Continuous Blood Purification on Influenza-associated Neurological Disease in Children: A Retrospective Cohort Study

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Research Article

Keywords: Continuous blood purification, Influenza, Children, Neurological complications, Retrospective cohort study

Posted Date: January 21st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-145075/v1

Version of Record: A version of this preprint was published at BMC Infectious Diseases on July 10th, 2021. See the published version at https://doi.org/10.1186/s12879-021-06265-7.

Continuous Blood purification on Influenza-Associated Neurological Disease in children：a retrospective cohort study

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ABSTRACT

Background: Due to lack of proven therapies, we evaluated the effect of CBP on Influenza-Associated Neurological Disease in children.

Methods: A single-center, retrospective, cohort study was conducted in Luoyang, Henan province China from January 2018 to January 2020. The children with Influenza-associated neurological disease (<18 years old) were enrolled into this study. The children with CBP indications and the parents' consent received CBP, and the others were treated with maximal intensive care due to failure of parents consent. The outcomes were compared between CBP group and non-CBP group.Categorical variables were presented as percentage and compared by Chi-square test or Fisher's exact test. Continuous variables were expressed as median (interquartile ranges) and compared with non-parametric independent sample test. Statistical analyses were finished by SPSS (version 26.0) and $p < 0.05$ (2 tailed) was considered statistically significant.

Results: 30 influenza children with Influenza-associated neurological disease were enrolled in this study. 18 received CBP and other 12 were treated with maximal intensive care. There were no differences between CBP and non-CBP children in age, sex, body weight, type of influenza virus, neurological complications, Glasgow score, PIM-2 score and PCIS at admission ($p > 0.05$). The inflammatory factors (CRP, PCT and IL-6) of 30 cases were tested at admission and after 3 days of admission. In CBP group, the level of IL-6 decreased significantly at 3-day of admission ($p = 0.003$), the level of CRP and PCT also decreased, but there was no significant difference ($p > 0.05$). In the non-CBP group, there were no significant difference on level of CRP, PCT and IL-6 between at admission and 3-day of admission ($p > 0.05$). The 28-day mortality in the CBP group was significantly lower compared to non-CBP group (11.11% vs 50%, $p = 0.034$).

Conclusions: CBP could Reduce inflammatory factors and may reduce 28-day mortality and improve neurologic function of influenza children.

Trial registration: http://www.chictr.org.cn/index.aspx (ChiCTR2000031754).

Key words: Continuous blood purification; Influenza; Children; Neurological complications; Retrospective cohort study

Background

Seasonal influenza epidemics cause between 3–5 million cases of severe illness and approximately 290,000 to 600,000 deaths every year in the world[1]. Most people are susceptibility to influenza and self-limited in the population, but some patients with high risk factor, especially for infants can develop to severe complications. These complications include pneumonia, neurological complications and even multi-organ dysfunction. Although pneumonia is the most common complication of childhood influenza, neurological disease is one of the most severe complications[2]. The Influenza-associated neurological disease include seizures, meningitis, transverse myelitis, acute disseminated encephalomyelitis, Guillain-Barre syndrome, and encephalopathy/encephalitis, and the incidence rate of children is significantly higher than that of adults[3]. The Influenza-associated neurological disease is associated with severe neurologic sequelae and high mortality[4]. Except supportive treatment, there is no effective treatment for the Influenza-associated neurological disease until now. The systemic inflammatory response syndrome after influenza virus infection have been shown to play an important role for neurological complications[5]. CBP can remove inflammatory factors and reduce the level of inflammatory factors in the serum of sepsis patients[6].

It is unknown whether the outcome and prognosis would be improved, if CBP is applied for removing inflammatory factors in influenza children with neurological complications. The aim of our study is to determine whether CBP have superior outcome and prognosis compared with non–CBP in influenza children with neurological complications.

Methods:

Study design

A single center, retrospective cohort study in Henan, China from January 2018 to January 2020 was conducted. A total of 545 pediatric patients (<18 years old) were admitted to PICU of Luoyang Maternal and Child Health Hospital for diagnosis of influenza. Among these children, the cases with neurological complications were enrolled into this study. The inclusion criteria include:①29d-18y; ②Diagnosed with influenza[7]; ③Nervous system abnormalities such as consciousness and convulsions quickly appeared; ④Respiratory support by ventilator. Exclusion standard: ①The children received cardiopulmonary resuscitation before admission,

and the pupils were dilated and fixed, or both pupils were not equal, or the EEG voltage was low (<5Hz); ②The children who gave up treatment due to family members within 72 hours of admission; ③There are only frequent convulsions, but no progressive aggravation of consciousness disorder during the course of the disease; ④There are high risk factors for bacterial purulent meningitis such as rhinorrhea, middle ear deformity or skull base fracture; ⑤The children who has basic brain disorders such as metabolic encephalopathy or epileptic encephalopathy.

Clinical management

The routine treatment for all the children included: neuraminidase inhibitors against influenza virus, ventilator-assisted ventilation, mannitol dehydration to lower intracranial pressure, midazolam and sufentanil for sedation and analgesia to reduce oxygen consumption, nutritional support etc. We treated with gamma globulin, methyprednisolone and plasma exchange for acute necrotizing encephalopathy of children. Elevation of the head of the bed, aspiration of subglottic secretions, control of the colonization of the oropharynx and the digestive tract to avoid ventilator-associated pneumonia. The vital signs, including heart rate, respiratory rate, transcutaneous oxygen saturation was monitored, as well as the 24 hours intake and output per day. The children with CBP indications and the parents' consent received CBP, and the others were treated with routine intensive care due to failure of parents' consent.

The internal jugular vein or femoral vein were selected for catheterization in all children. Blood filters were used according to the children's weight. The CBP treatment included PE and CVVHDF. On the first day and the second day, the plasma exchange was conducted firstly, with the plasma exchange of 60ml/kg/d. Standard volume CBP (25ml/kg/h) was performed after plasma exchange. The duration of treatment was ⩾16 hours per day.

Albumin, plasma or saline were selected as priming fluid before treatment according to body weight. For children less than 3kg, suspended red blood cells were selected as the priming fluid. For children with 3~15kg body weight, we selected albumin or plasma as priming fluid and saline for the children greater than 15kg. The right internal jugular vein was implanted with a double-lumen catheter for drainage and the left or right axillary vein with a 22G indwelling needle for blood return due to the limitation of vascular conditions in children

under 2 months old. Double lumen catheters were implanted into internal jugular vein and / or femoral vein in children over 2 months old. The type of double lumen catheter was selected according to the diameter of vascular minor axis measured by superficial ultrasound probe. A 5F double lumen catheter was used for vessels with diameter≤ 0.6cm, 7F double lumen for vessel between 0.6cm and 1.0cm and 11.5F for vessels with diameter over 1cm.

Outcomes

The primary outcome was 28-day mortality at admission. Secondary outcomes included ICU stay, Glasgow score, PIM-2, PCIS, ventilator-time, hospitalization costs.

Results

Working flow and basic information of influenza children in PICU

The study collected 545 children with influenza admitted to PICU from January 2018 to December 2019 for retrospective analysis. 39 of them had Influenza-associated neurological disease. 9 cases did not meet the inclusion criteria and were excluded。Among these 9 cases, 2 children received cardiopulmonary resuscitation before admission， after admission, the pupils were dilated and fixed or pupils were not large, and the brain voltage was lower than 5 Hz. One child was given up within 72 hours of treatment; 6 children gradually recovered their consciousness after admission and gradually recovered without receiving advanced life support such as ventilator-assisted ventilation.30 children were enrolled in this study. 18 received in CBP group with parents' consent, and other 12 were in non-CBP group due to failure of parents' consent (see Figure 1).

The demographic characters and clinical information at admission were showed as follow. There were no differences between CBP and non-CBP children in age, sex, body weight, type of influenza virus, neurological complications, Glasgow score, PIM-2 score and critical ill score and the level of Inflammatory factors at admission ($p > 0.05$). (see Table 1)

Inflammatory factors after CBP

The level of CRP, PCT and IL-6 of serum in CPB group were lower than in non-CBP group at 3-day of admission, there was no significant difference ($p > 0.05$). In CBP group, the level of IL-6 was significant lower at 3-day of admission than it at admission ($p = 0.003$), the level of CRP and PCT also decreased at 3-day of admission, but there was no significant difference

($p > 0.05$). In the non-CBP group, there were no significant difference on level of CRP, PCT and IL-6 between at admission and 3-day of admission ($p > 0.05$) (see Figure 2).

Outcomes

The 28-day mortality in CBP group was significantly lower than in non-CBP group (11.11% *vs* 50.00%, $p = 0.034$). Glasgow score, PIM-2 score and PCIS also significantly improved in CBP group. At the same time, the length of PICU stay was significantly prolonged, and the hospitalization costs were significantly increased (see Table 2).

2 children got hypothermia and severe hypophosphatemia, and 2 children got bleeding at the catheter puncture site due to early DIC in the course of the disease among the children treated with CBP.

Discussion

Of 545 influenza children were retrospective analyzed in our PICU, 30 children who developed to neurological complications were enrolled in this study. Influenza infection seriously threaten to children's health. In 2003-2004 influenza season, the average hospitalization rate was 36/100000 of American children, but in children under 5 years old was up to 80%[8]. A study on influenza-related neurological diseases from Australia showed that seasonal influenza is an important cause of children's neurological diseases in Australia. After extensive influenza vaccination, the mortality of children with influenza-related encephalopathy was significantly reduced[9]. Data of influenza-related encephalopathy reported through Japan's National Infectious Disease Epidemiological Surveillance Database from 2010 to 2015 showed a total of 385 patients got with influenza-related encephalopathy. The average incidence of influenza-related encephalopathy in children and adults (age ⩾18 years) was 2.83 and 0.19 per million, respectively. The median duration of fatal cases from the onset of influenza-related encephalopathy to death was 1 day [3].In China, the Beijing Children's Hospital conducted an analysis of the cause of death of 19 children with influenza virus infection from November 2017 to April 2018, 8 children had flu-related encephalopathy, and 7 of them died of flu-related encephalopathy[10].

Besides serious respiratory complications, some children can quickly progress to coma, and influenza related neurological complications are more severe in children and the main causes of influenza death[3,11,12]. Until now, the pathogenesis of influenza-related neurological

complications is still unclear. Autopsy of these patients showed necrosis and epithelial hemorrhage of thalamus and posterior cerebral cap of pons, pale myelin sheath in white matter of brain and cerebellum, and no clear obstruction of vascular endothelium and peripheral vascular edema[13]. Due to the acute onset of influenza-related neurological diseases, severe brain dysfunction can occur quickly. The treatment time window is tight. Before the symptoms of nervous system appear, the children's respiratory system disorder is not prominent or even no respiratory system performance, and lack of early warning indicators. Although immunization can reduce its incidence to a certain extent[9], but most children are not actively vaccinated. Once the patient developed into an Influenza-associated neurological disease, treatment is extremely difficult, and some children develop cardiopulmonary failure within a short period of time. Many children have undergone cardiopulmonary resuscitation before admission, and showed pupil light loss or even brain herniation after admission, the brain failure will soon appear even if with active treatment. Even if they survived, some children will still have serious neurological complications. The mortality of acute necrotizing encephalopathy is 30%, only 10% of patients can fully recover and more patients survive in the form of neurological sequelae. The neurological sequelae recover very slowly and some patients received unacceptable long-term rehabilitation [14]. Therefore, effective treatment of influenza-associated neurological disease, especially acute necrotizing encephalopathy is a problem that we urgently need to solve. In this study, we found that the mortality of children in the CBP group was lower than that of the non-CBP group, and the neurological coma score (Glasgow score), PCIS score and PIM-2 score were improved compared with the non-CBP group. It is suggested that CBP has association with decreased mortality.

The pathogenesis of influenza-associated neurological disease is unclear. Current opinion was that systemic inflammatory response syndrome triggered by influenza virus infection especially the elevated of cytokines (interleukin-6, -8, -10) were involved. Previous studies found that inflammatory factors significantly increased in the cerebrospinal fluid of patients, especially IL-6 and TNF-α[14].So, the elevated cytokines (interleukin-6, -8, -10), caused by systemic inflammatory response syndrome triggered by influenza virus infection, have been hypothesized to play an important role in the pathogenesis of neurological complications[11,15].

However, there is no effective therapy for the "system cytokine storm" caused by influenza virus. Corticosteroid is the most commonly used and the effect is still controversial. The current treatment for influenza-associated neurological disease is symptomatic treatment and immune regulation. Kawashima[16] reported three children with influenza encephalopathy recovered from influenza after hormone and plasma exchange. The CBP model in this subject includes PE and CVVHDF, which can remove inflammatory factors between 0.5k-60 kDa from serum. In this study, the level of inflammatory factors, including CRP, PCT and IL-6, reduced in CBP group after blood purification. IL-6 molecular weight 21-30kD. IL-6 levels were significantly lower after blood purification than at admission.

However, due to the effective number of samples in this study, the mechanism and efficacy of CBP therapy in the treatment of Influenza-associated neurological disease require further research and discussion.

Conclusions

CBP could Reduce inflammatory factors and may reduce 28-day mortality and improve neurologic function of influenza children. Due to the limited samples of this study, the correlation between the improvement of neurological function, mortality and blood purification still needs further well-designed clinical trials.

List of abbreviations

CBP: Continuous Blood purification

CRP: C-reactive protein

PCT: Procalcitonin

IL-6: Intereukin-6

PIM-2: pediatric index of mortality-2

PCIS: Pediatric critical illness score

CVVHDF: Continuous venovenous hemodiafiltration

PE: Plasma exchange

DIC: Disseminated intravascular coagulation

TNF-α: Tumor necrosis factor α

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committees of the Luoyang Maternal and Child Health Hospital (KY20190101) (Luoyang; Henan, China). All the informed consent has been obtained from the parents and/or legal guardian. All the methods were in accordance with the relevant guidelines and regulations. This study was registered at http://www.chictr.org.cn/index.aspx (ChiCTR2000031754).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest or funding to disclose.

Funding

The efficacy and mechanism of continuous blood purification in the treatment of children's Influenza-associated neurological disease ---a co-construction project of 2019 medical science and technology research in Henan province (LHGJ20191235).

The plasma exchange combined with hemofiltration on the clearing effect mechanism of YKL-40, IL-6, IL-10 and TNF-α in children with severe viral encephalitis---a youth cultivation fund project of 2019 the First Affiliated Hospital of Xinxiang Medical College (QN-2019-B15).

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Contributions

XY H, KN F and SJ L designed the study and reviewed the manuscript. KN F and JW N were responsible for the data acquisition, analyses and interpretation, contributed equally to this work. ZY W, Q H，LL L, GY Y and HZ G involved data collection, analysis. XY H, JW N and Z Z were responsible for manuscript preparation and manuscript review. All authors read and approved the final manuscript.

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Acknowledgement

None.

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Figure legends

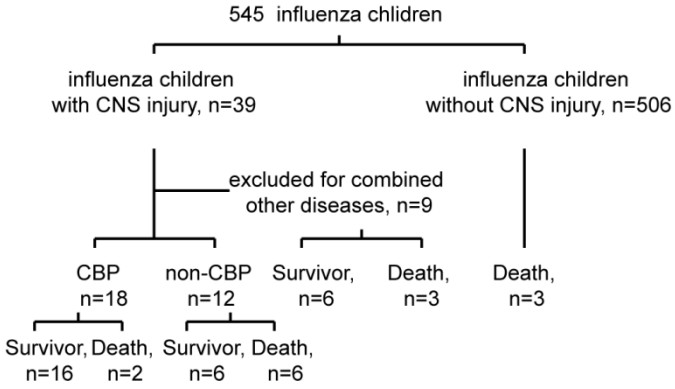

Figure 1 Workflow process to obtain influenza children with neurological complications.

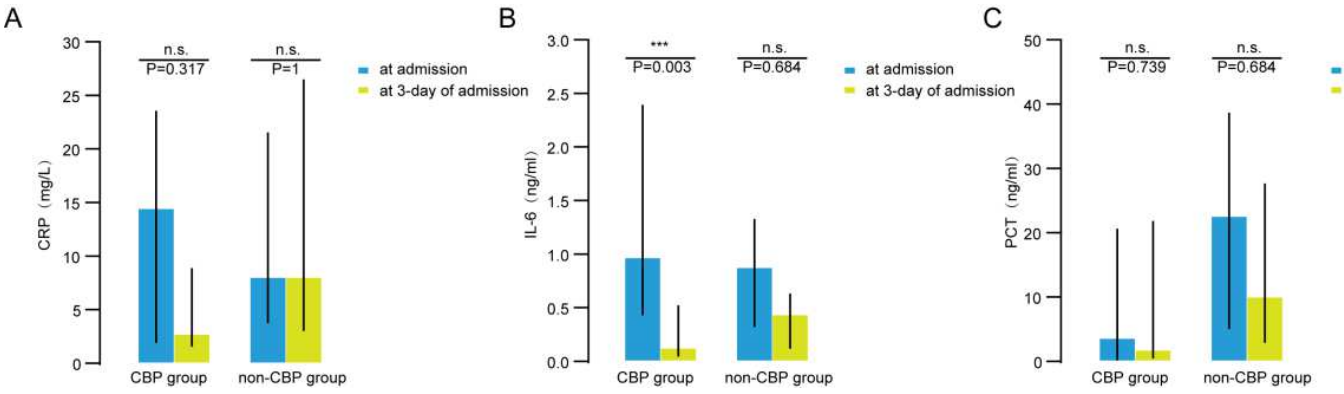

Figure 2 Statistical charts of the inflammatory mediators of CBP group and non-CBP group at admission and 3-day of admission. (A) Compared to 3-day of admission, statistics charts show decreasing of CRP in CBP group, but there was no significant difference (p = 0.317). There was no difference of CRP in non-CBP group (p = 1.0). (B) Compared to 3-day of admission, statistics charts show significantly decreasing of IL-6 in CBP group (***p = 0.003). There was no difference of IL-6 in non-CBP group (p = 0.684). (C) Compared to 3-day of admission, statistics charts show decreasing of PCT in both in CBP group and non-CBP group, but there was no significant difference (p = 0.739 and p = 0.684).

Table1. Demographic characteristics and clinical information at admission

characteristics		CBP group (n=18)	Non-CBP group (n=12)	*p*
Age (median [IQR]) (m)		19 (8.50-34.50)	20.5 (9.13-47.75)	0.932
Sex	Male	9	5	0.722
	Female	9	7	
Body weight (median [IQR])(kg)		10 (7.65-14.13)	11 (8.13-14.25)	0.734
Type of influenza	A	12	8	1.0
	B	6	4	
Neurological complications	encephalopathy	10	7	1.0
	encephalitis	8	5	
Glasgow score (median [IQR])		4.00 (4.00-5.25)	4.00 (3.00-5.00)	0.479
PIM-2 score (median [IQR])		25.05 (18.40-78.63)	20.25 (17.25-70.05)	0.498
Critical ill score (median [IQR])		74 (71.0-76.5)	81 (68.50-87.00)	0.349
Inflammatory factors	CRP(median [IQR]) (mg/L)	14.35 (1.85-23.63)	7.95 (3.71-21.48)	0.983
	PCT(median [IQR]) (ng/ml)	3.4 (0.28-20.50)	22.5 (5.13-38.75)	0.099
	IL-6(median [IQR]) (ng/ml)	0.96 (0.42-2.40)	0.69 (0.31-1.335)	0.611

CBP: continuous blood purification; IQR: interquartile range; PIM-2: pediatric index of mortality 2; CRP: C-reactive protein; PCT: procalcitonin; IL-6: interleukin-6

Table2. Outcomes of CBP and non-CBP groups

Outcomes	CBP group （n=18)	Non-CBP group （n=12)	*p*
28-day mortality, n (%)	2 (11.11)	6 (50)	0.034*
Glasgow score (median [IQR])	7.00 (4.00-7.25)	3.50 (3.00-5.75)	0.021*
PIM-2 score (median [IQR])	11.00 (7.78-22.55)	43.80 (9.28-85.03)	0.040*
Critical illness score (median [IQR])	93 (88.00-94.00)	81 (77.00-93.50)	0.038*
PICU stay (median [IQR]) (d)	19.00 (15.00-22.50)	10.00 (4.00-12.00)	0.008*
Ventilation time (median [IQR]) (d)	7.50 (5.75-15.25)	5.50 (4.00-6.75)	0.060
hospitalization costs(median [IQR]) (US dollars)	11350.67 (8670.36-16802.95)	6195.63 (3246.95-8000.03)	0.008*

CBP: continuous blood purification; IQR: interquartile range; PIM-2: pediatric index of mortality 2; PICU: pediatric intensive care unit; $*p < 0.05$

Figures

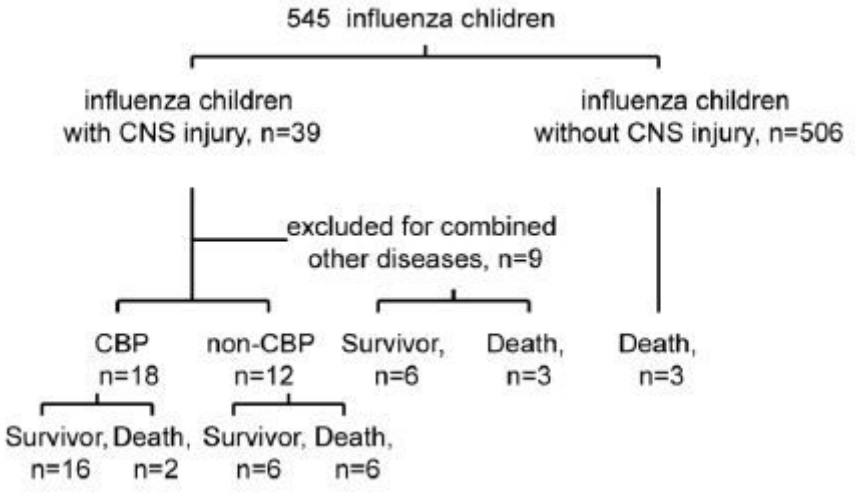

Figure 1

Workflow process to obtain influenza children with neurological complications.

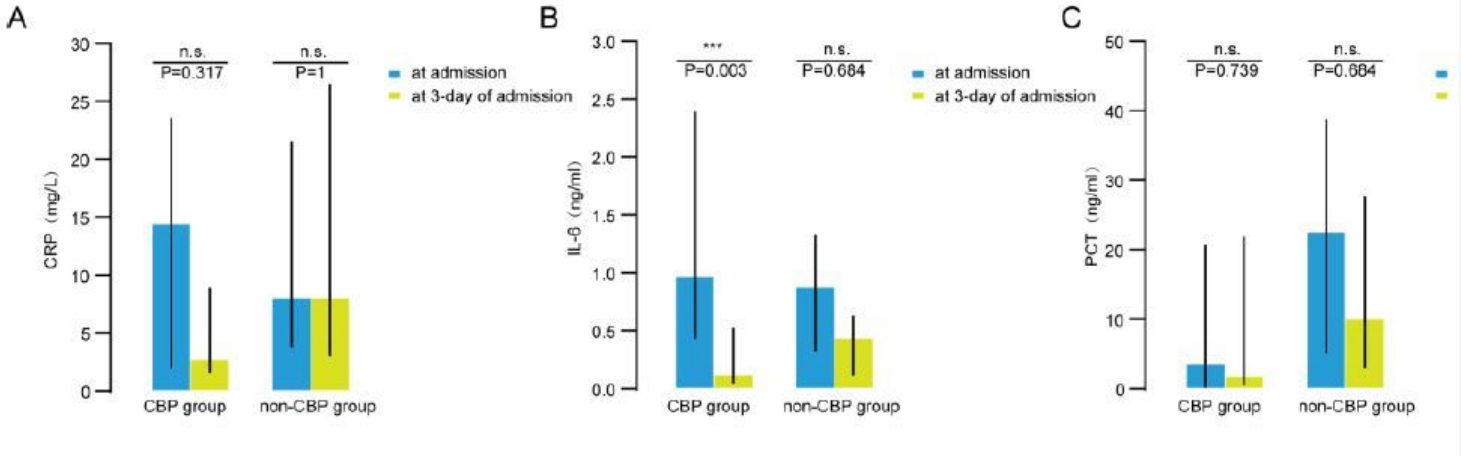

Figure 2

Statistical charts of the inflammatory mediators of CBP group and non-CBP group at admission and 3-day of admission. (A) Compared to 3-day of admission, statistics charts show decreasing of CRP in CBP group, but there was no significant difference (p = 0.317). There was no difference of CRP in non-CBP group (p = 1.0). (B) Compared to 3-day of admission, statistics charts show significantly decreasing of IL-6 in CBP group (***p = 0.003). There was no difference of IL-6 in non-CBP group (p = 0.684). (C) Compared to 3-day of admission, statistics charts show decreasing of PCT in both in CBP group and non-CBP group, but there was no significant difference (p = 0.739 and p = 0.684).