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Potential of Interleukin-6 in Cerebrospinal Fluid for Diagnosing EVD-associated Ventriculitis in Patients with Subarachnoid Hemorrhage, Intracerebral Hemorrhage or Traumatic Brain Injury

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Abbreviations and Symbols

AUC	Area under the curve
CNS	Central nervous system
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computer tomography
EVD	External ventricular drain
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
ICU	Intensive Care Unit
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IL-6R	Interleukin-6 receptor
IL-8	Interleukin-8
IL-10	Interleukin-10
N%	Percentage of neutrophils
NPV	Negative predictive value
PPV	Positive predictive value
RBC	Red blood cell count
ROC	Receiver Operating Characteristic
SAH	Subarachnoid hemorrhage
SE	Sensitivity
SP	Specificity
TBI	Traumatic brain injury
TNF-α	Tumor necrosis factor alpha
TREM-1	Triggering factor expressed on myeloid cells-1
VC	EVD-associated ventriculitis
WBC	White blood cell count
+LR	Positive likelihood ratio
-LR	Negative likelihood ratio

Abstract

Objective: Placement of external ventricular drains (EVD) is one of the most frequent neurosurgical procedures and EVD-associated ventriculitis (VC) one of its most frequent complications, associated with a longer hospital stay, higher costs and possibly a reduced outcome. Early diagnosis of VC is crucial but difficult since microbiological, clinical and serum laboratory parameters are of limited sensitivity and specificity in neurointensive patients with severe underlying neurological conditions. The aim of the present study was to assess the potential of Interleukin-6 (IL-6) in cerebrospinal fluid (CSF) and other serum or CSF biomarkers for diagnosing VC in patients with subarachnoid hemorrhage, intracerebral hemorrhage or traumatic brain injury.

Methods: In a retrospective design, we analyzed levels of different biomarkers in serum and CSF of patients with EVD placement after subarachnoid hemorrhage (n = 75), intracerebral hemorrhage (n = 53) or traumatic brain injury (n = 24). We performed a ROC analysis to determine the biomarkers' potential for diagnosing VC.

Results: VC occurred in 36 patients who showed significantly elevated IL-6, cell count and percentage of neutrophils in CSF. Their diagnostic potential was good, varying from AUC of 0.831, 0.867 to 0.856 for IL-6, cell count and percentage of neutrophils, respectively. Unlike previous reports, glucose and protein in CSF did not reach significance and did not show any diagnostic potential. Levels of IL-6 were not associated with the severity of subarachnoid or intracerebral hemorrhage.

Conclusion: IL-6 is a promising biomarker for diagnosing VC in patients with subarachnoid hemorrhage, intracerebral hemorrhage and traumatic brain injury. Future studies are needed to replicate those findings in bigger samples and in patients of other underlying neurosurgical conditions.

Introduction

External Ventricular Drainage

Since the first performance of EVD by Claude-Nicholas Le Chat in 1744, its technique, technology and management have continuously been improved and indications have been expanded. Since the 1950s, EVDs have become a common neurosurgical procedure to monitor and treat a multitude of conditions such as brain tumors, different kinds of intracranial bleedings, TBI, craniocerebral infections, shunt failure and other conditions leading to acute hydrocephalus.[1,2] The most common indications are neurovascular conditions such as SAH or ICH and trauma.[3,4]

EVD placement offers five main benefits: (1) drainage of CSF or intraventricular blood to lower ICP and avoid hypertension-associated brain damage, (2) clearance of intraventricular hemorrhage to prevent hydrocephalus, (3) Gold Standard for direct, continuous ICP monitoring, (4) sampling of CSF for microbiological and laboratory assessment and (5) instillation of medications.[5–7]

Given these different diagnostic and therapeutic options, ventriculostomy is one of the most common acute neurosurgical procedures and was performed over 42,000 times in 2006 in America according to the National Neurosurgical Procedural Statistics published by the American Association of Neurological Surgeons.[8] A German survey in 2016 stated that almost 10,000 patients are treated with EVD in Germany per year.[5]

The median EVD dwelling time varies between different studies from four to eight days[3,9–11] and is associated to the length of ICU stay. The mortality of patients treated with EVD reaches up to 46.9%.[9]

In Germany, EVD insertion usually takes place in the operating theater (two thirds of cases) or in the ICU, whereas in an institution in Montreal most catheters are inserted at the bedside and in Hong Kong all were placed in the operating room.[5,12,13] The majority of German neurosurgical units performs subcutaneous tunneling but does not use impregnated catheters.[5]

Despite its frequency, complications of ventriculostomy such as malposition, hemorrhage, obstruction and infection occur due to lack of evidence-based guidelines for EVD insertion and management as well as diagnosis and management of complications.[2,7,8,14,15] Further risks of this procedure are pneumocephalus, damage to deep brain structures and overdrainage of cerebrospinal fluid.[16]

EVD-associated Ventriculitis

Definition

The first difficulty to encounter when researching on VC is the lack of a universal definition.[13] When applying different definitions of VC, infection frequency among culture positive CSF samples varied from 22% to 94% depending on the respective definition.[17] The American Centers for Disease Control (CDC) stated that ventriculitis can be diagnosed either when organisms are cultured from CSF or when a combination of a clinical sign and a laboratory or microbiological blood or CSF marker point towards ventriculitis.[17] The latter part is important because cultures from CSF can be false negative due to an earlier administraion of antibiotics in neurocritical care patients.[18] Apart from that CSF cultures take a long time while the diagnosis of a VC in a critically ill patient should be made quickly. Gram stains from CSF on the other hand often result negative, even in culture positive CSF samples.[19] In general, it is hard to distinguish clearly between contamination and infection without taking clinical signs into consideration.[18] This is why the diagnosis of a VC cannot be restricted to positive CSF cultures only. However, many respective studies focus on culture positive CSF samples only.[20–25]

Epidemiology and Risk Factors

In line with this issue of definition, the reported incidence of VC varies from 0% to 45%, but is usually around 10%, depending on the definition, technique of EVD insertion and its management.[3,9–11,16,26–29] VC is also more prevalent among patients with lower GCS on arrival.[9] The infection occurs on average eight to 14 days after insertion.[12,13,30]

The dwelling time of EVDs is significantly longer in patients with VC[27] and VC also goes along with a longer hospital stay and higher costs of care.[13,29,31] Whether the infection is associated with poorer (neurological) outcome or higher mortality remains unclear.[13,16,27,31]

The pathogens most commonly identified are gram positive coagulase-negative staphylococcus (s. epidermidis), s. aureus and enterococcus spp. Other gram positive and negative bacteria are reported with some variety between centers.[9,11–13,16,26,27] It is important to note that infection of meninges and ventricular ependyma caused by staphylococci provokes lighter inflammation and is therefore harder to detect in clinical examination or laboratory parameters. Non-bacterial VC is possible, but the isolation of fungi in VC is rare.[18]

A 2019 review identified several patient related risk factors for VC such as age, female sex, co-infection or CSF leakage at the site of insertion, which might lead to colonization. The diagnosis,

with SAH and intraventricular hemorrhage being high-risk, seemed to be a relevant risk factor. An increased frequency of CSF sampling was also related to a higher infection rate, possibly due to more frequent manipulation. ICP above 20 mmHg, maybe only as a reason for longer EVD dwelling time, was another risk factor. Furthermore, any neurosurgical operation was related to a higher risk for infection, maybe due to consequent surgery-associated immunosuppression or trauma.[32,33]

Among catheter-related risk factors, they revealed that antibiotic-coated catheters were infected less often than standard catheters. A longer catheterization period was associated with infection, but the infection might also be the reason for longer EVD dwelling times and not the consequence.[32] However, prophylactic catheter exchange did not proof to alter the risk of infection[26] as had previously been suspected.[34] Instead, multiple catheters were also related to VC, again, possibly because of further irrigation of the catheter system, which was another identified risk factor.[32]

Typical clinical findings of patients with VC are unspecific signs like fever > 38°C and neurological symptoms such as headache, vomiting or neck stiffness. In contrast to that, GCS was shown to be higher when infection occurred than when EVD was inserted, suggesting that patients benefited of the EVD placement.[35]

Significance of Inflammatory Markers in Diagnosis of EVD-associated Ventriculitis

As can be seen above, relying on microbiological findings for diagnosing VC is not sufficient and will probably lead to missed or delayed diagnosis.

Clinical signs are non-specific, which can lead to over-diagnosis. They are also often not assessable due to reduced consciousness or sedation in neurocritical care patients, and can be misinterpreted given the patient's general health, the underlying neurological condition and its symptoms or other infections acquired during the ICU stay. Currently, clinical diagnosis does not correlate with or cannot predict a positive CSF culture.[19,36]

The usual serum infection markers such as white blood cell count or acute phase proteins are mostly confounded by other systemic inflammations or the underlying neurosurgical diagnosis.[18]

Therefore, laboratory parameters in CSF are already used as additional criteria in combination with clinical signs for the diagnosis of VC. However, we are still lacking sufficient data on adequate biomarkers and their standard values, sensitivity and specificity in patients with ventriculostomy.[37]

Inflammatory Markers in Diagnosis of Bacterial Meningitis

Since VC could be considered an iatrogenic ventriculitis or meningitis, it can be assumed that biomarkers used in community-acquired bacterial meningitis might be suitable for VC as well.

In over 90% of patients with bacterial meningitis the CSF white blood cell count is elevated over 100 /μL and the CSF total protein concentration is raised. Apart from that, an elevated percentage of polymorphonuclear cells and hypoglycorrhachia are characteristics of bacterial meningitis.[38] An increased CSF/blood glucose ratio[39] or high CSF lactate[40,41] are further indicators of bacterial meningitis. Last but not least, several studies reported higher levels of CSF IL-6 and other cytokines in different cohorts of patients with bacterial meningitis.[42–49]

Interleukin-6

In the following, on overview over IL-6, its metabolism, physiology and pathology in the blood and in the CNS is given.

Interleukin-6 in Serum or Plasma

Systemic IL-6 is produced by a multitude of different, mainly immune cell types like macrophages, dendritic cells, lymphocytes, endothelial cells, fibroblasts, and muscle cells. Thereby, systemic IL-6 induces several systemic reactions such as mediation of the acute phase response, inducing the immunoglobulin production by B-cells, T-cell differentiation and other stimulating effects on the immune system. It also stimulates hemostasis and the hypothalamic-pituitary-adrenal axis and induces fever.[50] Apart from that, systemic IL-6 also regulates hepatocytes, hematopoietic progenitor cells, the skeleton, the cardiovascular system, the placenta and the nervous system.[51]

IL-6 remains detectable in the blood for a long time and there are even rapid blood concentration measurement systems available. However, its detectability is compromised by the presence of chaperones in the blood and because of high intraindividual fluctuations of the IL-6 level, which makes repeated measurements necessary.[52]

In a study of 550 individuals randomly selected from the Bavarian population, the median concentration of IL-6 in serum was 1.13 pg/mL.[53] In another study of 113 otherwise healthy elective orthopedic or urologic surgical patients without signs of systemic inflammation a median IL-6 concentration in plasma of 1 pg/mL, ranging widely from 1 to 79 pg/mL, was found.[54]

Intriguingly, serum levels of IL-6 are elevated in CNS diseases such as stroke or traumatic brain injury.[52] The CNS efficiently induces IL-6 in the periphery and thereby provokes a systemic inflammatory response to CNS injury.[55,56]

Interleukin-6 in the Central Nervous System

In the CNS, neuronal, glial and endothelial cells, especially astrocytes, have been shown to express IL-6 and IL-6R to different levels. IL-6 regulation in the CNS is subject to a complex interaction of inflammatory factors, neurotransmitters and neuropeptides.[51,57]

IL-6 is assumed to influence the development and functional recovery of sympathetic cells, sensory cells and hippocampal cells as well as adult gliogenesis and neurogenesis. Furthermore, IL-6 affects glial and endothelial cells, for example by regulating glial differentiation and survival and myelin production of oligodendrocytes.[51,58]

In neuroinflammatory processes, such as the response of the brain to trauma or stroke, IL-6 is secreted mostly by endothelial cells, monocytes and T-cells. It stimulates angiogenesis and the infiltration of brain tissue with monocytes and lymphocytes and it protects against oxidative stress and so-called excitotoxicity, which is nerve cell damage due to pathologically high levels of neurotransmitters. Further, it hinders apoptosis and neutrophils' diapedesis, inhibits TNF-α and provokes an increase in body temperature, the transition from innate to adaptive immune system and T-cell differentiation.[51]

The level of IL-6 in CSF can be determined either by assessing its biological activity, measured in units/ml via bioassay, or by analyzing the mere protein concentration via ELISA or other immunoassays. Bioassays provide the more relevant biological information but are less standardized and therefore less objectively comparable between different laboratories.

Whether measured by either of these methods, IL-6 in both CSF and parenchyma has been shown to be low or undetectable under physiological conditions but to rise in several pathologies.[59] An above mentioned study evaluated IL-6 levels in CSF and serum in 113 otherwise healthy individuals undergoing elective orthopedic or urologic surgery under spinal anesthesia. They determined IL-6 concentrations by ELISA and reported a median IL-6 level in CSF of 6 pg/mL, ranging from 1 to 34 pg/mL and being significantly higher than the plasma level.[54] Another study of 22 neurologically healthy individuals stated a mean IL-6 CSF concentration of 4.3 pg/mL ± 4.6 pg/mL, also determined by ELISA.[60]

Accordingly, CSF IL-6 has been found to be elevated in a multitude of conditions such as bacterial meningitis, encephalitis, viral CNS infections including HIV, stroke, traumatic brain injury, subarachnoid hemorrhage, neuromyelitis optica, Parkinsons' disease, brain tumors, epilepsy, major depression, autism or systemic lupus erythematosus with CNS involvement.[51,59,61–65] Multiple sclerosis, Alzheimers' disease, Huntingtons' disease and posttraumatic stress disorder have been shown to relate to IL-6 as well.[51,66]

Considering SAH for instance, IL-6 has been studied extensively. Both serum[67,68] and CSF levels[69–72] of IL-6 are elevated in patients with SAH as compared to healthy controls. This elevation of IL-6 in CSF was reproduced in a meta-analysis of 13 studies.[73] Furthermore, elevated IL-6 in both serum and CSF of SAH patients is associated with an unfavorable outcome, which can be due to delayed ischemia or vasospasm.[74–78] Also, a meta-analysis of 20 studies and 630 patients revealed a strong relationship between CSF IL-6 and clinical outcome.[79]

As for ICH, plasma IL-6 is higher in patients with adverse outcome or exitus and correlated to 30-day mortality, neurologic outcome and ICH volume.[80–82] CSF IL-6 is elevated in ischemic stroke and associated with stroke severity and functional outcome.[83,84] Japanese neurologists also reported a case of cardiac myxoma with multiple cerebellar hemorrhages and elevated IL-6 in CSF.[85] SNPs in the IL-6 promoter were considered to elevate the individual risk for ICH but a meta-analysis of 3 case-control studies including 446 ICH cases and 2,322 controls could not confirm this relationship.[86] In experimental ICH in dogs, elevated IL-6 was neither found in serum nor in CSF.[87] To our knowledge, there is no study so far investigating CSF IL-6 in ICH patients, possibly because there is often no routine clinical indication to draw CSF and therefore no data to perform such an analysis.

In context of TBI as well, elevated IL-6 levels in serum[88] and in CSF[89,90] have been reported. IL-6 in serum could differentiate between favorable and unfavorable outcome and high or low ICP, whereas, in another study, parenchymal IL-6 could not be correlated with ICP or tissue oxygenation.[91] However, measurements of IL-6 in plasma or serum also respond to other, extracranial inflammations or injuries which are common in TBI patients.[92] Therefore, CSF IL-6 was also studied and found to predict worse six-month neurologic outcome in TBI patients.[93–95] Further, IL-6 in plasma is associated to TBI related complications such as ARDS.[96]

High levels of CSF IL-6 have also been measured in newborns,[47,48] children[97] and adults[42] with bacterial meningitis. Since many studies addressed the diagnostic potential of IL-6 for bacterial

meningitis, a meta-analysis, based on data from 315 patients and 510 controls in nine independent studies, was performed in 2015.[43] It revealed a pooled SE of 0.91, SP of 0.93, +LR of 12.38, -LR of 0.10 and AUC of 0.97, making CSF IL-6 a good biomarker for diagnosing or ruling out bacterial meningitis and possibly for VC as well.

Diagnosis of EVD-associated Ventriculitis in Different Etiological Conditions

In the following, biomarkers in serum and CSF are described that have been shown or are assumed to be helpful in the diagnosis of VC in general neurosurgical patients.

Inflammatory Markers in Serum or Cerebrospinal Fluid

A great number of studies have investigated different markers of VC in serum or CSF, such as cells, membrane proteins and receptors, acute phase proteins, cytokines or metabolites. Those studies typically include neurological ICU populations with EVD or all neurosurgical patients with EVD, thus not differentiating between the etiological conditions, of which SAH appears to be the most frequent. In the following, a brief overview over the essential findings of those studies is given.

Regarding cells, peripheral WBC[98] and CSF pleocytosis are commonly found in VC patients.[24,35,99,100] Cell index, the ratio of leucocytes to erythrocytes in CSF divided by the ratio of leucocytes to erythrocytes in serum, is elevated three days prior to the first culture-positive CSF sample.[30]

As far as membrane proteins and receptors are concerned, the combination of CD62L expression on neutrophils and CC in CSF showed promising diagnostic accuracy.[24] The neutrophil CD64 index, a measure of CD64 expression on neutrophils, reached a moderate diagnostic accuracy.[101] TREM-1, a glycoprotein in the membrane of neutrophils, macrophages and mature monocytes, in CSF was shown to be a sensitive marker of VC.[22] Presepsin, a fragment of the soluble coreceptor CD14, which was recently studied in the context of different kinds of bacterial infection,[102] is in CSF a good indicator for VC.[103]

Among acute phase proteins, α1-antitrypsin, haptoglobin, and C-reactive protein in serum were not related to VC.[99] Despite few studies suggesting elevated serum procalcitonin levels in patients with VC,[104–106] it is probably not helpful in diagnosing VC.[22,103] Procalcitonin in CSF was not associated with VC either.[25]

Concerning cytokines, IL-6, IL-1β, IL-8 and TNF-α in CSF are elevated four days prior to fever onset and on the day of fever onset in patients with EVD and bacterial meningitis compared to patients with EVD and aseptic meningitis or no meningitis.[25] In other studies, findings of moderate diagnostic accuracy were reported for CSF IL-6, IL-1β and IL-8.[23,107]

The total protein level in CSF seems to be raised in patients with VC[20,103] but the findings of diagnostic accuracy differ tremendously between studies.[22,23] In some studies total protein levels even failed to reach significance.[25,35]

Regarding metabolites, excellent diagnostic potential was reported for CSF glucose.[20,22] However, in both studies the level of glucose in CSF was part of the diagnostic criteria of VC. Therefore, it is not surprising that high AUC values were found. CSF lactate was reported to be a moderate parameter for diagnosing VC.[20,108] Nonetheless, a bigger study indicates that CSF lactate alone would not be a sufficient criterion for diagnosis.[21]

To investigate the time course of parameter levels, several blood and CSF parameters were assessed on the day of EVD placement, two days prior to infection and on the day of infection, but no significant differences in parameter levels were found.[109]

Interleukin-6 in Cerebrospinal Fluid

Regarding IL-6, concentrations in CSF were significantly elevated in VC cases. Even four days before fever occurred, IL-6 was raised within culture-positive patients as compared to patients without clinical suspicion of meningitis. This indicates that CSF IL-6 is elevated even earlier than first clinical signs and symptoms occur. However, four and two days prior to fever onset and on the day of fever onset only moderate diagnostic potential for CSF IL-6 has been reported.[25]

In another study, CSF IL-6 levels differed significantly from controls in patients with a positive culture and clinical findings on the second and third day of infection, but not earlier.[37]

Other authors did not find significant differences in the IL-6 CSF levels between culture-positive and culture-negative CSF samples at all. As can be expected, its diagnostic performance was only average.[23]

In these studies, the lack of significance and low diagnostic potential may be due to the small sample size of only eight, eleven or ten culture-positive patients respectively.

Inflammatory Markers for EVD-associated Ventriculitis and their Time Course in Specific Conditions

However, some of the above-mentioned parameters such as CSF pleocytosis, glucose or lactate are common criteria for diagnosing VC. In some studies they also contributed to the clinical diagnosis of VC, which then influenced the patients' assignment to study groups. Statistical significance and good diagnostic performance of these markers is therefore not surprising but can be expected. Furthermore, the underlying neurological or neurosurgical etiology must be considered in analyzing CSF parameters since conditions such as intracranial hemorrhage or open head trauma influence the occurrence of pathogens, the inflammatory process and thereby the presence of cell types, cytokines and other agents.

Therefore, we will focus on specific etiologies and cytokine levels in CSF, which in prior studies have shown promising diagnostic accuracy among the parameters that do not belong to VC criteria yet.

Subarachnoid Hemorrhage

When assessing lysozyme and several immunoglobines in CSF and serum, lysozyme was significantly elevated in SAH patients with VC and peaked few days after the microbiological confirmation of a positive CSF culture.[110] Another study of only 37% of subjects with EVD reported that only temperature and CSF RBC were significantly elevated in culture-positive VC cases. Other clinical signs and CSF WBC, glucose and protein did not differ significantly.[111]

Regarding cytokines, until up to 13 days post EVD insertion, CSF concentrations of IL-1ß, IL-1 receptor antagonist (IL-1Ra), IL-10, TNF-α and TNF receptor 1 (TNF-R1) were similar to those in plasma, whereas TNF receptor 2 (TNF-R2) and IL-1 receptor 2 (IL-1R2) concentrations were lower in CSF than in plasma. IL-1 and TNF receptor levels showed little variance between subjects. IL-1Ra and IL-1ß as well as TNF-R2 and IL-10 showed similar patterns. IL-6 and IL-8 were remarkably elevated in CSF compared to plasma and their patterns were similar. CSF IL-6 levels differed significantly between patients with and without VC. According to the published figures, IL-1ß, IL-1R2, IL-6 and IL-8 in CSF showed a peak on day seven after EVD insertion.[112]

Intracerebral Hemorrhage

To our knowledge, there are no reports on cytokine levels in patients with ICH and EVD.

Traumatic Brain Injury

Cytokines were assessed on days two to seven after SAH or TBI. CSF IL-1ß and IL-6 peaked on day two and significantly decreased afterwards. The overall and maximum response of IL-6 was stronger than IL-1ß, and IL-1ß and IL-6 levels were higher in SAH as compared to TBI patients. In contrast, IL-10 remained constant through days two to seven but was also higher among patients with SAH. In female patients higher levels of IL-1ß and IL-6 were detected.[113]

Comparing Subarachnoid Hemorrhage, Intracerebral Hemorrhage and Traumatic Brain Injury

When studied in patients with SAH, ICH and TBI, cell indexes differed significantly between cases with and without VC and showed excellent diagnostic potential. When calculating the relative variation of the cell index on the day of diagnosis compared to a previously obtained, patient specific baseline value, moderate diagnostic accuracy is reported. A subgroup analysis revealed also excellent diagnostic potential for cell index in SAH, ICH and TBI patients, respectively. However, this result should be interpreted cautiously since there were small numbers of subjects in the different conditions.[114]

We do not know of any studies that compared cytokine levels between patients with SAH, ICH or TBI.

Aim of the Work

For diagnosing VC, IL-6 in CSF seems to be a promising inflammatory marker, even better than many currently applied diagnostic criteria such as CSF pleocytosis or CSF glucose. Many of these studies referred to general neuro ICU patient populations. However, it can be expected that different neurosurgical conditions alter the presence of blood, cells or foreign materials in the ventricles and thereby influence the neuroinflammatory reaction and hence the levels of cytokines in CSF. We are still lacking sufficient data on levels of IL-6 in CSF and its diagnostic accuracy in specific patient subgroups, to determine whether CSF IL-6 could be useful in diagnosing VC.

The aim of this study was to investigate and compare levels of CSF IL-6 and other biomarkers in patients with SAH, ICH and TBI, with and without VC. We also analyzed the biomarkers' potential in diagnosing VC.

Furthermore, we investigated whether CSF IL-6 concentrations would be associated with the severity of SAH or ICH.

Materials and Methods

Study Design

We retrospectively selected patients of our neurosurgical ICU from January 2012 through October 2018 in whom an EVD was placed after SAH (n = 75), TBI (n = 24) or ICH (n = 53). Hospital charts were reviewed to gather epidemiological data such as age or gender as well as information on the clinical course such as day of infection, number of EVDs used, number of EVD changes, GCS on admission, GOS at discharge, antibiological treatment, immunosuppression and the occurrence of other infections, sepsis, aspiration, fever, infarction, seizures, or shunt dependency. Additionally, we documented for SAH patients Fisher and WFNS grades, CHESS score, localization of the aneurysm, therapy (clipping or coiling), the occurrence and day of vasospasm and steroid insufficiency. In ICH cases, we also gathered information on the localization of the bleeding and in TBI patients, on TBI severity. Then, we collected the individual biomarker data regarding serum levels of IL-6, CRP, WBC, and percentage of neutrophils, as well as CSF levels of IL-6, CC, percentage of neutrophils, glucose, and total protein from our patient data base. In SAH and TBI patients, we additionally documented serum levels of glucose, cortisol, procalcitonin, and liver enzymes, and CSF levels of cortisol. In SAH patients, finally, data on blood flow velocities in transcranial Doppler ultrasonography was gathered, as well.

We compared the levels of different inflammatory markers in serum and cerebrospinal fluid between a patient group (with ventriculitis) and a control group (without ventriculitis). In the patient group we used the marker level on the day of onset of ventriculitis. In the control group instead, we chose the marker level on day eleven, since ventriculitis occurred in our patients on average eleven days after admission.

Since we chose a retrospective design, no intervention and no diagnostic or therapeutic procedure was performed for the purpose of the study. Our study was approved by the institutional ethical committee (reference number: 557-16).

Clinical Management of Intensive Care Patients with Need for an EVD

SAH was diagnosed by an initial brain CT scan and confirmed by CT angiography or digital subtraction angiography (DSA), which was performed in all patients within 48 hours after initial bleeding. Existence and severity of TBI was diagnosed on admission using Glasgow Coma Scale (GCS) scores and CT findings. ICH was diagnosed by head CT scan and the Glasgow Coma Scale was used in the patients' clinical assessment.

An EVD was placed in case of intraventricular hemorrhage and acute hydrocephalus or SAH/ICH and clinically limited neurological evaluability because of GCS ≤ 8 or sedation.

The EVD implantation follows a routine procedure and is performed in the emergency department or in the operating room. Under strictly sterile conditions and after a routine preoperative antibiotic prophylaxis (1.5 g or 3 g of cefuroxime intravenously) the hair is shaved and the skin around the Kocher's point (12 cm posterior to the nasion and 2.5 cm from the midline) is disinfected with a povidone-iodine solution. Through the skin incision and a 4 mm drill hole an uncoated ventricular catheter (Accuracy Catheter, Integra, Germany) is inserted along a standardized trajectory into the lateral ventricle. After the catheter placement the spontaneous CSF flow is checked, and a control CT scan is performed to assure the accuracy of the catheter position and to exclude an early procedure-associated bleeding. We do not perform any subcutaneous tunneling of the distal catheter but stabilize it by suture ligature and cover the insertion side by sterile dressing. In the end, the ventricular catheter is connected to a closed CSF collection system under sterile conditions.

Routine Monitoring of Inflammatory Markers

As part of our clinical routine, several serum and CSF inflammatory markers were assessed on a daily base, amongst which the following are of interest for the present study: The serum white blood cell count ($_{s}$WBC), serum C-reactive protein ($_{s}$CRP), serum Interleukin-6 ($_{s}$IL-6), CSF glucose ($_{CSF}$Glc), CSF total protein ($_{CSF}$TP), CSF cell count ($_{CSF}$CC) and CSF Interleukin-6 ($_{CSF}$IL-6) were measured approximately daily. The percentage of neutrophils in serum ($_{s}$N%) and CSF ($_{CSF}$N%) were evaluated about twice a week in patients with suspicion of bacterial infection or blood count irregularities.

The CSF samples were aspirated by a physician via the proximal 3-way stock. All serum and CSF samples were analyzed in the Department of Laboratory Medicine at our hospital according to the respective standards and manufacturers' instructions.

Definition of Ventriculitis

Consistent with previous studies, we used a modification[35] of the CDC criteria for nosocomial infections[115] for diagnosing EVD-associated ventriculitis. Ventriculitis must meet one of the following criteria: (a) positive microbiological culture or Gram stain of CSF, EVD tip, or wound swab of the EVD insertion site, (b) one of the following clinical signs without another identifiable cause: fever (> 38° C), headache, stiff neck, meningeal sign, cranial nerve signs or irritability, AND any of the following laboratory results: $_{CSF}$CC > 5/µL, $_{CSF}$TP > 0.45 g/L, CSF/blood glucose ratio < 0.5, AND response to antibiotic treatment.

The day on which a specific antibiotic therapy was administered was defined as the onset of infection. According to our clinical standards, EVD-associated ventriculitis was typically treated with vancomycin and meropenem first.

Statistical Analysis

To determine statistically significant differences in the biomarker concentrations of patients with and without ventriculitis we performed a univariate ANOVA.

Secondly, we calculated receiver operating characteristic (ROC) curves and the corresponding area-under-the-curve (AUC) value to examine the diagnostic potential of the biomarkers. Positive (+LR) and negative (-LR) likelihood ratios were calculated as follows:

$$+LR = \text{sensitivity}/(1-\text{specificity})$$

$$-LR = (1-\text{sensitivity})/\text{specificity}$$

The optimal threshold was defined according to Youden's J statistic as the biomarker concentration that showed maximized sensitivity and specificity.

Apart from that we performed a Chi squared test to look for an association between the severity of the condition and the development of a ventriculitis. The severity of SAH was operationalized by WFNS grades, whereas we used GCS scores to measure the ICH severity.

Our statistical analysis was carried out by using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) 25.0 for Windows.

Results

Patient Population

The patient population consisted of 152 patients. Thereof 70 were male and 82 female, suffering from SAH (n = 75), TBI (n = 24) or ICH (n = 53). The average patient age was 55.8 ± 15.6 years (range 16 - 88 years). Ventriculitis occurred in 36 patients on average 11.4 ± 9.9 days (range 2 - 48 days) after admission. General patient characteristics are summarized in Table 1.

Statistically significant differences between VC cases and aseptic cases could not be found regarding age (t-test), gender and condition (chi-square test) and GOS score (mann-whitney u test). However, GCS scores on admission differed significantly, indicating that patients who developed an infection had been more severely injured and neurologically impaired on admission compared to those who showed an aseptic course. Intriguingly, GOS scores were lower (indicating more severe injury) in aseptic patients than in patients with VC. This comparison, though, missed statistical significance.

TABLE 1. Characteristics of the patient population

		All patients	EVD-associated ventriculitis	Aseptic course	p-value
Number		152	36 (23.7%)	116 (76.3%)	
Age Mean ± SD (y)		55.8 ± 15.6	56.8 ± 12.1	55.5 ± 16.5	0.672
Age range (y)		16 - 88			
Gender	**Male**	70 (46.1%)	16 (44.4%)	54 (46.6%)	0.825
	Female	82 (53.9%)	20 (55.6%)	62 (53.4%)	
Condition	**SAH**	75 (49.3%)	20 (55.6%)	55 (47.4%)	
	TBI	24 (15.8%)	5 (13.9%)	19 (16.4%)	0.695
	ICH	53 (34.9%)	11 (30.6%)	42 (36.2%)	
GCS on admission		9.6 ± 4.6	7.1 ± 4.2	10.2 ± 4.5	0.029
GOS		2.7 ± 1.1	3.1 ± 1.0	2.6 ± 1.1	0.056
Onset of ventriculitis Mean ± SD (d)			11.4 ± 9.9		
Onset of ventriculitis range (d)			2 - 48		

Percentage of group in brackets.

An overview of the patient population by condition is given in Table 2. Among the patients with SAH, 57.1% presented with SAH at WFNS grade 4 or 5. There were no significant age differences between conditions as determined by an ANOVA. However, a chi-squared test showed that the difference in gender distribution by conditions was strongly significant. While more women presented with SAH, TBI occurred predominantly in men and ICH cases in both males and females.

TABLE 2. Patient characteristics by condition

		SAH	TBI	ICH	p-value
Number		75 (49.3%)	24 (15.8%)	53 (34.9%)	
Age Mean ± SD (y)		55.7 ± 12.1	56.5 ± 19.5	55.6 ± 17.8	0.976
Gender	**Male**	21 (28%)	20 (83.3%)	29 (54.7%)	<0.001
	Female	54 (72%)	4 (16.7%)	24 (45.3%)	
Severity		**WFNS 1-3** 24 (42.9%)		**GCS 8-15** 29 (67.4%)	
		WFNS 4-5 32 (57.1%)		**GCS 0-7** 14 (32.6%)	
GCS on admission		9.6 ± 4.9		9.7 ± 4.5	

Percentage of group in brackets.

Diagnostic Value of Different Inflammatory Markers

Figures 1 and 2 show the distributions of all inflammatory parameters at onset of infection in the patient group (ventriculitis) or on day eleven for the control group (aseptic course).

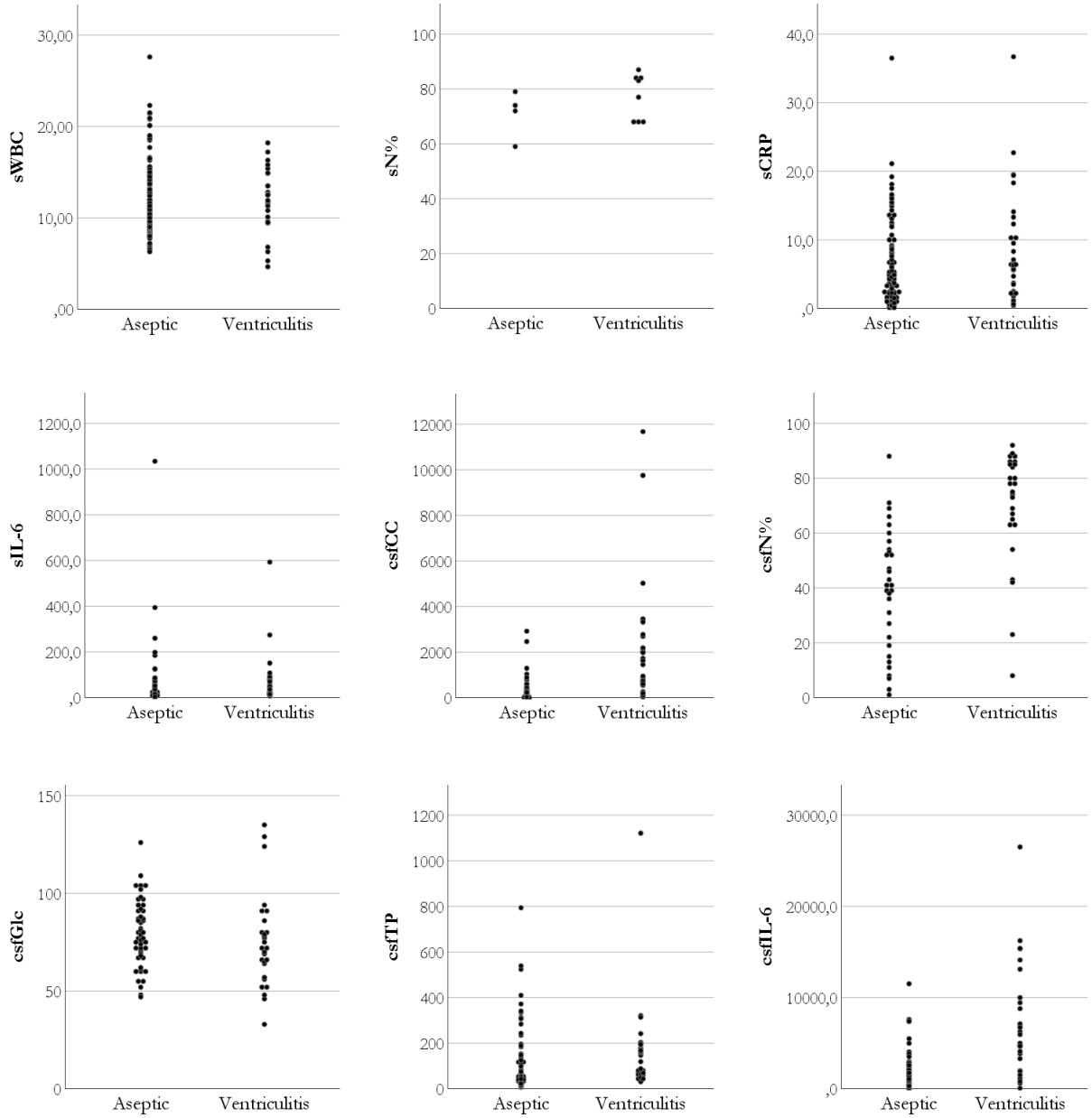

FIGURE 1. Scatterplots illustrate the levels of inflammatory markers in aseptic and infected patients. sWBC, white blood cell count in serum in G/L; sN%, percentage of neutrophils in serum; sCRP, C-reactive protein in serum in mg/dL; sIL-6, Interleukin-6 in serum in pg/mL; csfCC, cell count in cerebrospinal fluid in /µL; csfN%, percentage of neutrophils in cerebrospinal fluid; csfGlc, glucose in cerebrospinal fluid in mg/dL; csfTP, total protein in cerebrospinal fluid in mg/dL; csfIL-6, Interleukin-6 in cerebrospinal fluid in pg/mL.

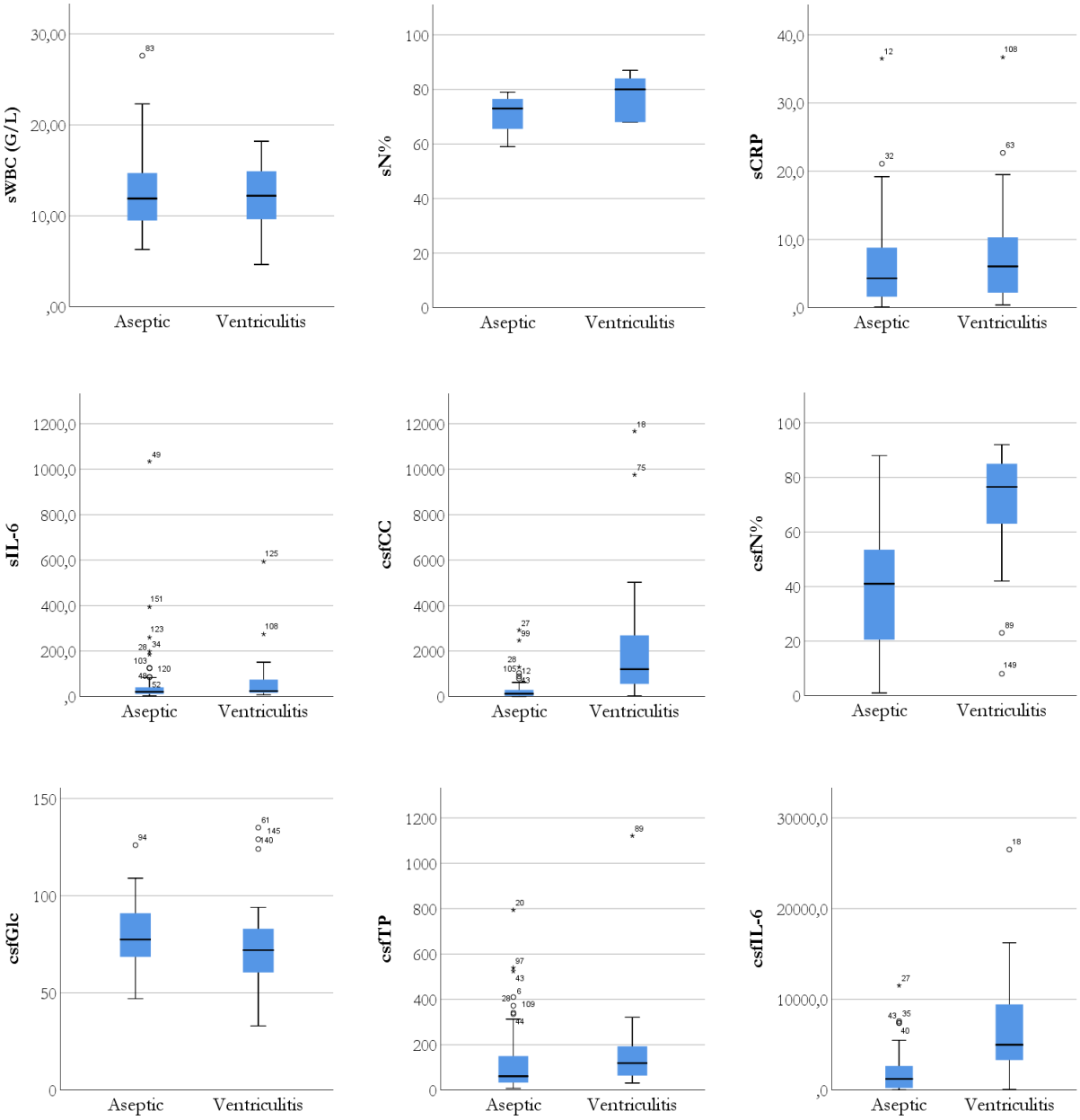

FIGURE 2. Box plots show the distribution of inflammatory marker levels in aseptic and infected patients. sWBC, white blood cell count in serum in G/L; sN%, percentage of neutrophils in serum; sCRP, C-reactive protein in serum in mg/dL; sIL-6, Interleukin-6 in serum in pg/mL; csfCC, cell count in cerebrospinal fluid in /µL; csfN%, percentage of neutrophils in cerebrospinal fluid; csfGlc, glucose in cerebrospinal fluid in mg/dL; csfTP, total protein in cerebrospinal fluid in mg/dL; csfIL-6, Interleukin-6 in cerebrospinal fluid in pg/mL.

An overview over the results of the ANOVA to detect mean differences of the inflammatory marker levels between the two groups is given in Table 3.

TABLE 3. Means and standard deviation of inflammatory marker levels in patients with VC and controls and result of ANOVA significance testing

Inflammatory Marker	n	Ventriculitis	Aseptic	Significance
$_{s}$WBC (G/L)	119	11.89 ± 3.55	12.58 ± 4.19	NS
$_{s}$N% (%)	12	77.38 ± 8.25	71.00 ± 8.52	NS
$_{s}$CRP (mg/dL)	131	8.05 ± 7.87	6.19 ± 6.15	NS
$_{s}$IL-6 (pg/mL)	128	63.61 ± 107.30	48.45 ± 116.80	NS
$_{CSF}$CC (/µL)	95	2072.93 ± 2669.27	277.88 ± 508.235	.001
$_{CSF}$N% (%)	57	69.92 ± 20.96	39.10 ± 22.33	.000
$_{CSF}$Glc (mg/dL)	80	164.38 ± 200.52	125.03 ± 148.60	NS
$_{CSF}$TP (mg/dL)	98	164.38 ± 200.52	125.03 ± 148.60	NS
$_{CSF}$IL-6 (pg/mL)	128	7073.50 ± 6015.70	1828.06 ± 2213.75	.000

sWBC, white blood cell count in serum; sN%, percentage of neutrophils in serum; sCRP, C-reactive protein in serum; sIL-6, Interleukin-6 in serum; csfCC, cell count in cerebrospinal fluid in; csfN%, percentage of neutrophils in cerebrospinal fluid; csfGlc, glucose in cerebrospinal fluid; csfTP, total protein in cerebrospinal fluid; csfIL-6, Interleukin-6 in cerebrospinal fluid, NS, not significant ($P > 0.05$).

ROC curves of all inflammatory markers are presented in figure 3.

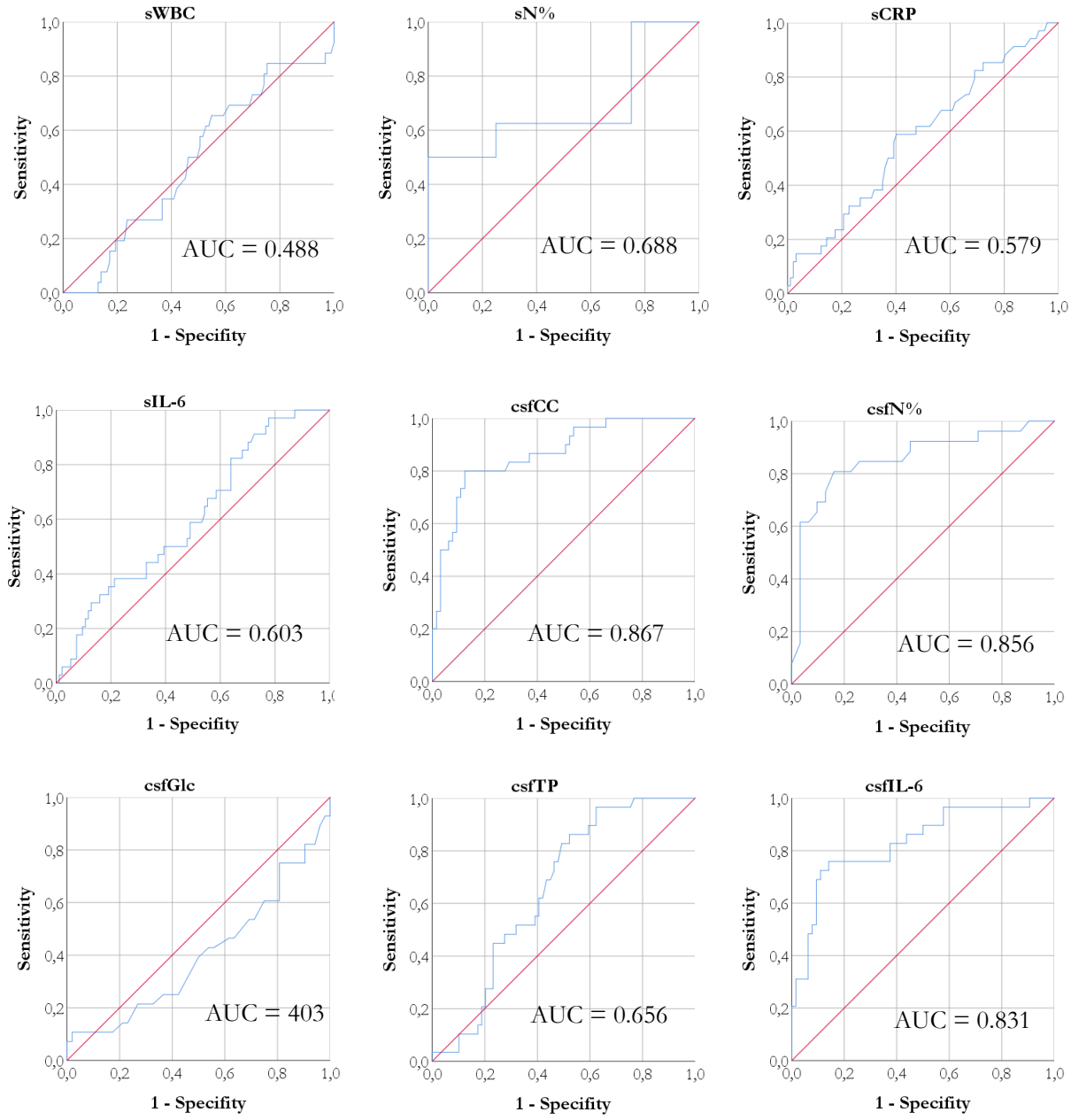

FIGURE 3. ROC curves illustrate the diagnostic potential of the inflammatory markers to differentiate between ventriculitis and aseptic course. sWBC, white blood cell count in serum; sN%, percentage of neutrophils in serum; sCRP, C-reactive protein in serum; sIL-6, Interleukin-6 in serum; csfCC, cell count in cerebrospinal fluid in; csfN%, percentage of neutrophils in cerebrospinal fluid; csfGlc, glucose in cerebrospinal fluid; csfTP, total protein in cerebrospinal fluid; csfIL-6, Interleukin-6 in cerebrospinal fluid.

In Table 4 the results of the ROC analysis for all inflammatory parameters are displayed.

TABLE 4. Characteristics of the diagnostic potential of different biomarkers to differentiate between ventriculitis and aseptic courses

Inflammatory Marker	AUC	Cutoff	SE	SP	+LR	-LR
$_{s}$WBC (G/L)	0.488 (0.365-0.611)	11.25	0.654 (0.462-0.806)	0.452 (0.354-0.553)	1.192 (0.853-1.667)	0.766 (0.432-1.360)
$_{s}$N% (%)	0.688 (0.373-1.000)	81.00	0.500 (0.215-0.785)	1.000 (0.510-1.000)	ND	0.500 (0.250-1.000)
$_{s}$CRP (mg/dL)	0.579 (0.467-0.690)	5.55	0.588 (0.422-0.736)	0.598 (0.498-0.690)	1.463 (1.009-2.121)	0.689 (0.446-1.062)
$_{s}$IL-6 (pg/mL)	0.603 (0.496-0.711)	10.25	0.971 (0.851-0.995)	0.223 (0.151-0.318)	1.250 (1.105-1.414)	0.132 (0.018-0.942)
$_{CSF}$CC (/µL)	0.867 (0.788-0.946)	517.00	0.800 (0.627-0.905)	0.877 (0.776-0.936)	6.500 (3.316-12.742)	0.228 (0.111-0.469)
$_{CSF}$N% (%)	0.856 (0.751-0.961)	61.50	0.808 (0.621-0.915)	0.839 (0.674-0.929)	5.008 (2.196-11.420)	0.229 (0.103-0.512)
$_{CSF}$Glc (mg/dL)	0.403 (0.268-0.538)	116.50	0.107 (0.037-0.272)	0.981 (0.899-0.997)	5.571 (0.608-51.096)	0.910 (0.796-1.041)
$_{CSF}$TP (mg/dL)	0.656 (0.549-0.762)	43.50	0.966 (0.828-0.994)	0.377 (0.272-0.495)	1.549 (1.274-1.885)	0.092 (0.013-0.643)
$_{CSF}$IL-6 (pg/mL)	0.831 (0.737-0.925)	3144.0	0.759 (0.579-0.878)	0.859 (0.754-0.924)	5.395 (2.846-10.226)	0.281 (0.146-0.540)

sWBC, white blood cell count in serum; sN%, percentage of neutrophils in serum; sCRP, C-reactive protein in serum; sIL-6, Interleukin-6 in serum; csfCC, cell count in cerebrospinal fluid in; csfN%, percentage of neutrophils in cerebrospinal fluid; csfGlc, glucose in cerebrospinal fluid; csfTP, total protein in cerebrospinal fluid; csfIL-6, Interleukin-6 in cerebrospinal fluid, AUC, Area under the curve; SE, sensitivity, SP, specificity, +LR, positive likelihood ratio, -LR, negative likelihood ratio.

Cell Count in Cerebrospinal Fluid

The mean cell count in the CSF of 2072.93 ± 2669.27 /µL in the patient group (range 34 /µL to 11670 /µL) was significantly higher (P = .001) than the mean of 277.88 ± 508.235 /µL in the control group (range 1 /µL to 2922 /µL).

Examining the diagnostic potential of the CSF cell count we determined an AUC value of 0.867 and the optimal threshold at 517 /µL (SE = 80%, SP = 87%, +LR = 6.50, -LR = 0.23).

Percentage of Neutrophils in Cerebrospinal Fluid

The percentage of neutrophils in CSF showed another significant mean difference (P = .000) between the ventriculitis group (69.92% ± 20.96%, range 8% to 92%) and the aseptic group (39.10% ± 22.33%, range 1% to 88%).

The respective AUC value reached a level of 0.856 and we calculated the ideal cutoff value to be at 61.5% (SE = 81%, SP = 84%, +LR = 5.01, -LR = 0.23).

Interleukin-6 in Cerebrospinal Fluid

Interleukin-6 in CSF also differed significantly (P = .000) between the infection group with a mean of 7073.50 ± 6015.70 pg/mL (range 70 pg/mL to 26515 pg/mL) as compared to the control group at 1828.06 ± 2213.75 pg/mL (range 16 pg/mL to 11519 pg/mL).

We identified an AUC value of 0.831 and the optimal threshold at 3144 pg/mL (SE = 76%, SP = 86%, +LR = 5.40, -LR = 0.28).

Other Inflammatory Markers

All assessed serum inflammatory markers and the remaining CSF parameters did not proof to vary significantly between infected and aseptic patients.

No significant difference (P = .448) could be detected in the white blood cell count of the serum of patients (11.89 ± 3.55 G/L, range 4.65 G/L to 18.2 G/L) and controls (12.58 ± 4.19 G/L, range 6.3 G/L to 27.6 G/L). Accordingly, the percentage of neutrophils in serum in the infected group (77.38% ± 8.25%, range 68% to 87%) and the aseptic group (71.00% ± 8.52%, range 59% to 79%) did not differ significantly (P = .240). Moreover, the C-reactive protein value in the serum of patients with ventriculitis (8.05 ± 7.87 mg/dL, range 0.4 mg/dL to 36.7 mg/dL) and without (6.19 ± 6.15 mg/dL, range 0.1 mg/dL to 36.5 mg/dL) showed no significant difference (P = .161). Furthermore, also the mean difference of Interleukin-6 in the serum of the infected patients (63.61 ± 107.30 pg/mL, range 7.1 pg/mL to 593 pg/mL) and of aseptic patients (48.45 ± 116.80 pg/mL, range 2.2 pg/mL to 1034 pg/mL) was not statistically significant (P = .509).

Among the CSF parameters the CSF glucose value did not differ significantly (P = .390) between our patient group (164.38 ± 200.52 mg/dL, range 33 mg/dL to 135 mg/dL) and our control group (125.03 ± 148.60 mg/dL, range 47 mg/dL to 126 mg/dL). Finally, no significant mean difference (P = .285) in the CSF total protein value of patients with ventriculitis (164.38 ± 200.52 mg/dL, range 31 mg/dL to 1121 mg/dL) and without (125.03 ± 148.60 mg/dL, range 7 mg/dL to 794 mg/dL) could be detected.

Association between the Severity of the Condition and the Development of Ventriculitis

By using chi squared tests we determined whether there was an association between the severity of the bleeding and the probability to develop an EVD-associated infection.

Subarachnoid Hemorrhage

Table 5 shows the frequencies of ventriculitis and aseptic course in patients with low grade SAH (WFNS grades 1-3) or high grade SAH (WFNS grades 4-5) respectively. A chi squared test found no significant association ($P = .179$).

TABLE 5. Number of patients with low grade and high grad SAH in the patient and control group and p-value from chi squared test

	WFNS grades 1-3	WFNS grades 4-5	p-value
Aseptic course	19	20	0.179
Ventriculitis	5	12	

Intracerebral Hemorrhage

Analogously, we tested the association between the GCS score on admission as a measure of ICH severity and the development of ventriculitis, which did not proof to be significant ($P = .442$). The result of the chi squared test crosstabulation table can be seen in Table 6.

TABLE 6. Number of patients with low grade and high grad ICH in the patient and control group and p-value from chi squared test

	GCS 8-15	GCS 0-7	p-value
Aseptic course	24	10	0.442
Ventriculitis	5	4	

Discussion

The aim of the current work was to investigate levels of CSF IL-6 and other biomarkers in patients with SAH, ICH and TBI, with and without VC, to analyze the biomarkers' potential in diagnosing VC in those patients and to look for an association between levels of IL-6 in CSF and the severity of SAH or ICH.

Our principal findings include that IL-6 in CSF, cell count in CSF and the percentage of neutrophils in CSF differ significantly among patients with SAH, ICH or TBI and VC as compared to patients without VC. These parameters showed good potential in diagnosing VC in our population. Furthermore, we could not find a significant association between the levels of IL-6 in CSF and the severity of SAH, measured by WFNS grades, or ICH, measured by GCS on admission, in our study population.

All other assessed biomarkers, which are white blood cell count, percentage of neutrophils, CRP and IL-6 in serum, as well as glucose and total protein in CSF, did not differ significantly between patients with and without VC and hence did not show any accuracy in diagnosing VC in our population.

Diagnostic Value of Different Inflammatory Markers

Our results regarding the diagnostic accuracy of our principal biomarkers are discussed in the following.

Interleukin-6 in Cerebrospinal Fluid

In our study, CSF IL-6 was significantly elevated in patients with VC ($P < 0.000$) and showed good diagnostic potential, even better than other conventional biomarkers that belong to the CDC criteria for ventriculitis and were simultaneously assessed in our study. The optimal cutoff for IL-6 in CSF was 3144 pg/mL (AUC 0.831, SE 0.759, SP 0.859, +LR 5.395, -LR 0.281). This indicates that, given an IL-6 CSF level > 3144 pg/mL, the patient's probability to suffer from VC is 5.4-fold higher than his pretest probability. On the other hand, an IL-6 concentration < 3144 pg/mL decreases the patient's posttest probability to about one fourth.[116]

Table 7 gives an overview of our results and previously reported findings regarding the diagnostic potential of IL-6 in CSF for diagnosing VC.

Table 7. Results of the present study and previous findings regarding the accuracy of IL-6 in CSF in diagnosing VC

	Present study	Hopkins et al. 2012	Liu et al. 2015	Boeer et al. 2011	Schade et al. 2006
n (VC / controls)		7 / 14	8 / 11	10 / 40	10 / 11
Mean in VC cases (pg/mL)	7073.50				
Mean in controls (pg/mL)	1828.06				
p	0.000	0.04	< 0.05	> 0.05	< 0.001
Cutoff (pg/mL)	3144.0		2636.0	6418	
AUC	0.831		0.731	0.69	
SE	0.759		0.875	0.50	
SP	0.859		0.539	0.90	
PPV				0.56	
NPV				0.88	
+LR	5.395				
-LR	0.281				
Population	SAH, TBI, ICH	SAH	general	general	
Remark			on day of fever onset		second and third day of infection

Liu et al. (2015)[25] studied 32 patients with EVD and fever, and distinguished between nonmeningitis patients, who did not develop clinical signs of meningitis, patients with aseptic meningitis, who presented with adequate symptoms but with a negative CSF culture, and bacterial meningitis cases, who showed both clinical signs and a positive CSF culture. On the day of fewer onset and two days prior to fever onset, IL-6 level differences varied significantly between bacterial or aseptic meningitis versus no meningitis cases and between bacterial meningitis and no meningitis patients. Even four days before fever occurred, IL-6 was significantly elevated within culture-positive patients as compared to patients without clinical suspicion of meningitis. Four and two days prior to fever onset and on the day of fever onset they reported moderate AUCs of 0.587, 0.7404 and 0.731, SEs of 0.75, 0.625 and 0.875, and SPs of 0.539, 0.7692 and 0.539 with cutoffs of 2364 pg/mL, 3973 pg/mL and 2636 pg/mL, respectively. Hence CSF IL-6 was elevated even before symptoms of VC occurred.

Schade et al. (2006)[37] assessed 21 patients with EVD and found CSF IL-6 to be elevated in culture-positive cases with laboratory findings corresponding to VC only on the second and third

day of infection. They could not determine a cutoff that would permit SE and SP of more than 0.6. However, in their study, detected IL-6 levels did not exceed 3600 pg/mL which can easily be outreached under pathological conditions.

Boeer et al. (2011)[23] did not find significant differences in IL-6 levels between culture-positive and culture-negative CSF samples. As can be expected, its diagnostic performance was only average. They reported an AUC of 0.69, SE of 0.50, SP of 0.90, PPV of 0.56 and NPV of 0.88 with an optimal cutoff of 6418 pg/mL. High SP and low SE indicate that elevated IL-6 levels were not present in all culture-positive patients but rare among culture-negative samples, meaning that elevated CSF IL-6 should always lead to the suspicion of VC.

In these studies, lack of significance and low AUCs, SEs and SPs might be due to the small sample size of only eight, eleven or ten culture-positive patients respectively.

When studying 21 patients with SAH and EVD, Hopkins et al. (2012)[112] reported that IL-6 was significantly elevated in patients with symptoms of VC as compared to those without.

Finally, several studies on bigger samples have shown that IL-6 in CSF is significantly elevated or has potential in diagnosing community-acquired bacterial meningitis in children and adults.[42–49] Since VC can be considered a condition of iatrogenic bacterial meningitis, underlying inflammatory reactions and hence biomarker levels can be assumed to be similar, which also points towards a benefit in using CSF IL-6 for diagnosing VC.

Both our reported cutoff and the diagnostic performance fit to previous reports, and we could replicate those findings in a bigger and more specific sample. We conclude that CSF IL-6 shows potential for diagnosing VC in patients with SAH, ICH or TBI and studies on big samples of different etiologies are needed to confirm a reliable cutoff for all kinds of patient groups.

Cell count in Cerebrospinal Fluid

In our study, CSF cell count was significantly higher in VC cases ($p = 0.001$) and performed well in the ROC analysis using the optimal cutoff of 517 cells/µL (AUC 0.867, SE 0.800, SP 0.877, +LR 6.500, -LR 0.228) in our analysis.

As can be seen in Table 8, our result is in line with most of the previous studies on CSF cell count or CSF WBC, that reported strongly significant differences between cell counts of patients with and without VC, such as in a study of more than 500 patients by van Mourik et al. (2011), who also included lumbar drains,[117] or in the above mentioned cohort studied by Liu et al. (2015).[25] However, in a study of eleven VC patients and 37 controls with SAH, Hoogmoed et al.

(2017)[111] reported no significant differences regarding CSF WBC, glucose or total protein. They compared both patients with and without clinical suspicion of VC or culture-positive and culture-negative patients among those with clinical suspicion of VC. Boeer et al. (2011)[23] investigated ten patients and 40 controls, but reported no significance for CSF CC and CSF total protein. They considered only culture-positive samples as patients, despite the previously discussed high risk of false-negative or false-positive results. In both studies, the lack of significance might be due to rather small sample sizes. Furthermore, cell counts can always be confounded by the presence of blood and hence blood cells or inflammatory cells that degrade the blood in the ventricles.

Table 8. Results of the present study and previous findings regarding the accuracy of cell count in CSF in diagnosing VC

	Present study	**Montes et al. 2019**	**Grille et al. 2017**	**Hoogmoed et al. 2017**	**Liu et al. 2015**	**Stubljar et al. 2015**	**Gordon et al. 2014**	**Walti et al. 2013**	**Boeer et al. 2011**	**van Mourik et al. 2011**	**Boer et al. 2010**
CC / WBC	CC	WBC	WBC	WBC	WBC	WBC	WBC	WBC	CC	WBC	CC
n (VC / controls)		37 / 74	14 / 22	11 / 37	8 / 11	38 / 28	6 / 57	48 / 0	10 / 40	82 / 455	23 / 41
Mean in VC cases (cells/µL)	2072.93	2213.3	1100	3225.0	323.8	579.84	4480	175		1040	
Mean in controls (cells/µL)	277.88	192.3	105	1722.0	25.8	91.36	89	46		140	
p	0.001	0.005	0.013	> 0.05	< 0.05	0.004	0.007	0.021	> 0.05	< 0.001	< 0.05
Cutoff (cells/µL)	517.00		306			102.0	1320		610		277
AUC	0.867	0.653; corrected WBC: 0.770	0.789			0.798	0.904	0.66	0.68		0.86
SE	0.800		0.78			0.774	0.80		0.56		0.86
SP	0.877		0.70			0.773	0.839		0.88		0.74
PPV			0.62			0.828	0.3077		0.50		0.29
NPV			0.83			0.793	0.9772		0.90		0.98
+LR	6.500		2.6				4.98				
-LR	0.228		0.31				0.24				
Population	SAH, TBI, ICH	intra-cranial hemor-rhage	general	SAH	general	general	general	general	general	general	general
Remark		corrected WBC: subtract 1 from the CSF WBC count for every 500 CSF RBC		culture-positive vs. culture-negative	on day of fever onset	pediatric sample		day of EVD insertion vs. day of VC		EVD and lumbar drains	

The results of our ROC analysis fit into the picture of previously reported cutoffs and AUCs which are ranging widely as is displayed in Table 8. Stubljar et al. (2015)[103] reported the lowest cutoff for WBC at 102 cells/µL, which could be due to their pediatric sample at a median age of 21 months. In an adult sample, the lowest cutoff for cell count at 277 cells/µL was found by Boer et al. (2010).[24] This is surprising since they analyzed samples with a majority of visually noticeable blood contamination so that higher cell counts because of the presence of erythrocytes are expected. Gordon et al. (2014)[22] reported the highest cutoff for WBC at 1320 cells/µL after using a strict definition of VC which included only culture-positive cases. They also reported the highest diagnostic potential with an AUC of 0.904 and a negative predictive value of almost 98%. However, by applying a very strict definition of VC they might have missed patients with false negative cultures who might have needed antibiotic treatment. The least diagnostic accuracy (AUC of 0.66) was found by Walti et al. (2013),[35] who compared CSF cell counts on the day of EVD insertion to the day of infection instead of comparing to controls without infection, questioning whether cell counts might had been elevated even before infection occured. Montes et al. (2019)[100] performed a case-control study on 111 patients and reported an AUC of 0.653 for WBC in CSF. Intriguingly, they proposed a corrected WBC, meaning that for every 500 RBC in CSF 1 WBC in CSF is subtracted in order to control for the presence of blood cells due to hemorrhage. This had previously been successfully done in pediatric patients after traumatic lumbar puncture. Calculating the corrected WBC increased the diagnostic potential to a moderate AUC of 0.770. Finally, Grille et al. (2017)[20] also report a moderate diagnostic potential for CSF WBC (AUC of 0.789), suggesting that CSF WBC or cell count is a useful marker even though it can be influenced by the presence of blood cells due to hemorrhage.

CSF pleocytosis is also a well-established criterion for the diagnosis of similar infections such as community-acquired bacterial meningitis[118,119] and are related to infections of ventriculoperitoneal shunts.[120–124] All reports taken together support the CDC criteria for VC, of which CSF WBC is one.

Percentage of Neutrophils in Cerebrospinal Fluid

We found the percentage of neutrophils in CSF to be significantly raised in VC patients ($p < 0.000$) and report a cutoff of 61.5% with good diagnostic accuracy (AUC 0.856, SE 0.808, SP 0.839, +LR 5.008, -LR 0.229).

Van Mourik et al. (2011)[117] with their big sample and Stubljar et al. (2015)[103] found significantly or almost significantly elevated percentages of neutrophils, as well. However, Liu et al. (2015)[25]

missed significance for CSF percentage of neutrophils and other parameters such as CSF glucose or protein, possibly due to a small sample size of only eight patients.

Table 9. Results of the present study and previous findings regarding the accuracy of the percentage of neutrophils in CSF in diagnosing VC

	Present study	**Liu et al. 2015**	**Stubljar et al. 2015**	**van Mourik et al. 2011**
n (VC / controls)		8 / 11	38 / 28	82 / 455
Mean in VC cases	0.6992	0.760	0.5412	0.850
Mean in controls	0.3910	0.495	0.3778	0.478
p	0.000	> 0.05	0.051	< 0.001
Cutoff	0.615		0.550	
AUC	0.856		0.663	
SE	0.808		0.625	
SP	0.839		0.789	
PPV			0.789	
NPV			0.625	
+LR	5.008			
-LR	0.229			
Population	SAH, TBI, ICH	general	general	general
Remark		on day of fever onset	pediatric sample	EVD and lumbar drains

In comparison to previous reports, the percentage of neutrophils in CSF performed very well in our ROC analysis with its AUC of 0.856 being bigger than a previous report of 0.663.[103] Especially, specificity and positive likelihood ratio seem very promising in our study. Neutrophils have previously been associated to community-acquired bacterial meningitis[39,125,126] and infections of ventriculoperitoneal shunts,[121] as well. Considering all these findings, CSF percentage of neutrophils is a promising biomarker for VC that should be included in future studies.

Glucose and Protein in Cerebrospinal Fluid

Despite CSF glucose and CSF protein being criteria for diagnosing VC in our study, their levels did not differ significantly between groups and hence did not show any potential for diagnosing VC in patients with SAH, ICH or TBI. Previous studies showed CSF glucose[20,100,103] and CSF protein[20,103] to be elevated, in accordance with the CDC criteria for VC.[115] In the largest study of over 500 patients with EVD or lumbar drains, both CSF glucose and CSF protein were significantly raised in patients with VC. However, other investigations also report non-significant associations of CSF glucose[25] and CSF protein[24,25] with VC. Our AUCs of 0.403 for CSF glucose and 0.656 CSF protein fit well into the picture of great variance of reported AUCs ranging from 0.324[103] to 0.996[22] for CSF glucose and from 0.46[23] to 0.918[22] for CSF protein.

This suggests that other factors such as the underlying neurosurgical condition or metabolic issues of the patient crucially influence the diagnostic potential of these two biomarkers. We should therefore reconsider whether our diagnostic criteria can be applied to all patients without differentiating between the patients' conditions.

Serum Inflammatory Markers

We found no significant elevation and no diagnostic potential of serum WBC, serum percentage of neutrophils, serum CRP or serum IL-6 in patients with VC and SAH, ICH or TBI, which is in line with previous studies. In the above mentioned study by Liu et al. (2015)[25] on 32 patients with EVD and fever, serum WBC and serum CRP did not differ significantly between patients with or without positive CSF culture or without symptoms of VC. When studying 66 episodes of clinical suspicion of VC in 18 children, serum WBC, serum percentage of neutrophils and serum CRP were not significantly elevated in cases with identified bacteria and/or clinical improvement after the administration of antibiotics.[103] Also, in 29 patients with positive CSF cultures after EVD placement, levels of serum CRP did not differ significantly between the day of EVD insertion and the occurrence of VC symptoms, whereas serum WBC only missed significance (P = 0.057).[109] Despite having assessed serum IL-6 in 25 patients with SAH with and without VC, Hopkins et al. (2012)[112] only report the association between CSF IL-6 and VC, probably because no significant association between serum IL-6 and VC could be found.

This supports the hypothesis that VC is a predominantly local inflammatory reaction with an only light systemic response that is probably masked by other systemic inflammatory processes going on in neurosurgical ICU patients.

Association between the Severity of the Condition and the Development of Ventriculitis

Furthermore, in our investigation CSF IL-6 concentrations were not significantly associated with the severity of SAH or ICH, measured by WFNS grade in the case of SAH and by GCS on admission in the case of ICH.

Regarding SAH, several studies reported significantly or almost significantly elevated serum or CSF IL-6 levels in patients with more severe SAH, as measured by Hunt-Hess grade[67,71,73,127] or WFNS grade.[69,128] In many studies, higher systemic or CSF levels of IL-6 were found in patients with adverse outcome,[71,74,75] which is, of course, related to an adverse SAH severity score. Nonetheless, there is also one other study on 19 patients that could not determine significant associations between CSF IL-6 and Hunt-Hess grade, Fisher grade or GOS.[78]

Concerning ICH, to our knowledge, this is the first study to investigate the relation between CSF IL-6 and ICH severity. However, CSF IL-6 is associated with severity of ischemic stroke, ischemic lesion size and functional outcome.[83] IL-6 in serum was in previous studies found to relate to ICH volume, GCS on admission, poor outcome and mortality.[80–82]

The lack of significance in our study might be due to the sample size of 75 patients with SAH and 53 patients with ICH. Furthermore, a selection bias is possible, since this is a tertiary medical care center that accepts more severe cases which might lead to higher WFNS grades or lower GCS scores and less variance in our sample. More than 50% of our SAH patients presented with WFNS grades 4 or 5.

Study Population

Our sample consisted of 70 men and 82 women, aged 16 to 88 years with an average of 56 years, who had been admitted to our neurosurgical ICU because of SAH, ICH or TBI. SAH was the most frequent etiology with a female predominance, whereas TBI was the least common condition with a majority of male patients. There was no difference in age between etiologies. SAH, ICH and TBI are the most common conditions in several studies on VC in neurointensive patients.[22,23,109] A slight female predominance and age mean around 50 to 60 years have been reported in other studies as well.[22,23,25,37,109]

VC occurred in 23.7% of patients on average eleven days after EVD placement. The incidence of VC in our sample is slightly above previously reported infection rates, which lie around 10%, but vary from 0% to 45%.[3,9–11,16,26–29] This might be due to different definitions of VC in these studies. Whether some infections could have been prevented by altering the EVD insertion

procedure (e.g., tunneling the catheter) or EVD management protocols remains unclear. Also, VC cases had been more severely impaired on admission (as measured by GCS score) compared to aseptic cases, which has previously been shown.[9] This might indicate that in more severely injured patients EVD insertion protocols are less strictly respected (e.g. when the EVD is inserted in the emergency department) and infections occur more often. In severely impaired TBI patients septic courses may be more frequent due to open head trauma. Intriguingly, GOS scores were almost significantly lower ($P = 0.056$) in patients with aseptic course. Previous studies have shown conflicting results regarding a possible association of infection and poorer (neurological) outcome or higher mortality.[13,16,27,31]Apart from that, septic and aseptic courses did not differ regarding age, gender or etiologic condition.

Strengths and Limitations of this Study

Strengths of this study lie in its relatively big sample size as compared to most publications in this field. Our sample corresponds to epidemiologic data and to usual study samples in this field regarding age, gender and infection and can therefore be considered representative of neurosurgical ICU patients with SAH, ICH or TBI. Furthermore, we distinguished between different etiological conditions and only included patients with SAH, ICH or TBI. Our definition of ventriculitis included not only culture-proven VC, but also cases of culture-negative VC with respective clinical and laboratory signs and clinical improvement after administration of antibiotics. Thereby, we did not miss patients with false negative cultures who need to be diagnosed and treated, as well.

Limitations of this study lie in its retrospective design. Secondly, there is no universal definition of VC, which makes misdiagnosis likely and hinders comparability of different studies. Because of a high rate of false-negatives and time loss in determining bacterial cultures, in contrast to other studies, we also took clinical and laboratory findings into consideration. However, this leads to the dilemma of overlapping diagnostic criteria and investigated biomarkers. Also, other infectious diseases occur frequently in neurointensive patients and can confound serum biomarkers and maybe even CSF biomarkers. Furthermore, measuring IL-6 in CSF is not identical to the more invasive parenchymal measurement, which might be more accurate. Besides, it is to consider that glucocorticoids, which are frequently used in intensive care patients, were shown to suppress expression and production of IL-6.[129,130] Apart from that, we measured and reported CSF cell count without differentiating between CSF RBC and CSF WBC, which might however be crucial since the presence of blood in the ventricles is common in patients with SAH, ICH or TBI, and confound the diagnostic potential of CSF cell count.

Conclusion and Future Directions

Diagnosing VC in neurointensive patients remains a challenge for attending physicians, especially because there are still no universal, evidence-based diagnostic criteria. Identifying bacteria from CSF sample or wound swab is time consuming and difficult due to frequent admission of antibiotics. Common infection markers such as cell counts, metabolites or acute phase proteins are not sensitive and specific enough. Their levels are confounded by the underlying neurosurgical condition or other systemic inflammations. Cytokines such as IL-6 are assumed to be helpful since they can be analyzed easily via ELISA and IL-6 has shown promising diagnostic accuracy in several studies. More studies are needed to replicate those findings in bigger study samples and especially to distinguish between different neurointensive diseases which are likely to crucially influence IL-6 levels in CSF, for example because of blood or blood degradation products in the ventricles and therefore in the CSF. Another step is to analyze a combination of several parameters as a prediction rule, which can reach higher sensitivities and specificities than single biomarkers. This was successfully done in predicting postoperative meningitis with an AUC of 0.94.[131]

VC remains a serious, but frequent complication of EVD placement, which is associated with adverse outcome. Therefore, we should also develop, evaluate and apply infection control protocols, which have previously been shown to prevent VC effectively.[28,132,133]

Emerging studies also consider therapeutic approaches to alter IL-6 levels. A recent study showed for instance that subcutaneous administration of Interleukin-1 receptor antagonist in SAH patients decreases IL-6 levels and might be associated with a better neurological outcome.[134] Future studies are needed to determine the effects on the outcome of ICU patients with SAH, ICH or TBI.

Summary

Diagnosing and defining VC remains challenging. On one hand, microbiological findings take time and can result in false negative results because of previous antibiotic treatment. Clinical signs, on the other hand, are unspecific in critically ill patients. Therefore, cytokines like IL-6 seem to be promising inflammatory markers, but we are still lacking reliable data on their diagnostic potential in different etiological conditions which influence the occurrence of pathogens and types of inflammatory reactions. The aim of the present study was to assess the levels of CSF IL-6 and other inflammatory markers in cases with and without VC among patients with SAH, ICH or TBI, as well as their diagnostic potential. Furthermore, we investigated whether CSF IL-6 concentrations would be associated with the severity of SAH or ICH.

Our principal findings include that IL-6 in CSF was significantly elevated in patients with VC and showed good diagnostic potential (AUC of 0.831). This replicates the results from previous studies on smaller and general neurosurgical study populations, which makes IL-6 a promising biomarker in diagnosing VC.

The cell count in CSF was also significantly elevated and showed good diagnostic accuracy (AUC of 0.867), fitting into the picture of widely ranging AUCs that have previously been found. This supports the CDC criteria for VC, of which WBC in CSF is one. However, differentiating clearly between RBC, WBC, cell count and cell index as well as different etiological conditions will be helpful since the presence of blood in the ventricles alters the presence of red and white blood cells and hence influences the validity of different parameters to diagnose inflammation.

Furthermore, the percentage of neutrophils in CSF was significantly elevated and showed promising diagnostic potential (AUC of 0.856). The diagnostic accuracy was even higher than among the parameters that belong to the CDC criteria for VC. Therefore, the percentage of neutrophils in CSF seems to be a promising diagnostic parameter that should be considered in future studies.

Despite CSF glucose and CSF total protein being part of the CDC criteria for VC as well as those applied in our protocol, both parameters did not differ significantly and hence did not show any potential for diagnosing VC in our population. Accordingly, it should be questioned whether the underlying neurosurgical condition or metabolic issues in these ICU patients critically influence the diagnostic accuracy of these inflammatory parameters and how they can be applied to different patient groups.

In line with previous reports, there was no significant elevation and no diagnostic potential in our serum markers (WBC, percentage of neutrophils, CRP and IL-6). Thus, VC seems to correspond to a predominantly local inflammatory process with only slight systemic involvement that might be concealed by other systemic infections in critically ill patients.

Unlike previous studies, we did not find any significant association between CSF IL-6 levels and the severity of SAH or ICH, measured by WFNS grades or GCS on admission, respectively. This might be due to relatively small sample sizes and a selection bias of more severe cases in this tertiary medical care center.

In summary, IL-6 in CSF seems to be a promising inflammatory marker in diagnosing VC in patients with SAH, TBI or ICH. Future studies are needed to replicate those findings in larger samples and to distinguish between different etiological conditions. Furthermore, future work can address the development of a prediction rule by combing several parameters which can reach higher diagnostic accuracy compared to single inflammatory markers only.

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Potential of Interleukin-6 in Cerebrospinal Fluid for Diagnosing EVD-associated Ventriculitis in Patients with Subarachnoid Hemorrhage, Intracerebral Hemorrhage or Traumatic Brain Injury

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