Neutrophil-to-Lymphocyte Ratio is Associated With Increased Cerebral Blood Flow Velocity in Acute Bacterial Meningitis

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Research

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Abstract

Objective

In community-acquired bacterial meningitis(CABM) intracranial vascular alterations are devastating complications which are triggered by neuroinflammation and result in worse clinical outcome. The neutrophil-to-lymphocyte ratio(NLR) represents a reliable parameter of the inflammatory response. So far, in CABM-patients the association between NLR and elevated cerebral blood flow velocity(CBFv) remains unclear.

Methods

This study included all (CABM)-patients admitted to a German tertiary center between 2006-2016. Patient demographics, in-hospital measures and neuroradiological data were retrieved from institutional databases. CBFv was assessed by transcranial Doppler sonography transcranial doppler(TCD). Patients', radiological and laboratory characteristics were compared between patients with/without elevated CBFv. Multivariate-analysis investigated parameters independently associated with elevated CBFv. Receiver operating characteristic(ROC-)curve analysis was undertaken to identify the best cut-off for NLR to discriminate between increased CBFv.

Results

108 patients with CABM were identified. 27.8%(30/108) showed elevated CBFv. These patients had a worse clinical status on admission(Glasgow Coma Scale:12[9-14*vs.*14[11-15]; p=0.005) and required more often intensive care (30/30[100%]vs.63/78[80.8%];p=0.01).The causative pathogen was S. pneumoniae in 70%. These patients developed more often cerebrovascular complications with delayed cerebral ischemia(DCI) within hospital stay(p=0.031). A significantly higher admission-NLR was observed in patients with elevated CBFv(median[IQR]:elevated CBFv:24.0[20.4-30.2]*vs.* normal CBFv:13.5[8.4-19.5];p<0.001). After adjusting for significant parameters in univariate testing, NLR on admission was significantly associated with increased CBFv(Odds ratio[95%CI]:1.042[1.003-1.084];p=0.036). ROC-analysis identified a NLR of 20.9 as best cut-off value to discriminate between elevated CBFv(area under the curve=0.713, p<0.0001,Youden's Index=0.441;elevated CBFv:NLR≥20.9 19/34[55.9%]*vs.*NLR<20.9 11/74[14.9%];p<0.001).

Conclusions

Intracranial vascular complications are common among CABM-patients and are a risk factor for unfavorable outcome at discharge. NLR is independently associated with elevated CBFv.

Introduction

Bacterial meningitis is a severe infection of the central nervous system [1,2]. Intracranial vascular alterations are considered to be associated with cerebral inflammation [3] and represent a devastating

complication leading to unfavorable outcome and increased morbidity [4]. The inflammatory process in bacterial meningitis can be monitored by numerous biochemical markers [5,6].

The Neutrophil-to-Lymphocyte ratio (NLR) represents information on both the innate and adaptive immune system and is a reliable parameter for the general immune response to various stimuli. Neutrophil-to-Lymphocyte ratio (NLR), calculated by absolute neutrophil count divided by absolute lymphocyte count, is easy to perform in routine practice and cost-effective. Neutrophil-to-lymphocyte ratio (NLR) has proven its prognostic value in cerebrovascular[7,8] and inflammatory diseases[9], several types of tumors[10-12] and infections[13,14]. This study aimed to analyze the association between NLR and elevated cerebral blood flow velocity (CBFv) which may potentially translate into ischemic complications.

Methods

Patients und Inclusion criteria

All consecutive patients with diagnosis of CABM admitted to the Department of Neurology, University Hospital Erlangen, Germany were included in a prospective longitudinal institutional database, which was approved by the institutional ethics committee. Out of this database, all patients (N= 141) admitted between 2006 and 2016 for treatment of CABM have been recruited to this study. We excluded patients receiving permanent immunomodulatory treatment (e.g. corticosteroids, methotrexate, cytostatic drugs and biologicals) on admission (n=14). Patients without follow-up data or refused consent were also excluded (n=19). 108 patients remained for final analysis *(Figure 1).*

Data collection

Data of all patients were retrieved from our institutional prospective database: patients' history (hypertension, diabetes mellitus, alcohol abuse or other comorbidities), GCS (Glasgow Coma Scale) on admission, clinical symptoms on admission, laboratory findings on admission (cerebrospinal fluid and blood work, causative pathogen), clinical course, outcome and neurologic findings at discharge, and treatment.

Arterial vascular alterations and incidence of cerebral ischemia were assessed using computed tomography imaging (CT-scan, (SIEMENS Somatom Volume Zoom, Somatom Sensation 64, Somatom Definition AS+; Siemens Healthcare, Forchheim, Germany) or magnetic resonance imaging (MRI) (SIEMENS Magnetom Sonata 1.5T, Magnetom Aera 1.5T, Siemens Healthcare, Erlangen, Germany).

NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count (NLR days 1, 2, 3, 4, 5, 6, 7, 8).

Diagnosis of acute bacterial meningitis (ABM)

The diagnosis of acute bacterial meningitis was confirmed by identification of the causative pathogen in cerebrospinal fluid and/or blood via microscopic Gram stain and CSF/blood cultured isolates[15]. In case the causative pathogen could not be identified bacterial meningitis was diagnosed by typical CSF findings as mainly granulocytic CSF white blood cell count greater than 1,000 cells/µl, an increase of CSF protein of more than 100 mg/dl, and a CSF/serum glucose ratio less than 0.3 and/or presence of clinical symptoms as fever, neck stiffness, headache, impaired consciousness.

Detection of increased cerebral blood flow velocity

Presence of vascular alterations was assessed by TCD routinely termed as cerebral blood flow velocitiy (CBFv) of the anterior cerebral artery (ACA), middle cerebral artery (MCA), internal cerebral artery (ICA), posterior cerebral artery (PCA), and the basilar artery (BA). Systolic CBFv greater than 150 cm/s were considered increased [16,17].

Outcome

Outcome at discharge was evaluated according to the Glasgow Outcome Scale (1-5) by two physicians, trained and certified for data collection: A score of 1 on this scale indicates death; a score of 2, a vegetative state; a score of 3, severe disability (the patient is not able to live independently but can follow commands); a score of 4, moderate disability (the patient is capable of living independently but unable to return to work); and a score of 5, mild or no disability (the patient is able to return to work). A favorable outcome was defined as a score of 5, and an unfavorable outcome as a score of 1 to 4. The Glasgow Outcome Scale is a well-validated instrument with high interobserver agreement[18,19].

Statistical analysis

Statistical analysis was performed using SPSS 22.0 (IBM Analytics) and GraphPad Prism 8 (GraphPad Software). Categorial variables were presented as frequency and percentage, Pearson chi square and Fisher's exact test were used to compare between these groups. For continuous variables, the Kolmogorov-Smirnov test was used to test the distribution of data. If data showed normal distribution, data was presented with mean ± SD and the Student t test was used for analysis. Data lacking normal distribution, median and interquartile range were shown and the Mann-Whitney U test was used for comparison. Significance level was set at $\alpha=0.05$. All parameters showing a statistical trend ($p<0.1$) were included in a multivariate model to identify parameters independently associated with elevated cerebral blood flow. A Receiver Operating Characteristic (ROC) curve and Youden's J statistic was used to determine the cut-off value for NLR [20]. Then, patients were dichotomized according to the identified cut-off value.

Results

Patient characteristics

Overall 108 patients with CABM remained for final analysis (Figure 1). The overall cohort of patients was 59 ± 16 years old. 51.9% (56/108) were female. More than half of the patients presented with clinical signs suggestive of bacterial meningitis as fever 57.4% (62/108), headache 51.9% (56/108) and meningism 63.9% (69/108). Only 24.1% (26/108) of these patients showed further neurological deficits. 74.1 % (80/108) received dexamethasone on admission (*Table 1*).

Vascular complications

30/108 (27.8%) patients developed elevated cerebral blood flow velocity within 4 (3-5) days after admission. These patients had a worse clinical status on admission (median[IQR]: Glasgow Coma Scale 12[9-14] *vs.* 14[11-15]; p=0.005, neurologic deficit 13/30 [43.3%] vs. 17/78 [21.8%]; p=0.025), required more often intensive care (30/30 [100%] vs. 63/78 [80.8%]; p=0.010) with need of osmotherapy (13/30 [43.3%] vs. 6/78 [7.7%]; p<0.001), therapy with nimodipine (23/30 [76.7%] vs. 3/78 [3.9%]; p<0.001) and/or catecholamines (22/30 [73.3%] vs. 31/78 [39.7%]; p=0.002). They needed longer ventilation (167h [45-510] vs. 0h [0-206]; p=0.001) because of reduced consciousness. In patients with increased CBFv CSF analysis confirmed typical abnormalities as polymorphonuclear leukocytosis, decreased glucose concentration, and increased protein concentration. Whereas only protein concentrations were significantly increased (2.910g/L [1.491-4.287] vs. 1.501g/L [0.629-3.038]; p=0.009). The most common causative microorganism was Streptococcus pneumoniae *(70%* [21/30] vs. 26.9% [21/78]; p<0.001) identified by CSF (28/30 [93.3%] vs. 51/78 [65.4%]; p=0.003). These patients showed a higher rate of infectious complications (sepsis: 17/30 [56.7%] *vs.* 30/78 [38.5%]; p=0.087). Cerebral infarctions during hospital stay occurred more frequently (9/27 [33.3%] vs. 3/30 [10.0%]; p=0.031) translating into an unfavorable outcome at discharge (Glasgow Outcome Scale 3 [3-4] vs. 4 [3-5]; p=0.028, *Table 2*).

Further, a significantly higher NLR on admission was observed in patients with elevated blood flow velocity (median[IQR]: elevated CBFv: 24.0[20.4-30.2] vs. normal CBFv: 13.5[8.4-19.5]; p<0.001). Parameters with tendency for significance (p<0.1) in univariate testing were included into a multivariable model. In this model NLR levels on admission were associated with increased cerebral blood flow velocity (1.042 (1.003-1.084); p=0.036; *Table 3*) as well as need of osmotherapy (p=0.026). Need of catecholamine therapy (p=0.561), clinical status on admission (p=0.116) and need of ventilation (p=0.178) were not significantly associated with increased cerebral blood flow velocity.

Association of Neutrophil-to-Lymphocyte ratio with increased cerebral blood flow velocity

ROC-analysis identified a NLR of 20.9 as the best cut-off threshold on admission to discriminate between increased CBFv within hospital stay (AUC = 0.713; $p < 0.001$, Youden's index = 0.441; sensitivity, 63.3%; specificity, 80.8%; elevated CBFv: NLR≥20.9 19/34[55.9%] vs. NLR<20.9 11/74 [14.9%]; p<0.001; *Figure 2*). These patients showed an unfavorable outcome (GOS 1 - 4) at discharge (elevated CBFv 27/30[90.0%] vs. normal CBFv 51/78[65.4%]; p=0.01, *Figure 3*).

Discussion

There are three major findings from this cohort study on CABM-patients: 1) We identified Neutrophil-to-Lymphocyte ratio (NLR) on admission to be associated with increased cerebral blood flow velocity within hospital stay. 2) ROC-analysis identified a NLR of 20.9 as the best cut-off threshold on admission to discriminate between increased CBFv within hospital stay. 3) These patients showed an unfavorable outcome (GOS 1 - 4) at discharge.

Of 108 patients 30 (27.8%) developed increased cerebral blood flow velocity within hospital stay due to infection with S. pneumoniae in 70% in agreement of published data[21,22]. Among these patients ischemic complications were observed in 21.1%. TCD was performed routinely whereas cerebral imaging was performed according to clinical signs and symptoms. As not every patient with increased cerebral blood flow velocity underwent CT/MRI-imaging there may have been subclinical strokes remaining undetected. Further, increased flow velocities do not necessarily cause impending ischemic complications[17].

In our cohort of patients with community acquired bacterial meningitis we identified a predictive NLR-cut off level to be $\geq$ 20.9. This cut-off value is increased compared to published data for e.g. prediction of ICH after endovascular thrombectomy in acute ischemic stroke [23].

In development of bacterial meningitis the host inflammatory response plays an important role resulting in activation of both noncellular and cellular components of the immune system[24,25]. In the circulation neutrophils constitute the dominant cell type mediating the earliest innate immune responses getting to the site of infection[26]. Massive neutrophil recruitment is required across the blood-brain-barrier (BBB) to evoke a strong inflammatory response to react to the microorganisms at the bacterial infection site[25]. This activation of the immune response with subsequent rapid influx of leukocytes into the brain also causes adverse effects for the host. Activated immune cells within the brain, such as microglia, astrocytes and infiltrating leukocytes amplify the cascade of pro-inflammatory cytokines and cytotoxic agents. This subsequently leads to damage to cortical and subcortical structures[27,28] which further results in edema, hydrocephalus and increased intracranial pressure[29].

Unexpectedly and contrary to published data[30,31] we did not identify dexamethasone administration to be independently associated with increased cerebral blood flow velocity in multivariate analysis. Prior to the wide spread use of adjunctive steroids in bacterial meningitis[32,33] cerebral vascular alterations were devastating but common complications mediated by cerebral vasculitis, septic emboli, intraarterial thrombosis or disseminated intravascular coagulation [31,34-36]. This emphasizes the need for specific anti-inflammatory drugs in bacterial meningitis [37,38] beyond adjuvant corticosteroid treatment which has been proven beneficial on case fatality rates in adult patients with pneumococcal meningitis but only in high-income countries [33].

In acute intracerebral haemorrhage [8], subarachnoid haemorrhage [39] and ischemic stroke [40] elevated NLR-levels were linked to unfavorable functional outcome. This could be shown by our data only in univariate

testing (GOS 3[3-4] vs. 4[3-5]; p=0.028, mRS 4 [2-5] vs. 1 [1-4]; p=0.020). Regarding long-term-outcome we did not identify significant differences. Reasons for this finding may be the small cohort size.

Taken together, increased cerebral blood flow velocity is associated with neuroinflammation and represents a devastating complication in bacterial meningitis. NLR is an easy accessible and cost-effective biomarker that has proven its prognostic value in several conditions also among cerebrovascular [8,41] and infectious diseases [13,42]. As a reliable parameter for the general immune response to various stimuli, NLR does not represent an inflammatory marker within a specific entity. Therefore, it remains unclear whether increased NLR-levels on admission reflect the state of bacterial infections or if high NLR values represent an independent surrogate to predict intracranial vascular alterations[30]. Future studies should investigate whether elevated NLR-levels in CABM-patients help to identify patients suitable for immune modulating treatments.

Our study has several limitations. It lacks a prospective and multi-center design. Except for admission laboratory data were not available every day within hospital stay. Bloodwork and CSF stains are done as required by clinical practice and not by scheduled timing. This may impose bias to the reported data. Further, above findings do not provide any mechanistic evidence confirmed by specific blood sampling analyses or detailed immunoprofiling, and therefore depict a phenomenological finding.

Conclusions

Among CABM-patients NLR on admission is associated with increased cerebral blood flow velocity. Future studies are required to investigate whether the impact of NLR on functional outcome at discharge represents an independent clinical implication or a preexisting comorbidity.

Declarations

Ethics approval and consent to participate: All procedures involving human participants were in accordance with the ethical standards of the institutional research committee of the University of Erlangen-Nuremberg and with the 1964 Helsinki declaration and its later amendments. The Institutional Ethics Committee of the University of Erlangen-Nuremberg had approved the study protocol.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests:

Name	Disclosures
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Authors' contributions:

Name	Location	Contribution
Antje Giede-Jeppe, MD	University of Erlangen-Nuremberg, Germany	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
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Anne Mrochen, MD	University of Erlangen-Nuremberg, Germany	Revised the manuscript for intellectual content
Hannes Luecking, MD	University of Erlangen-Nuremberg, Germany	Major role in the acquisition of data
Philip Hoelter, MD	University of Erlangen-Nuremberg, Germany	Revised the manuscript for intellectual content
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Abbreviations

AUC: Area Under the Curve

ACA: Anterior Cerebral Artery

BA: Basilar Artery

BBB: Blood Brain Barrier

CABM: community-acquired bacterial meningitis

CBFv: cerebral blood flow velocity

CSF: Cerebrospinal Fluid

CT: Computed Tomography

DCI: Delayed cerebral ischemia

GCS: Glasgow Coma Scale

GOS: Glasgow Outcome Scale

ICA: Internal Cerebral Artery

MCA: Middle Cerebral Artery

MRI: Magnetic resonance imaging

NLR: neutrophil-to-lymphocyte ratio

PCA: Posterior Cerebral Artery

ROC: Receiver operating characteristic

TCD: transcranial doppler

YI: Youden’s Index

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Tables

Table 1 Baseline Characteristics, Laboratory Data, In-hospital Measures and Outcome Parameters for all Patients with communitiy-acquired bacterial meningitis.

Meningitis	**(N=108)**
Age [yrs] #	59 ± 16
Gender[♀]*	52 (48.1%)
Prior medical history	
Premorbid mRS‡	0 (0-1)
Hypertension*	58 (53.7%)
s.p. Ischemic stroke*	4 (3.7%)
s.p. intracerebral hemorrhage*	2 (1.9%)
Coronary heart disease*	12 (11.1%)
Diabetes mellitus*	19 (17.6%)
Malignom*	20 (18.5%)
Cardiac insufficiency*	16 (14.8%)
Immunosuppression*	14 (13.0%)
Admission status	
Neurologic deficit*	30 (27.8%)
Glasgow Coma Scale (GCS)‡	14 (11-15)
Length of ventilation(LOV)[h]‡	9 (0-245)
Fever*	62 (57.4%)
Meningismus*	69 (63.9%)
Headache*	56 (51.9%)
Dexamethasone on admission*	80 (74.1%)
Stay on Neurointensive Care Unit*	103 (95.4%)
Osmotherapy*	19 (17.6%)
Catecholamine therapy*	54 (50.0%)
Intraventricular antibiotics*	1 (0.9%)
Nimodipine therapy*	26 (24.1%)
Laboratory values on admission	
First spinal tap	
Leucocytes[x 10^6/L]‡	1160 (187-5894)

Erythrocytes[x 10^6/L] ‡	37 (2-275)
Proteine[g/L]‡	1.565 (0.681-3.387)
Glucose[mmol/L]‡	2.2 (0.1-3.4)
Lactate [mmol/L]‡	8.4 (3.9-15.5)
Causative pathogen identified by blood*	48 (44.4%)
Causative pathogen identified by CSF*	79 (73.1%)
Most frequent causative Pathogen:	
S. pneumoniae*	42 (38.9%)
Group B Streptococcus (GBS) *	6 (5.6%)
Staph. aureus*	7 (6.5%)
N. meningitidinis*	6 (5.6%)
L. monocytogenes*	4 (3.7%)
H. influenza*	4 (3.7%)
E.coli*	2 (1.9%)
Serum	
Neutrophil-Lymphocyte-Ratio‡	14.5 (6.7-23.1)
Hemoglobin[mmol/L]#	7.5 ± 1.0
Leucocytes [10^9/L]#	15.5 ± 6.6
Thrombocytes[10^9/L]#	200 ± 91
Granulocytes[10^9/L]‡	13.5 (9.0-16.4)
Lymphocytes[10^9/L]‡	0.9 (0.6-1.2)
Monocytes[10^9/L]‡	0.8 (0.4-1.3)
C-reactive protein[mg/L]‡	219.8 (115.0-306.0)
Procalcitonin[µg/L]‡	2.9 (0.6-11.1)
Sodium[mmol/L]#	136 ± 5
Potassium[mmol/L]#	4.1 ± 0.6
Glucose[mmol/L]‡	7.9 (6.8-9.9)
Urea[mmol/L]‡	6.35 (4.18-8.18)
Creatinine[µmol/L]‡	78.77 (61.95-106.2)

Troponin[µg/L]‡	0.04 (0.01-0.12)
In-hospital measures	
Temperature [°C]‡	38.7 (38.0-39.3)
Sepsis*	47 (43.5%)
Increased cerebral blood flow velocity*	30 (27.8%)
Development of cbfv after admission[d]‡	4 (3-5)
Radiological Data	
First CT on admission	
Abscess*	3 (2.8%)
Ischemia*	4 (3.7%)
Obstructive hydrocephalus*	5 (4.6%)
CT within hospital stay- follow up (only 57/108 patients received more than one cerebral imaging)	
Abscess*	6/57 (10.5%)
Ischemia*	12/57 (21.1%)
Obstructive hydrocephalus*	4/57 (7.0%)
Discharge status	
Symptomatic epilepsy*	9 (8.3%)
Neurologic deficit at discharge*	31 (28.7%)
Glasgow Outcome Scale (GOS)‡	4 (3-5)
Length of stay [d]‡	16 (10-23)
Length of ventilation‡	9 (0-245)

‡= median (IQR), * = No. (%), # = mean ± standard deviation.

Demographic, laboratory data and outcome parameters for the study cohort.

Abbreviations: cbfv, cerebral blood flow velocity; GOS, Glasgow outcome scale (range, 5 no or mild deficit, to 1, death); mRS, modified Rankin Scale (range 0, no deficit, to 6, death); NLR, Neutrophil-to-Lymphocyte ratio; IQR, interquartile range; CSF, Cerebrospinal fluid.

Table 2 Baseline Characteristics, Laboratory Data, In-hospital Measures and Outcome Parameters for all Patients with community-acquired bacterial meningitis developing increased cerebral blood flow velocity.

Meningitis	Increased cerebral blood flow velocity (N= 30)	Normal cerebral blood flow velocity (N= 78)	p-value
Gender[♀]*	23 (76.7%)	33 (42.3%)	**0.001**
Prior medical history - admission status - in hospital measures			
Premorbid mRS‡	0 (0-1)	0 (0-1)	0.278
Alcohol abuse*	9 (30.0%)	6 (7.7%)	**0.003**
Neurologic deficit*	13 (43.3%)	17 (21.8%)	**0.025**
Glasgow Coma Scale‡	12 (9-14)	14 (11-15)	**0.005**
Length of ventilation(LOV) [h]‡	167 (45-510)	0 (0-206)	**0.001**
Dexamethason on admission*	26 (86.7%)	54 (69.2%)	*0.064*
Stay on Neurointensive Care Unit*	30 (100.0%)	63 (80.8%)	**0.010**
Osmotherapy*	13 (43.3%)	6 (7.7%)	**<0.001**
Nimodipine therapy*	23 (76.7%)	3 (3.9%)	**<0.001**
Need of Catecholamines*	22 (73.3%)	31 (39.7%)	**0.002**
Temperature on admission [°C]	38.3 (37.5-39.2)	38.8 (38.1-39.4)	*0.064*
Sepsis*	17 (56.7%)	30 (38.5%)	*0.087*
Laboratory values on admission			
First spinal tap			
Leucocytes[x 10^6/L]‡	2328 (187-5788)	1020 (216-5104)	0.661
Erythrocytes[x 10^6/L]‡	234 (5-555)	27 (1-160)	**0.032**
Proteine[g/L]‡	2.910 (1.491-4.287)	1.501 (0.629-3.038)	**0.009**
Glucose[mmol/L]‡	1.28 (0-3.61)	2.28 (0.22-3.44)	0.676
Lactate[mmol/L]‡	9.8 (5.2-16.9)	7.1 (3.5-13.8)	0.178
Causative pathogen identified by blood*	17 (56.7%)	31 (39.7%)	0.113
Causative pathogen identified by CSF*	28 (93.3%)	51 (65.4%)	**0.003**
Most frequent causative Pathogen:			

S. pneumoniae*	21 (70.0%)	21 (26.9%)	**<0.001**
Group B Streptococcus (GBS) *	2 (6.7%)	4 (5.1%)	0.534
Group Non B Streptococcus *	3 (10.0%)	3 (3.8%)	0.211
Staph. aureus*	0 (0.0%)	7 (9.0%)	0.090
N. meningitidinis	0 (0.0%)	6 (7.7%)	0.118
L. monocytogenes*	0 (0%)	4 (5.1%)	0.206
H. influenzae*	0 (0%)	4 (5.1%)	0.206
E.coli*	0 (0.0%)	2 (2.6%)	0.376
Serum			
Neutrophil-Lymphocyte-Ratio‡	24.0 (20.4-30.2)	13.5 (8.4-19.5)	**<0.001**
Thrombocytes[10^9/L]#	172.7 ± 62	208.0 ± 98	*0.078*
Granulocytes[10^9/L]‡	15.6 (13.7-20.8)	12.1 (8.1-15.4)	**0.017**
Lymphocytes[10^9/L]‡	0.7 (0.6-1.0)	0.9 (0.8-1.3)	**0.024**
Radiological Data			
First CT on admission			
Abscess*	1 (3.3%)	2 (2.6%)	0.627
Ischemia*	2 (6.7%)	2 (2.6%)	0.308
Obstructive hydrocephalus*	4 (13.3%)	1 (1.3%)	**0.020**
CT within hospital stay- follow up *(57/108 patients received a second cerebral imaging)*			
Abscess*	3/27 (11.1%)	3/30 (10.0%)	0.613
Ischemia*	9/27 (33.3%)	3/30 (10.0%)	**0.031**
Obstructive hydrocephalus*	3/27 (11.1%)	1/30 (3.3%)	0.266
Discharge status			
Symptomatic epilepsy*	6 (20.0%)	3 (3.8%)	**0.013**
Glasgow Outcome Scale (GOS)	3 (3-4)	4 (3-5)	**0.028**
LOV*	167 (45-510)	0 (0-206)	**0.001**
Length of stay [d]‡	22 (18-26)	15 (9-20)	**<0.001**
mRS at discharge ‡	4 (2-5)	1 (1-4)	**0.020**

mRS at 3 months ‡	2 (2-4)	2 (1-3)	0.166
mRS at 12 months ‡	2 (1-4)	1 (0-3)	0.238

‡= median (IQR), * = No. (%),# = Mean ± standard deviation.

Demographic, laboratory data and outcome parameters for the study cohort.

Abbreviations: cbfv, cerebral blood flow velocity; GOS, Glasgow outcome scale (range, 5 no or mild deficit, to 1, death); mRS, modified Rankin Scale (range 0, no deficit, to 6, death); NIHSS Scale, National Institutes of Health Stroke Scale; NLR, Neutrophil-to-Lymphocyte ratio; IQR, interquartile range; CSF, Cerebrospinal fluid.

Table 3 Multivariate analysis of parameters associated with increased cerebral blood flow velocity

Parameters	95% CI	p-value
NLR D1	1.042 (1.003-1.084)	**0.036**
Catecholamine Therapy	0.634 (0.137-2.944)	0.561
Osmotherapy	0.181 (0.040-0.819)	**0.026**
Neurologic deficit on admission	2.693 (0.784-9.254)	0.116
Ventilation	3.001 (0.606-14.857)	0.178

Multivariable regression analysis was calculated for the association with increased cerebral blood flow velocity. Only parameters showing a statistical trend ($p<0.1$) in prior univariate testing were included in the multivariable model. For each parameter risk ratio and 95% confidence interval are provided. Significant findings are expressed in bold.

Abbreviations: NLR, Neutrophil-to-Lymphocyte ratio; 95% CI, Confidence Interval.

Figures

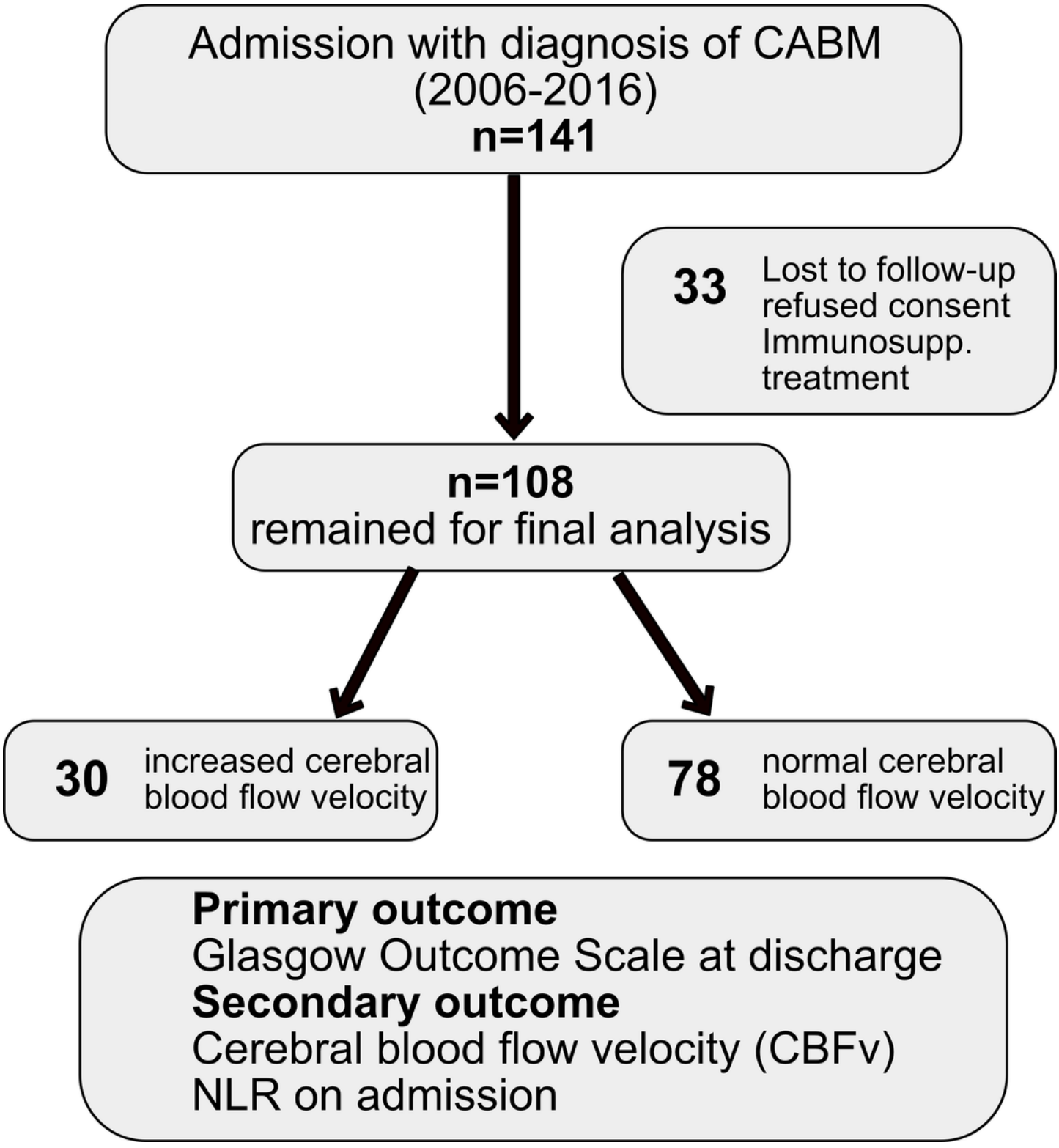

Figure 1

Flowchart of patients 141 patients with community-acquired bacterial meningitis were identified during the study period. After exclusion of 33 patients 108 patients remained for further analysis. Patients were dichotomized according to increased cerebral blood flow velocity (N = 30) and normal cerebral blood flow velocity (N = 78). Abbreviations: CABM, community acquired bacterial meningitis; cbfv, cerebral blood

flow velocity; GOS, Glasgow outcome scale (range, 5 no or mild deficit, to 1, death); NLR, Neutrophil-to-Lymphocyte ratio.

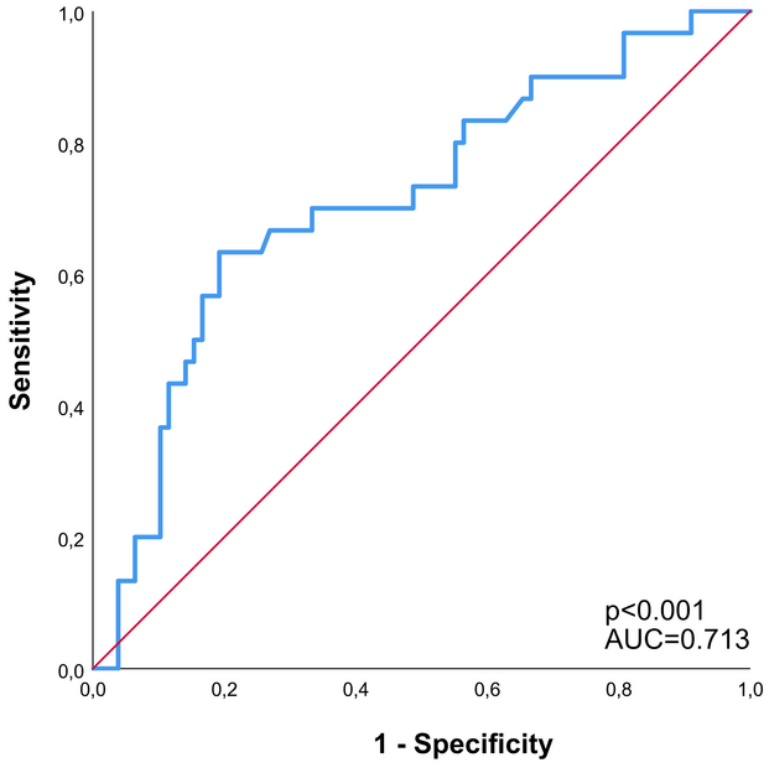

Figure 2

Association of Neutrophil-to-Lymphocyte ratio (NLR) with increased cerebral blood flow velocity. Receiver operating characteristic (ROC) - curve for prediction of increased cerebral blood flow velocity. ROC plot demonstrated the AUC for increased cerebral blood flow velocity (AUC = 0.713; p < 0.001, Youden's index = 0.441; sensitivity, 63.3%; specificity, 80.8%). The cut-off value was detected at 20.9.

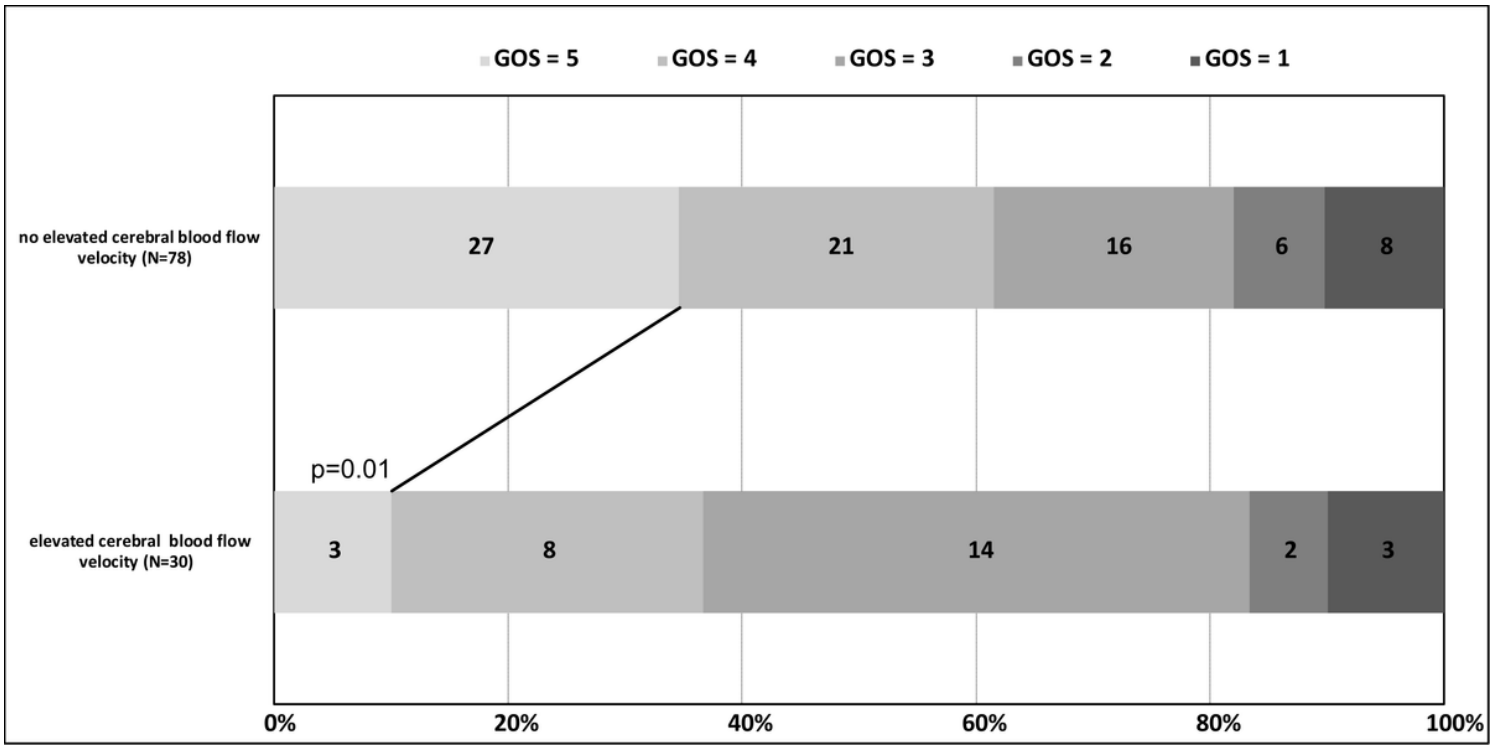

Figure 3

Glasgow Outcome Scale at discharge with elevated CBF vs. no elevated CBF. Illustration of the proportion of patients with elevated cerebral blood flow velocity (n=30) and no/normal elevated cerebral blood flow velocity (n=78). Favorable functional outcome was defined as GOS = 5, unfavorable functional outcome as GOS = 1-4. P-values were calculated for the comparison of unfavorable functional outcome among patients elevated and normal CBFv (p=0.01). Abbreviations: CBFv, cerebral blood flow velocity; GOS, Glasgow outcome scale (range, 5 no or mild deficit, to 1, death).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEStatement.pdf