The Diagnostic and Antibiotic Reference Values of Procalcitonin for Intracranial Infection After Craniotomy

Lei Zhu[1], Lun Dong[2], Yuping Li[2], Guangyu Lu[3], Hengzhu Zhang[2], Xingdong Wang[2], Xiaoguang Liu[2], Zhenfei Teng[1], Boming Xia[1], Peng Zhang[1]

■ OBJECTIVE: **To evaluate values of cerebrospinal fluid (CSF) and serum procalcitonin (PCT) for diagnosis of intracranial infection after craniotomy and relationship between them and to explore value of PCT in guiding clinical use of antibiotics.**

■ METHODS: **The incidence of intracranial infection in 21 patients undergoing craniotomy was reviewed. CSF samples and venous blood were collected for analysis. Diagnostic parameters were calculated via receiver operating characteristic curves, and inflammatory indicators were analyzed before and after administration of antibiotics in the infection group. As a control group, 32 patients without infection were recruited for the same measurements.**

■ RESULTS: **CSF and serum PCT levels in the infection group were higher than levels in the noninfection group ($P < 0.05$), and diagnostic efficiency of CSF PCT (area under the curve = 0.86, diagnostic odds ratio = 41.40) was superior to serum PCT (area under the curve = 0.66, diagnostic odds ratio = 3.40). Diagnostic efficiency was more powerful when serial testing was used (specificity = 0.99, positive likelihood ratio = 37.10, diagnostic odds ratio = 54.45). All inflammatory indicators decreased after administration of antibiotics except CSF protein ($P = 0.129$), and no obvious correlation was seen between CSF and serum PCT. Dynamic change of PCT can be used as a reference for adjusting antibiotics. CSF PCT can also be used as an indicator to identify intracranial infection with gram-negative bacteria.**

■ CONCLUSIONS: **CSF PCT is a good marker for intracranial infection and could be used to help confirm intracranial infection and provide guidance for clinical use of antibiotics when combined with serum PCT.**

INTRODUCTION

Intracranial infection, especially bacterial infection, is a common occurrence with a reported incidence of 2.6%,[1] particularly in the neurosurgery intensive care unit (NICU). It is the most common complication following craniotomy and characterized by high morbidity rate and poor prognosis.[2] Timely and accurate diagnosis of intracranial infection after craniotomy at an early stage is critical to improve outcomes in clinical practice. However, with the nonstrict application of clinical antibiotics and the emergence of bacterial resistance,[3] the bacterial culture rate in cerebrospinal fluid (CSF) is generally low,[4] which makes the diagnosis of intracranial infection quite difficult. White blood cell (WBC) and neutrophil counts, C-reactive protein concentrations, and glucose and chloride levels in CSF are the traditional indicators for preliminary

Key words
- Antibiotics
- Diagnosis
- Intracranial infection
- Procalcitonin

Abbreviations and Acronyms
AUC: Area under the curve
CSF: Cerebrospinal fluid
GN: Gram-negative
NICU: Neurosurgery intensive care unit
NLR: Negative likelihood ratio
NPV: Negative predictive value
PCT: Procalcitonin
PLR: Positive likelihood ratio
PPV: Positive predictive value
WBC: White blood cell

From the [1]Department of Neurosurgery, DaLian Medical University, DaLian, Liaoning; [2]Department of Neurosurgery, Clinical Medical College of Yangzhou University, Yangzhou, Jiangsu; and [3]Department of Preventive Medicine, Yangzhou University, Yangzhou, Jiangsu Province, China

To whom correspondence should be addressed: Hengzhu Zhang, Ph.D. [E-mail: zhanghengzhu@sina.com]

Lei Zhu, Lun Dong and Yuping Li are co—first authors.

Citation: World Neurosurg. (2019) 126:e1-e7.
https://doi.org/10.1016/j.wneu.2018.10.241

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

identification of infections and noninfectious conditions, but there can be similar changes in the aforementioned indicators in some cases without infection, such as acute stroke.[5] In addition, these commonly used markers have high sensitivity but low specificity.[6] Distinguishing between intracranial infections and noninfectious conditions is challenging; however, procalcitonin (PCT) brought a new dawn to the field of intracranial infections.

PCT, a precursor to calcitonin, is synthesized in C cells of the thyroid gland and secreted from leukocytes.[7] PCT is generally believed to be an endogenous nonsteroidal substance, a glycoprotein without hormone activity. The concentration of PCT in healthy individuals is very low, and it is a very stable protein both in vitro and in vivo.[8] The concentration of PCT could reflect the degree of systemic inflammatory response,[9,10] and therefore it can be used as an acute parameter to differentially diagnose bacterial and nonbacterial infections and inflammation. Furthermore, related research has demonstrated that PCT has advantages over traditional indicators in the diagnosis of intracranial inflammatory infection at an early stage and is able to provide guidance in clinical treatment.[6,11]

Although PCT has been widely studied in recent years, some scholars[12,13] claim that it is not a good predictor of infection. Moreover, some previous studies were retrospective, so publication bias was inevitable. Also, these studies may have been more valuable if they had addressed the relationship between CSF PCT and serum PCT. Subsequently, few studies have explored the value of PCT in the field of antibiotics about clinical management. Therefore, we performed this study to evaluate the diagnostic usefulness of CSF PCT and serum PCT for intracranial infection and reference value of antibiotics for the purpose of providing new evidence for clinical diagnosis and treatment of intracranial infection after craniotomy.

MATERIALS AND METHODS

Patients and Standards for Intracranial Infection Diagnosis

This study was evaluated and approved by Subei People's Hospital of Jiangsu province Ethical Committees. An informed consent was presented to and signed by the relative responsible for the patient.

We conducted a prospective study of 21 patients admitted to the NICU in Subei People's Hospital of Jiangsu province who underwent craniotomy from January 2016 to March 2018. Patients who showed clinical symptoms of intracranial infection were recruited for this study according to the following criteria for intracranial infection diagnosis: 1) presence of clinical manifestation of intracranial infection; 2) presence of risk factors, such as human immunodeficiency virus/acquired immunodeficiency virus, hematopoietic stem cell transplant, lymphoid malignancies, neutropenia, and hereditary immune defects and patients with drainage or CSF leakage; 3) inflammatory indicators in CSF, including WBC count $>100 \times 10^6$/L and multinuclear leukocytes >70%, glucose levels <2.25 mmol/L and CSF glucose/serum glucose <0.66, and chloride <120 mmol/L and protein >0.45 g/L; 4) positive results for bacteria in CSF culture or confirmed by polymerase chain reaction or other molecular biology techniques.[14,15] Diagnosis of intracranial infection was made individually in patients with criteria 4. Intracranial infection was also diagnosed in patients with negative CSF culture results but with the first 3 diagnostic criteria. Also, 32 patients with no apparent intracranial infection after craniotomy were recruited for measurement of PCT and other related indices.

Statistical Analysis

All statistical analysis was performed with IBM SPSS software Version 20.0 (IBM Corp., Armonk, New York, USA). Normal distribution data were compared using the *t* test and shown in the form of mean and SD, and median values of non–normally distributed measurement data were compared using the nonparametric Mann-Whitney *U* test and presented in the form of median and minimum, maximum value. *P* value < 0.05 was considered to be significant. The optimal cutoff value of PCT was calculated using the receiver operating characteristic curve. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were analyzed. The Youden index and diagnostic odds ratio were applied to determine the capability to find true patients and nonpatients and the link between the results of the diagnostic test and the disease.[16,17]

RESULTS

Patient Information

All 53 patients after craniotomy who were enrolled were divided into 2 groups, 21 in the infection group and 32 in the noninfection group. In the infection group, patients were divided into CSF culture positive ($n = 6$) and negative ($n = 15$) subgroups according to the results of bacterial culture of CSF. Demographic and clinical data obtained were age, sex, diagnosis at admission, Glasgow Coma Scale, Acute Physiology and Chronic Health Evaluation score, Ramsay score, Sequential Organ Failure Assessment score, emergency and selective surgery and related duration, and blood loss. In the subgroup analysis, the only differences that were statistically significant were Glasgow Coma Scale score ($P = 0.039$) and Ramsay score ($P = 0.030$). Demographic and clinical details for all enrolled subjects are presented in **Tables 1** and **2**. All microorganisms isolated from CSF cultures were gram-negative (GN) bacteria (6 of 6; 100%) as shown in **Table 3**.

CSF PCT and Serum PCT Levels in Infection and Noninfection Groups

The level of CSF PCT in the infection group was higher than in the noninfection group, and the difference was statistically significant ($P = 0.000$) (**Figure 1A**). The median value was 0.69 ng/mL (range, 0.08–4.79 ng/mL) in the infection group and 0.22 ng/mL (range, 0.01–1.29 ng/mL) in the noninfection group. In the subgroup analysis, the median value was 1.08 ng/mL (range, 0.50–4.79 ng/mL) in the CSF culture positive group and 0.68 ng/mL (range, 0.08–2.11 ng/mL) in the CSF culture negative group; the difference was not statistically significant ($P = 0.074$) (**Figure 1B**). The difference of serum PCT between the infection group and noninfection group was also statistically significant ($P = 0.046$) (**Figure 2A**). The median value was 0.36 ng/mL (range, 0.07–11.7 ng/mL) in the infection group and 0.22 ng/mL (range, 0.04–3.87 ng/mL) in the noninfection group. In the infection group, subgroup analysis showed there was no

Table 1. Demographic and Clinical Details of All Included Patients

Variable	Infection Group	Noninfection Group	*P* Value
Age, years	60.62 ± 10.67	54.31 ± 15.51	0.086
Sex			0.869
Men	16	25	
Women	5	7	
Diagnosis			0.931
Subarachnoid hemorrhage	4	8	
Intracerebral hemorrhage	9	14	
Head trauma	6	8	
Others	2	2	
GCS score	6 (3–15)	5.5 (3–15)	0.404
APACHE II score	17 ± 7.93	19.97 ± 7.21	0.175
Ramsay score	6 (2–6)	6 (2–6)	0.351
SOFA score	4 ± 2.07	4 (0–8.00)	0.770
Surgery			0.894
Emergency	18	27	
Selective	3	5	
Surgery duration, hours	3.24 ± 1.40	3.82 ± 1.72	0.186
Surgical blood loss, mL	300 (5–1000)	300 (10–1000)	0.254

There was no significant difference in general demographic and clinical information between the 2 groups of patients. All *P* values were > 0.05. Normal distribution data were presented as mean ± SD. Non-normal distribution data were presented as median (range).
GCS, Glasgow Coma Scale; APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

Table 2. Demographic and Clinical Details of Patients with Infection

Variable	CSF Culture Positive	CSF Culture Negative	*P* Value
Age, years	60.33 ± 7.06	60.73 ± 12.03	0.940
Sex			0.627
Men	5	11	
Women	1	4	
Diagnosis			0.869
Subarachnoid hemorrhage	1	3	
Intracerebral hemorrhage	2	7	
Head trauma	2	4	
Others	1	1	
GCS score	5 (5–15)	6 (3–15)	0.039
APACHE II score	13.50 ± 7.26	18.40 ± 7.98	0.209
Ramsay score	3.50 ± 1.97	6 (2–6)	0.030
SOFA score	3.17 ± 2.56	4 (2–9)	0.254
Surgery			0.115
Emergency	4	14	
Selective	2	1	
Surgery duration, hours	3.90 (1.17–4.00)	4.30 (0.58–4.30)	0.897
Surgical blood loss, mL	193.33 ± 160.21	300 (5–1000)	0.327

Subgroup analysis showed that there was no significant difference in the general demographic and clinical information between the 2 subgroups of patients with infection except for the GCS and Ramsay scores ($P = 0.039$ and $P = 0.030$ respectively). Normal distribution data were presented as mean ± SD. Non-normal distribution data were presented as median (range).
CSF, cerebrospinal fluid; GCS, Glasgow Coma Scale; APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

statistically significant difference in the CSF culture positive and CSF culture negative groups (P = 0.588) (Figure 2B). The mean and SD were 0.94 ng/mL and 0.93 ng/mL, respectively, in the CSF culture positive group, and the median was 0.31 ng/mL (range, 0.07–11.7 ng/mL) in the CSF culture negative group.

Diagnostic Efficacy of CSF PCT and Serum PCT and Their Relationship

The diagnostic parameters of CSF PCT and serum PCT are summarized in Table 4. CSF PCT was shown to be a good biomarker for intracranial infection after craniotomy and was better than serum PCT. The receiver operating characteristic curves of CSF PCT and serum PCT revealed the cutoff values were 0.67 ng/mL (area under the curve [AUC] = 0.86) and 0.40 ng/mL (AUC = 0.67), respectively (Figure 3). Other indicators, such as sensitivity, specificity, PPV, NPV, PLR, NLR, and diagnostic odds ratio, are also presented in Table 4. No significant difference was observed between CSF PCT and serum PCT in the infection group (Figure 4). No obvious

Table 3. Microorganisms Isolated from Cerebrospinal Fluid in Culture-Positive Patients

Bacterial Species	Overall ($n = 6$)	SAH	Intracerebral Hemorrhage	Head Trauma	Other
GN	6	1	3	2	0
Acinetobacter baumannii	3	1	0	2	0
Stenotrophomonas maltophilia	1	0	1	0	0
Serratia marcescens	1	0	1	0	0
Enterobacter aerogenes	1	0	1	0	0

SAH, subarachnoid hemorrhage; GN, gram-negative.

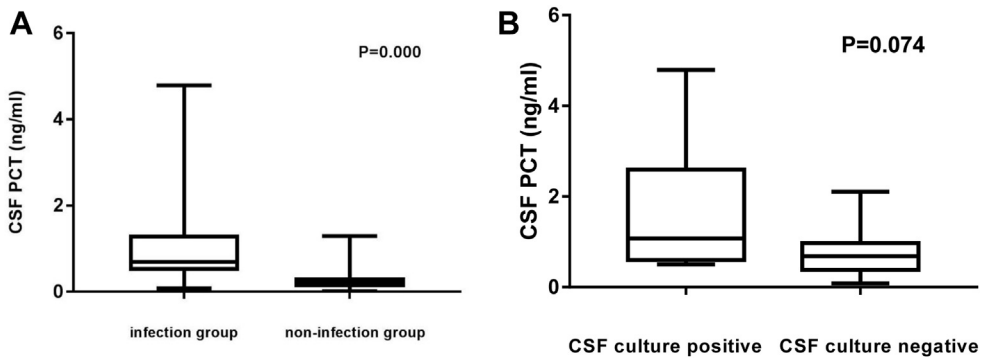

Figure 1. (**A**) Concentration of cerebrospinal fluid procalcitonin was significantly greater in the infection group than in the noninfection group ($P < 0.05$). (**B**) Subgroup analysis showed the difference of cerebrospinal fluid procalcitonin between the cerebrospinal fluid culture-positive and culture-negative groups was not statistically significant ($P = 0.074$). CSF, cerebrospinal fluid; PCT, procalcitonin.

correlation was seen between CSF PCT and serum PCT after regression analysis (Figure 5).

Changes of Inflammation Indicators in the Infection Group

In the infection group, 3 patients left the hospital without enough treatment because of various reasons. Some inflammation indicators of intracranial infection, such as CSF biomarkers, temperature, WBCs, neutrophils, and C-reactive protein, returned to normal range after administration of antibiotics according to bacteriologic test results and our past experiences. The difference between before and after inflammatory markers was statistically significant ($P < 0.05$) except for CSF protein ($P = 0.129$) (Table 5). PCT concentrations also gradually decreased and roughly returned to normal on the third to fifth day (Figure 6).

DISCUSSION

CSF bacterial culture is still considered to be the gold standard for intracranial infections, but the low positive rate and the time-consuming process of bacterial culture restrict its role.[18] Routine tests of infection often fail to result in high specificity in clinical diagnosis and can contribute significantly to the cost of time and care. Traditional biochemical markers, such as WBCs, protein, and chloride, in CSF usually are of high sensitivity but low specificity,[6] so it is not easy to exclude patients who are not infected, reflecting the poor capability of these frequently used screening tests. The emerging detection method, polymerase chain reaction testing, is not widely available at all hospitals because of the high cost and complicated technology.[19] Given the importance and complexity of intracranial infection in clinical work, looking for a new auxiliary marker for clinical diagnosis and guiding treatment is particularly urgent and

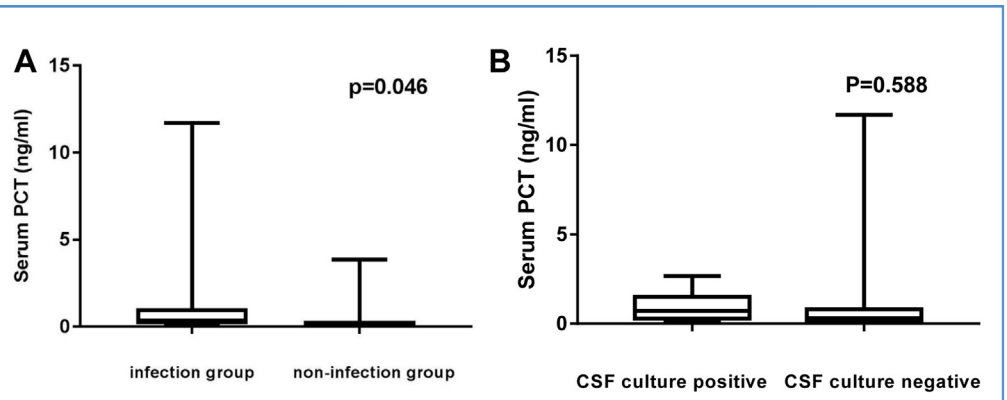

Figure 2. (**A**) Concentration of serum procalcitonin was also significantly greater in the infection group than that in the noninfection group ($P < 0.05$). (**B**) Subgroup analysis showed the difference of serum procalcitonin between the cerebrospinal fluid culture-positive and culture-negative groups was not statistically significant ($P = 0.588$). CSF, cerebrospinal fluid; PCT, procalcitonin.

Table 4. Diagnostic Parameters of Cerebrospinal Fluid and Serum Procalcitonin in Intracranial Infection

	AUC	Cutoff	Sens	Youden Index	Spec	PPV	NPV	PLR	NLR	DOR
CSF PCT	0.86	0.67	0.54	0.57	0.97	0.92	0.78	18.31	0.44	41.40
Serum PCT	0.66	0.40	0.29	0.57	0.72	0.57	0.72	2.03	0.60	3.40
CSF + serum			0.32	0.33	0.99	0.99	0.70	37.10	0.68	54.45
CSF/ serum			0.51	0.82	0.70	0.63	0.85	2.69	0.26	10.18

AUC, area under the curve; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; CSF, cerebrospinal fluid; PCT, procalcitonin.

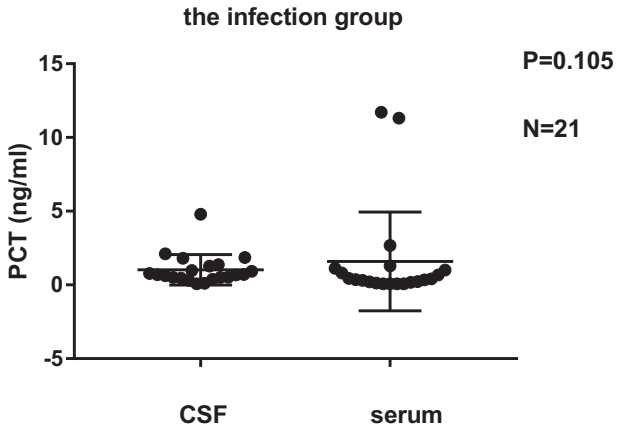

Figure 4. Subgroup analysis showed the difference of serum PCT between the CSF culture positive and negative groups was not statistically significant ($P = 0.588$). PCT, procalcitonin.

pivotal. Craniotomy destroys the blood-brain barrier and increases its permeability, so PCT enters the CSF and increases with inflammation. Several studies[6,9,12,17] have already explored the diagnostic and prognostic values of PCT, providing a new means to help confirm intracranial infection and guide clinical treatment. Nevertheless, some researchers[20,21] also have published articles stating PCT may not a helpful parameter for predicting intracranial infections. Moreover, little work regarding the relationship between CSF PCT and serum PCT has been conducted. To further investigate the value of PCT in CSF and serum in intracranial infection and unmask the correlation between them preliminarily, we studied a cohort of 53 patients at NICU in our hospital, aiming to share our experience regarding medical therapy of intracranial infections as well.

The diagnostic value of PCT in CSF and serum was analyzed in this study, and the results offer a reference for clinical diagnosis and treatment. The AUC of CSF PCT was 0.86, which showed a good diagnostic effect according to the receiver operating characteristic curve evaluation criteria. A cutoff value was 0.67 ng/mL, a little higher than 0.5 ng/mL (the upper limit of the normal range of clinical recommendations). Specificity (0.97) and PLR (18.31) are excellent tools for diagnosis in patients with noninfectious conditions and reduce the chance of misdiagnosis. However, other parameters, such as sensitivity (0.57), NPV (0.78), and NLR (0.44), are not powerful enough to accurately diagnose intracranial infection in patients and could lower the true-positive rate. The diagnostic efficiency of serum PCT is disappointing, and the corresponding parameters are inferior to those in CSF. We calculated the cutoff value (0.40 ng/mL) and AUC (0.66), and the cutoff values is not in line with a previous report[6] and is lower than the upper limit of the normal range (0.5 ng/mL). This is partly due to the small number of

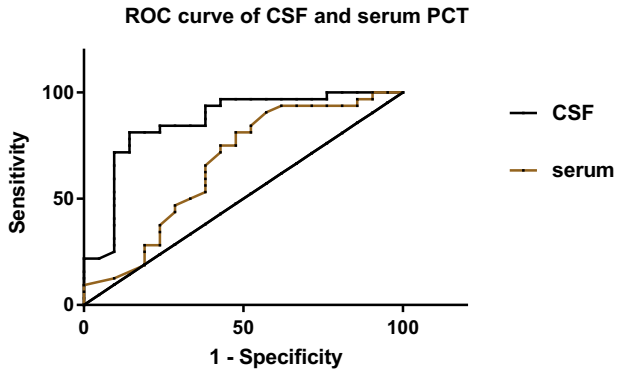

Figure 3. The comparison between CSF and serum PCT about ROC curve. The ROC curves of CSF PCT showed a good biomarker for intracranial infection after craniotomy, which was better than serum PCT. CSF, cerebrospinal fluid; PCT, procalcitonin; ROC, receiver operating characteristic.

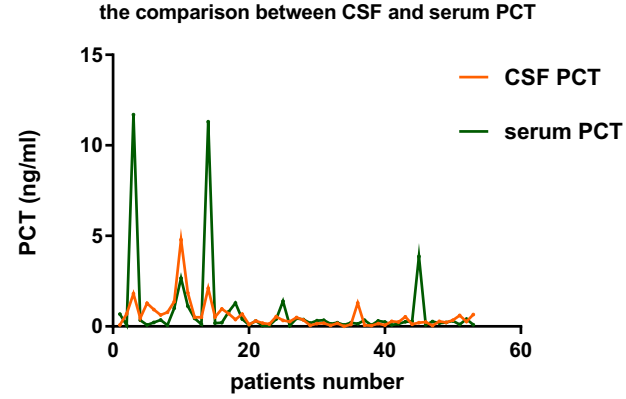

Figure 5. No apparent correlation can be summarized from the CSF and serum PCT. There is no significant difference between them. CSF, cerebrospinal fluid; PCT, procalcitonin.

Table 5. Changes of Inflammation Indicators Before and After Treatment

	CSF WBCs (10^9/L)	CSF Glucose (mmol/L)	CSF Chloride (mmol/L)	CSF Protein (g/L)	T (°C)	WBCs (10^9/L)	Neutrophils (10^9/L)	CRP (mg/L)
Before treatment	1275.5 (102—38,593)	1.81 (0.83—6.27)	119.278 ± 6.711	1.295 (0.47—3.61)	38.872 ± 0.265	14.671 ± 3.433	12.251 ± 3.270	81.111 ± 44.879
After treatment	58 (6—257)	4.182 ± 1.775	114.056 ± 5.985	1.061 ± 0.537	36.733 ± 0.214	7.731 ± 1.913	5.747 ± 1.638	11.35 (2.93—69.92)
P value	0.000	0.000	0.019	0.129	0.000	0.000	0.000	0.000

CSF, cerebrospinal fluid; WBCs, white blood cells; T, temperature; CRP, C-reactive protein.
Normal distribution data were presented as mean ± SD. Non-normal distribution data were presented as median (range).

patients. Similarly, the other factors (local infection, multiple-organ dysfunction syndrome) could influence the PCT level. Another reason accounting for this outcome is the sterile inflammatory alterations. Coincidentally, the sensitivity of serum PCT was also 0.57, indicating a poor ability to diagnose true infection in patients and potentially increasing the rate of missed diagnosis. Compared with the CSF PCT, the serum PCT parameters, such as AUC (0.66), PPV (0.57), and PLR (2.03), are not satisfactory to predict the accurate diagnosis rate and decrease the misdiagnosis rate. The importance of the sensitivity and specificity of a diagnostic test are well known; the morbidity rate is also a factor that must be considered in clinical diagnosis otherwise having a great impact on positive screening results. As mentioned earlier, to improve the credibility of diagnostic results and compensate for the defects of a single test, we combined CSF PCT and serum PCT to confirm the efficiency of diagnosis (sensitivity, specificity, PPV, NPV, PLR, NLR) of the serial and the parallel tests, hoping to find a novel method for the diagnosis of intracranial infection. The serial test demonstrated the extremely high specificity (0.99), PLR (37.10 >>10), and diagnostic odds ratio (54.45), indicating that combined CSF PCT and serum PCT is an exceptionally useful tool to confirm intracranial infection and a true negative rate to exclude patients without intracranial infection. The sensitivity (0.82) was also increased in the parallel test compared with the level of either marker alone. All of these tests are ultimately clinically important. Therefore, different testing methods should be selected for different purposes. For example, to screen all patients suspected to have intracranial infection, parallel testing is preferred with high sensitivity and NPV and lower NLR. To make a definite diagnosis of intracranial infection, serial testing is preferred with high specificity, PPV, and PLR. Furthermore, testing CSF PCT alone is enough to obtain improved diagnostic efficiency. Indeed, the low levels of the various blood and CSF biochemical parameters do not always rule out intracranial infection and should be used with caution.

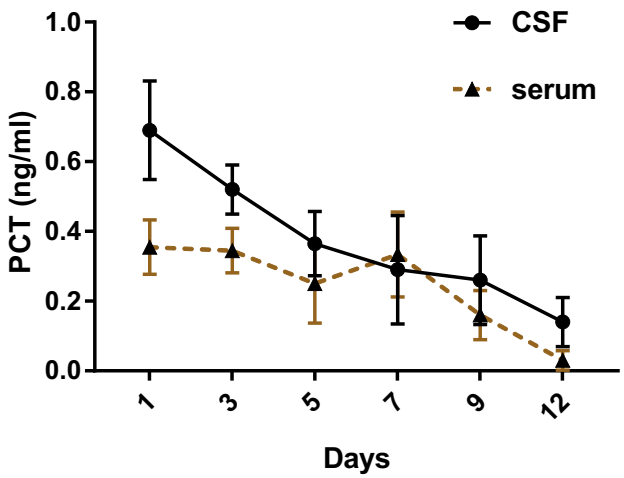

Figure 6. The curve of the PCT concentration with the time of treatment, CSF and serum PCT concentrations gradually decreased, and it roughly returned to normal on the 5th day. CSF, cerebrospinal fluid; PCT, procalcitonin.

GN bacteria have exceeded gram-positive bacteria as the causative agent of intracranial infection in the NICU at our hospital. We calculated a rough statistic on patients with bacteria culture positive intracranial infections and found that GN bacteria have become much more than gram-positive bacteria, accounting for approximately 70% of infections. In this study, 6 patients had CSF positive cultures in the infection group and all were GN bacteria (the specific microorganisms are shown in Table 3). Therefore, it is reasonable to believe that CSF PCT can also be regarded as a powerful indicator for identifying intracranial GN bacteria. Our results showed the PCT levels in the CSF culture positive group were higher than in the CSF culture negative group, although the differences were not statistically significant. This is consistent with the study by Wang et al.,[22] pointing out that the GN bacteria group showed higher levels of PCT and endotoxin than the gram-positive bacteria and fungi groups.

Dynamic changes in PCT can also provide a reference for clinical treatment. When the PCT concentration is becoming normal, we downgrade antibiotics according to the patient's clinical response to avoid drug resistance at any stage of treat. As we can infer from Figure 6, CSF PCT and serum PCT levels returned gradually to normal range after treatment. However, serum PCT showed a slight rebound on approximately the seventh day; this is probably a consequence of incomplete controlled inflammation. Consequently, PCT concentration on the third to

fifth day can be used as a reference for adjusting medication. In the infection group, patients' symptoms ameliorated, and biochemical indicators gradually returned to normal range. The difference was statistically significant ($P < 0.05$) before and after treatment except for the CSF protein ($P = 0.129$). The low CSF protein content itself and small sample numbers are possibly responsible for this outcome.

This study has some limitations. First, the small sample of patients studied may have caused the PCT value and other parameters to deviate from the norm and an increased corresponding error, which may mislead clinical diagnosis and treatment. Second, the cutoff values of CSF PCT and serum PCT were very different from the commonly used clinical recommended value, implying the little clinical significance and unimportant role of assisting intracranial infection. Third, we concentrated on only the PCT diagnostic value and neglected its prognostic value. Fourth, this study was aimed at adults and did not include children. Finally, other CSF and serum inflammatory indicators, such as interleukins, lactate, and lactate dehydrogenase were not studied, and these could have more potential usefulness in intracranial infection. Notwithstanding its limitations, this study does suggest the diagnostic and antibiotic reference value of CSF PCT.

CONCLUSIONS

Our study shows that CSF PCT is a reliable biomarker to distinguish between intracranial infection and no infection, especially when combined with serum PCT. It provides a feasible, quick, inexpensive, and simple method to help confirm infection in patients in whom clinical suspicion exists. Moreover, the empiric use of PCT to guide administration of antibiotics is worthwhile.

ACKNOWLEDGMENTS

We thank the Department of Clinical Laboratory at Subei People's Hospital of Northern Jiangsu Province for their support and Guangyu Lu at Yangzhou University for help with statistical calculations.

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Conflict of interest statement: This study was supported by the Program of Study on the Significance and Prognosis of Reoperation After Multi-modal Monitoring in Patients with Severe Head Injury (Grant No. YZ2018088), Yangzhou City Key Research and Development Project, China and the project of Jiangsu Commision of Health, China (Grant No. H2018064).

Received 24 July 2018; accepted 15 October 2018

Citation: World Neurosurg. (2019) 126:e1-e7. https://doi.org/10.1016/j.wneu.2018.10.241

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