

Main observational indexes: pre- and post-treatment expression levels of PLT and CRP in the observation group.

Secondary observational indexes: clinical data of the patients in the two groups; clinical symptoms, post-treatment signs and efficacy (effective and invalid) in the observation group. According to the post-treatment expression levels of PLT and CRP, the receiver operating characteristic (ROC) curve was used to analyze the diagnostic values and optimal cut-off values of PLT and CRP for efficacy in the severely pneumonic cases. Pearson test analyzed the correlation of PLT, CRP and PSI scores in the post-treatment serum in the observation group.

Evaluation criteria for efficacy

Based upon the evaluation criteria for efficacy proposed in guidelines of Respiratory Society, Chinese Medical Association in 2016, the efficacy was categorized into effective and invalid (18). Posttreatment stable disease (SD) was considered as effective. SD should meet all the following five indexes: 1) body temperature ≤ 37.8 °C; 2) heart rate ≤ 100 bpm; 3) respiratory frequency ≤ 24 times/min; 4) systolic blood pressure ≥ 90 mmHg; 5) oxygen saturation ≥ 90% or PaO_2≥ 60 mmHg under suction air condition. Invalid: 1) progressive pneumonia: during 72 hours of admission, the disease progressed to acute respiratory failure and the patients required mechanical ventilatory support; the disease progressed to septic shock and the patients required vasoactive drug therapy; 2) no response to treatment: 72 hours after treatment, the patients failed to reach standards for SD.

Statistical analysis

To analyze statistically and to plot figures, we used SPSS20.0 (SPSS Inc., Chicago, IL, USA) medical statistical analysis software and Graph Pad Prism 7 (Graph Pad Software, Inc., San Diego, CA, USA), respectively. Countable data were expressed by ratio (%), and tested by Chi-square. Measurable data, conformed its normal distribution, were expressed by Means±SD. Independent samples t-test compared between the groups, whereas paired samples t-test compared within them and represented by 't'. Pearson test analyzed the corre-

lation of PLT, CRP and PSI scores in the post treatment observation group, and ROC curve evaluated the diagnostic values of PLT and CRP for efficacy. P-value < 0.05 indicated significant differences.

Results

Clinical data

According to the clinical data in the observation and control groups, significant differences existed between the groups in terms of ventilatory reserve percentage, residual volume, and forced vital capacity (P< 0.05) but not in terms of gender, age, BMI, body temperature, previous medical history (hypertension, diabetes, hyperlipidemia), history of smoking, history of alcoholism, and residence (P> 0.05). More details are shown in Table 1.

Pre and post-treatment expression levels of PLT and CRP in observation and control groups

The pretreatment PLT expression level in the observation group (415.42±76.73) was higher than that in the control group (135.07±42.36) (P< 0.05). In the observation group, the post-treatment PLT expression level (267.77±56.07) was significantly lower than the pretreatment one but higher than that in the control group (P< 0.05). The pretreatment CRP expression level in the observation group (56.75±22.46) was higher than that in the control group (4.45±2.34) (P< 0.05). In the observation group, the post-treatment CRP expression level (28.07±14.52) was significantly lower than the pretreatment one but higher than that in the control group (P< 0.05). More details are shown in Figure 1.

Expression levels of PLT and CRP in effective and invalid groups

Based upon the evaluation criteria, 64 effective cases and 17 invalid cases existed in the observation group after treatment. According to the efficacy, the patients were categorized into the effective group (n=64) and the invalid group (n=17). The post-treatment expression levels of PLT and CRP in the effective group were lower than those in the invalid group (P< 0.05). More details

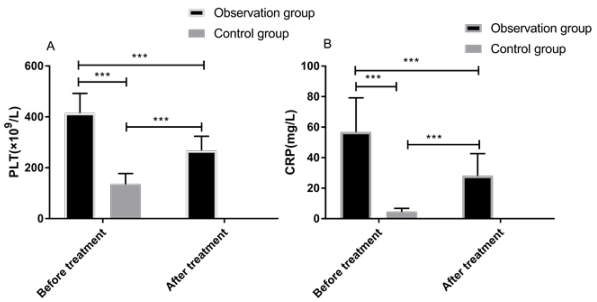

Figure 1. PLT and CRP in pre- and post-treatment in the two groups. **A:** PLT in the observation group before treatment was significantly higher than the control group (t=31.819, P< 0.001); PLT in the observation group after treatment was significantly lower than that before treatment (t=13.095, P< 0.001); PLT after treatment in the observation group was significantly lower than that after treatment (t=18.439, P< 0.001). **B:** CRP in the observation group before treatment was significantly higher than the control group (t=23.825, P< 0.001); CRP in the observation group after treatment was significantly lower than that before treatment (t=10.184, P< 0.001); CRP in the observation group after treatment was significantly lower than that after treatment (T=16.484, P< 0.001). *** means P< 0.001.

Table 1. Clinical data that were achieved in current research.

Factors		Observation group (n=81)	Control group (n=106)	t/χ^2 value	P-value
Gender					
	Male	50(61.73)	61(57.55)	0.333	0.564
	Female	31(38.27)	45(42.45)		
Age (Years)		52.44±13.75	51.83±11.74	0.327	0.744
BMI(kg/m^2)		20.37±4.87	21.24±5.13	1.175	0.242
Body temperature (°C)		38.17±0.71	36.53±0.35	1.179	0.240
Past medical history					
Hypertension		21(25.93)	27(25.47)	0.005	0.944
Diabetes		17(20.99)	22(20.75)	0.002	0.969
Hyperlipidemia		14(17.28)	19(17.92)	0.013	0.909
History of smoking					
	Yes	37(45.68)	48(45.28)	0.003	0.957
	No	44(54.32)	58(54.72)		
History of alcoholism					
	Yes	21(25.93)	27(25.47)	0.005	0.944
	No	60(74.07)	79(74.53)		
Residence					
	City	58(71.60)	75(70.75)	0.016	0.127
	Countryside	23(28.40)	31(29.25)		
Ventilatory reserve percentage (%)		89.37±0.89	94.41±1.47	27.264	<0.001
Residual volume (L)		1.22±0.32	1.38±0.41	2.901	0.004
Forced vital capacity (mL)		2242±53	2871±93	54.466	<0.001
PSI score		142.36±17.18			

Table 2. Expression levels of PLT and CRP in effective and invalid groups.

Groups	Effective group (n=64)	Invalid group (n=17)	t-value	P-value
PLT(×10^9/L)	259.58±51.27	331.04±59.52	8.968	<0.001
CRP(mg/L)	22.67±12.33	40.78±18.96	6.343	<0.001

Table 3. The ROC curve data obtained from this experiment.

Indicators	AUC	95%CI	Specificity	Sensitivity	Youden index	Cut-off
PLT	0.843	0.737~0.949	76.56%	76.47%	53.03%	>287.766
CRP	0.864	0.745~0.983	92.19%	70.59%	62.78%	>45.242
Joint detection	0.886	0.781~0.993	98.44%	70.59%	68.19%	>0.579

are shown in Table 2.

Diagnostic values of PLT and CPR for efficacy

According to the expression levels of PLT and CRP in the effective and invalid groups, the ROC curve was plotted to analyze their diagnostic values for efficacy on severe pneumonia. The area under the curve (AUC) of PLT was 0.843, 95%CI was 0.737~0.949, the specificity was 76.56%, the sensitivity was 76.47%, and the cut-off was 287.766. Those of CRP were 0.864, 0.745~0.983, 92.19, 70.59% and 45.242, respectively. Those of joint detection were 0.886, 0.781~0.993, 98.44, 70.59% and 0.579, respectively. More details are shown in Table 3 and Figure 2.

The AUC of PLT was 0.843, 95% CI was 0.737~0.949, the specificity was 76.56%, the sensitivity was 76.47%, and the cut-off was 287.766. Those of CRP were 0.864, 0.745~0.983, 92.19, 70.59% and 45.242, respectively. Those of joint detection were 0.886, 0.781~0.993, 98.44, 70.59% and 0.579, respectively.

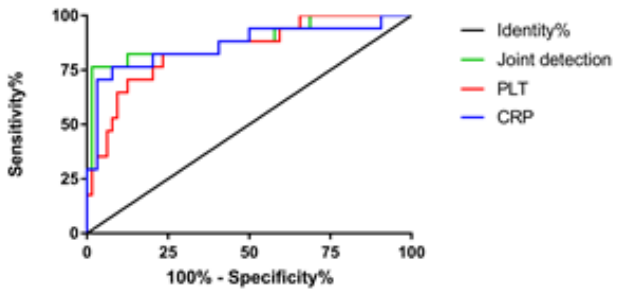

Figure 2. ROC curves of PLT and CPR in predicting efficacy on severe pneumonia.

Correlation of PLT with CRP in the observation group

According to Pearson correlation analysis was used to analyze the correlation of PLT, CRP and PSI score. There was a positive correlation between PLT and CRP (r=0.664, P< 0.001), a positive correlation between PLT and PSI scores (r=0.721, P< 0.001), and a positive correlation between CRP and PSI scores (r=0.735, P< 0.001). As shown in Figure 3.

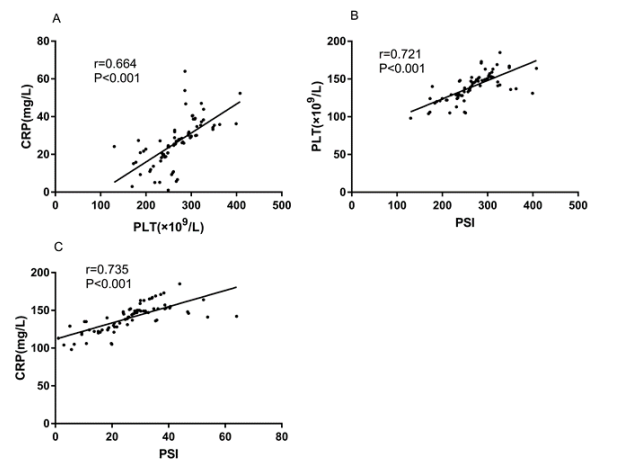

Figure 3. Correlation between PLT and CRP. A: There was a positive correlation between PLT and CRP expression (r=0.664, P< 0.001). B: PLT was positively correlated with PSI score (r=0.721, P< 0.001). C: CRP was positively correlated with PSI score (r=0.735, P< 0.001).

Discussion

Severe pneumonia as a common disease in ICU today is the leading cause of death from infectious diseases whose incidence rates have been increasing year by year in recent years (19, 20). Bacteria, fungi and other pathogens induce large enrichment of neutrophils and macrophages which release a large number of inflammatory factors, and cascade reactions of the factors aggravate inflammations, thus resulting in severe pneumonia (21). Patients with the disease suffer from severe pulmonary lesions at the onset. In addition, infections that are not limited in the lung cause systemic inflammatory responses, thereby leading to multiple organ failure and acute respiratory distress syndrome (22, 23).

PLT, which is found to be involved in pulmonary tuberculosis and tumors, predicts the prognosis of diseases (24-26). In this study, the expression level of PLT in the observation group was significantly higher than the control group before treatment, possibly because neutrophils in patients with pneumonia were enriched and released a large number of inflammatory mediators, causing PLT to be higher than normal people. According to Huang et al (27), the expression level of PLT in children with severe pneumonia was significantly higher than healthy children. The age of their samples is different from ours, but their results are similar to ours, possibly indicating that the expression level of PLT in children, middle-aged and elderly patients with severe pneumonia is higher than normal people. However, in the observation group, the expression level of PLT after treatment was significantly lower than that before treatment (P< 0.05), which may be because the antibacterial effect of antibiotics reduced inflammations and infections. Therefore, the expression level of PLT is likely to be used to evaluate the efficacy of severe pneumonia. CRP is a predictor recently found to be closely related to the death and prognosis of patients with communi-

ty-acquired pneumonia. CRP on the 3rd day is related to the 30-day mortality rate of hospitalized patients, so failure to reduce it is not conducive to the prognosis of the patients (28).

In this study, the expression level of CRP in the observation group was significantly higher than the control group before treatment, speculated that inflammatory cells in patients with pneumonia infiltrate and release endogenous neurotransmitters to stimulate liver cells, thus accelerating the synthesis of CRP. In a study, the serum CRP level of the patients diagnosed with pneumonia was higher than that of the patients with chronic obstructive pulmonary disease or acute bronchitis. Their findings are similar to ours, indicating that the expression level of CRP could be used as a diagnostic standard for severe pneumonia. In the observation group, the expression level of CRP after treatment was significantly lower than that before treatment ($P< 0.05$), which may be because the antibacterial effect of antibiotics reduced patients' inflammations, weakened the infiltration of inflammatory cells and reduced the expression level of CRP. This indicates that CRP may be a potential diagnostic indicator for the efficacy of severe pneumonia (29-40).

According to the Pearson correlation analysis, the expression levels of PLT and CRP were positively correlated, suggesting that there might be a close relationship between PLT and CRP. It is suspected that the increase of PLT activates platelets to be involved in inflammatory responses, thereby aggravating inflammations. The expression level of CRP as an inflammatory indicator increases with the aggravation of inflammations. At the same time, regarding the relationship of PLT, CRP and the PSI score of the severe index of pneumonia, it was found that there was a positive correlation between PLT, CRP and PSI score. Exacerbated inflammation leads to worsening of the disease, which is also in line with our view that PLT and CRP will increase with the inflammation.

Recently, there have been studies on the expression level of PLT or CRP alone in pneumonitis, and their expression levels are used as indicators for the severity and prognosis of the disease. In some previous studies, ROC curves have also been adopted to find the predictive value of CRP in pneumonia. However, the ROC curve is rarely used to evaluate efficacy. Therefore, the patients were divided into effective and invalid groups according to the efficacy in this study. According to the ROC curve, the AUC of PLT was 0.843, that of CRP was 0.864 and that of joint detection was 0.886. When the cut-off point was > 0.579, the best specificity and sensitivity were 98.44 and 70.59% respectively, which were significantly better than those of single detection. Therefore, the expression levels of PLT and CRP could be used as diagnostic indicators for the efficacy on patients with severe pneumonia.

However, there are limitations to this study. Firstly, whether the drugs and therapeutic schemes used in this study affected the expression levels of PLT and CRP were not studied. Secondly, there may be errors in the efficacy evaluation due to the short treatment time. Finally, the relationship between PLT and CRP in this study remains unclear. Therefore, it is hoped that relevant basic experiments will be added in future studies to explore their relationship and verify the results of this study.

In summary, based upon the positive correlations between PLT, CRP and PSI, we concluded that exacerbated inflammation leads to worsening of the disease. The expression levels of PLT and CRP can be used as diagnostic indicators for the efficacy on severely pneumonic patients. We suggest investigating the relationship between PLT and CRP in future studies.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Saussereau J, Reboux G, Sfeir G, Dalphin JC. Two cases of hot tub lung disease: Environmental investigations. Rev Mal Respir 2018; 36: 204-208.

2. Baqir M, White D, Ryu JH. Emphysematous changes in hypersensitivity pneumonitis: A retrospective analysis of 12 patients. Respir Med Case Rep 2018; 24: 25-29.

3. Rudan I, Tomaskovic L, Boschi-Pinto C, Campbell H. Global estimate of the incidence of clinical pneumonia among children under five years of age. Bull World Health Organ 2004; 82: 895-903.

4. Torres A, Chalmers JD, Dela Cruz CS, Dominedò C, Kollef M, Martin-Loeches I, Niederman M, Wunderink RG. Challenges in severe community-acquired pneumonia: a point-of-view review. Intensive Care Med 2019; 45: 159-171.

5. Mo X, Tang H, Zeng L, Lu H, Guo L, Ma Z. The value of determination of serum cholinesterase levels in judgment of severity and prognosis in patients with severe pneumonia. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2016; 28: 38-43.

6. Pius AKA, Ray A. Factors influencing severe community-acquired pneumonia few points to ponder. Lung India 2018; 35: 536-537.

7. Torres A, Sibila O, Ferrer M, Polverino E, Menendez R, Mensa J, Gabarrús A, Sellarés J, Restrepo MI, Anzueto A, Niederman MS, Agustí C. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. JAMA 2015; 313: 677-686.

8. Espinoza R, Silva JRLE, Bergmann A, de Oliveira Melo U, Calil FE, Santos RC, Salluh JIF. Improvement of antibiotic therapy and ICU survival in severe non-pneumococcal community-acquired pneumonia: a matched case-control study. J Crit Care 2018; 50: 82-86.

9. Voudoukis E, Karmiris K, Koutroubakis IE. Multipotent role of platelets in inflammatory bowel diseases: a clinical approach. World J Gastroenterol 2014; 20: 3180-3190.

10. He YJ, Mai CY, Chen LJ, Zhang XM, Zhou JY, Cai M, Chen YX, Qi QL, Yang ZD. Clinical characteristics and risk factors in pregnancy with severe community-acquired pneumonia. Zhonghua Fu Chan Ke Za Zhi 2018; 53: 842-848.

11. Unsal E, Aksaray S, Köksal D, Sipit T. Potential role of interleukin 6 in reactive thrombocytosis and acute phase response in pulmonary tuberculosis. Postgrad Med J 2005; 81: 604-607.

12. Almirall J, Bolíbar I, Toran P, Pera G, Boquet X, Balanzó X, Sauca G. Contribution of C-Reactive Protein to the Diagnosis and Assessment of Severity of Community-Acquired Pneumonia. Chest 2004; 125: 1335-1342.

13. Nordestgaard BG, Zacho J. Lipids, atherosclerosis and CVD risk: is CRP an innocent bystander? Nutr Metab Cardiovasc Dis 2009; 19: 521-524.

14. Silaba M, Ooko M, Bottomley C, Sande J, Benamore R, Park K,

Ignas J, Maitland K, Mturi N, Makumi A, Otiende M, Kagwanja S, Safari S, Ochola V, Bwanaali T, Bauni E, Gleeson F, Deloria Knoll M, Adetifa I, Marsh K, Williams TN, Kamau T, Sharif S, Levine OS, Hammitt LL, Scott JAG. Effect of 10-valent pneumococcal conjugate vaccine on the incidence of radiologically-confirmed pneumonia and clinically-defined pneumonia in Kenyan children: an interrupted time-series analysis. Lancet Glob Health 2019; 7: e337-e346.

15. Qu JM, Cao B. Guidelines for the diagnosis and treatment of adult community acquired pneumonia in China (2016 Edition). Zhonghua Jie He He Hu Xi Za Zhi 2016; 39: 241-242.

16. Fernández Pérez ER, Kong AM, Raimundo K, Koelsch TL, Kulkarni R. Epidemiology of Hypersensitivity Pneumonitis among an Insured Population in the United States: A Claims-based Cohort Analysis. Ann Am Thorac Soc 2018; 15: 460-469.

17. Kreuter M, Calaras D. Interstitial lung diseases: course report. Breathe (Sheff) 2018; 14: 184-185.

18. Monsel A, Zhu YG, Gennai S, Hao Q, Hu S, Rouby JJ, Rosenzwajg M, Matthay MA, Lee JW. Therapeutic Effects of Human Mesenchymal Stem Cell-derived Microvesicles in Severe Pneumonia in Mice. Am J Respir Crit Care Med 2015; 192: 324- 336.

19. Kasotakis G, Galvan M, King E, Sarkar B, Stucchi A, Mizgerd JP, Burke PA, Remick D. Valproic acid mitigates the inflammatory response and prevents acute respiratory distress syndrome in a murine model of Escherichia coli pneumonia at the expense of bacterial clearance. J Trauma Acute Care Surg 2017; 82: 758-765.

20. Chen C, Shi L, Li Y, Wang X, Yang S. Disease-specific dynamic biomarkers selected by integrating inflammatory mediators with clinical informatics in ARDS patients with severe pneumonia. Cell Biol Toxicol 2016; 32: 169-184.

21. Reed GL, Fitzgerald ML, Polgár J. Molecular mechanisms of platelet exocytosis: insights into the “secrete” life of thrombocytes. Blood 2000; 96: 3334-3342.

22. Reed GL, Fitzgerald ML, Polgár J. Molecular mechanisms of platelet exocytosis: insights into the "secrete" life of thrombocytes. Blood 2000; 96: 3334-3342.

23. Brockmann MA, Giese A, Mueller K, Kaba FJ, Lohr F, Weiss C, Gottschalk S, Nolte I, Leppert J, Tuettenberg J, Groden C. Preoperative thrombocytosis predicts poor survival in patients with glioblastoma. Neuro Oncol 2007; 9: 335-342.

24. McAllister DA, Liu L, Shi T, Chu Y, Reed C, Burrows J, Adeloye D, Rudan I, Black RE, Campbell H, Nair H. Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than 5 years between 2000 and 2015: a systematic analysis. Lancet Glob Health 2018; 7: e47-e57.

25. Andersen SB, Baunbæk Egelund G, Jensen AV, Petersen PT, Rohde G. Failure of CRP decline within three days of hospitalization is associated with poor prognosis of Community-acquired Pneumonia. Infect Dis (Lond) 2016; 49: 251-260.

26. Tao RJ, Luo XL, Xu W, Mao B, Dai RX, Li CW, Yu L, Gu F, Liang S, Lu HW, Chen KB, Bai JW, Ji XB, Gu SY, Sun XL, Dai FH, Jiang P, Cao WJ, Xu JF. Viral infection in community acquired pneumonia patients with fever: a prospective observational study. J Thorac Dis 2018; 10: 4387-4395.

27. Hung NT, Lei HY, Lan NT, Lin YS, Huang KJ, Lien LB, Lin CF, Yeh TM, Ha DQ, Huong VT, Chen LC. Dengue hemorrhagic fever in infants: a study of clinical and cytokine profiles. J Infec Dis 2004; 189(2): 221-32.

28. Fodor AA, Klem ER, Gilpin DF, Elborn JS, Boucher RC, Tunney MM, Wolfgang MC. The adult cystic fibrosis airway microbiota is stable over time and infection type, and highly resilient to antibiotic treatment of exacerbations. PloS One 2012; 7(9): e45001-e450015.

29. Bircan A, Gokirmak M, Kilic O, Ozturk O, Akkaya A. C-reactive protein levels in patients with chronic obstructive pulmonary disease: role of infection. Med Princ Prac 2008; 17(3): 202-208.

30. Liang Y, Lin Q, Huang P, Wang Y, Li J, Zhang L, Cao J. Rice Bioactive Peptide Binding with TLR4 To Overcome H2O2-Induced Injury in Human Umbilical Vein Endothelial Cells through NF-κB Signaling. J Agri Food Chem 2018; 66(2): 440-448.

31. Guo T, Lin Q, Li X, Nie Y, Wang L, Shi L, Luo F. Octacosanol attenuates inflammation in both RAW264. 7 macrophages and a mouse model of colitis. J Agri Food Chem 2017; 65(18): 3647-3658.

32. Li W, Jia MX, Wang JH, Lu JL, Deng J, Tang JX, Liu C. Association of MMP9-1562C/T and MMP13-77A/G polymorphisms with non-small cell lung cancer in southern Chinese population. Biomol 2019; 9(3): 107-119.

33. Nie Y, Luo F, Lin Q. Dietary nutrition and gut microflora: A promising target for treating diseases. Trends Food Sci Technol 2018;75: 72-80.

34. Ren Y, Jiao X, Zhang L. Expression level of fibroblast growth factor 5 (FGF5) in the peripheral blood of primary hypertension and its clinical significance. Saudi J Biol Sci 2018; 25(3): 469-473.

35. Nie Y, Luo F, Wang L, Yang T, Shi L, Li X, Shen J, Xu W, Guo T, Lin Q. Anti-hyperlipidemic effect of rice bran polysaccharide and its potential mechanism in high-fat diet mice. Food Func 2017; 8(11): 4028-4041.

36. Lou Y, Yang J, Wang L, Chen X, Xin X, Liu Y. The clinical efficacy study of treatment to Chiari malformation type I with syringomyelia under the minimally invasive surgery of resection of Submeningeal cerebellar Tonsillar Herniation and reconstruction of Cisterna magna. Saudi J Biol Sci 2019; 26(8): 1927-1931.

37. Lou Y, Guo D, Zhang H, Song L. Effectiveness of mesenchymal stems cells cultured by hanging drop vs. conventional culturing on the repair of hypoxic-ischemic-damaged mouse brains, measured by stemness gene expression. Open Life Sci 2016; 11(1): 519-523.

38. Chen X, Xu Y, Meng L, Chen X, Yuan L, Cai Q, Shi W, Huang G. Non-parametric partial least squares–discriminant analysis model based on sum of ranking difference algorithm for tea grade identification using electronic tongue data identify tea grade using e-tongue data. Sens Actuators B Chem 2020; 127924.

39. Wang L, Lin Q, Yang T, Liang Y, Nie Y, Luo Y, Luo F. Oryzanol modifies high fat diet-induced obesity, liver gene expression profile, and inflammation response in mice. J Agri Food Chem 2017; 65(38): 8374-8385.

40. Lou Y, Shi J, Guo D, Qureshi AK, Song L. Function of PD-L1 in antitumor immunity of glioma cells. Saudi J Boil Sci 2017; 24(4): 803-807.