Sepsis and delayed cerebral ischemia are associated and have a cumulative effect on poor functional outcome in aneurysmal subarachnoid hemorrhage

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Objective: Although sepsis and delayed cerebral ischemia (DCI) are severe complications in patients with aneurysmal subarachnoid hemorrhage (aSAH) and share pathophysiological features, their interrelation and additive effect on functional outcome is uncertain. We investigated the association between sepsis and DCI and their cumulative effect on functional outcome in patients with aSAH using current sepsis-3 definition.

Methods: Patients admitted to our hospital between 11/2014 and 11/2018 for aSAH were retrospectively analyzed. The main explanatory variable was sepsis, diagnosed using sepsis-3 criteria. Endpoints were DCI and functional outcome at hospital discharge (modified Rankin Scale (mRS) 0−3 vs. 4−6). Propensity score matching (PSM) and multivariable logistic regressions were performed.

Results: Of 238 patients with aSAH, 55 (23.1%) developed sepsis and 74 (31.1%) DCI. After PSM, aSAH patients with sepsis displayed significantly worse functional outcome ($p < 0.01$) and longer ICU stay ($p = 0.046$). Sepsis was independently associated with DCI (OR = 2.46, 95%CI: 1.28−4.72, $p < 0.01$). However, after exclusion of patients who developed sepsis before (OR = 1.59, 95%CI: 0.78−3.24, $p = 0.21$) or after DCI (OR = 0.85, 95%CI: 0.37−1.95, $p = 0.70$) this statistical association did not remain. Good functional outcome gradually decreased from 56.3% (76/135) in patients with neither sepsis nor DCI, to 43.8% (21/48) in those with no sepsis but DCI, to 34.5% (10/29) with sepsis but no DCI and to 7.7% (2/26) in patients with both sepsis and DCI.

Conclusion: Our study demonstrates a strong association between sepsis, DCI and functional outcome in patients with aSAH and suggests a complex interplay resulting in a cumulative effect towards poor functional outcome, which warrants further studies.

1 Introduction

Both sepsis and delayed cerebral ischemia (DCI) are severe complications in patients with aneurysmal subarachnoid hemorrhage (aSAH) and are significant determinants for poor outcome (1–4). Although sepsis and DCI share pathophysiological features (5–10), their interrelation is insufficiently understood (11). Therefore, we investigated the association between sepsis and DCI in a cohort of aSAH patients.

While the term DCI presents a pro-ischemic complication in patients who survive the initial aSAH ictus (12, 13), sepsis can also result in acute and long-term brain damage via cerebral ischemia (5, 6). Both sepsis and DCI are characterized by a dysregulation in vascular regulation and integrity (7, 8). DCI was mainly thought to be caused by cerebral vasospasm however, recent studies support the concept of a multifactorial pathophysiology, including microcirculatory disturbances due to microthrombosis and neuroinflammation (4, 9, 10). Microcirculatory dysfunction is also a key mechanism of septic organ dysfunction caused by direct effects of circulating mediators, capillary leak and microthrombus formation, which can affect any organ including the brain (5, 8). In this context, it was recently shown that systemic infection can amplify intracranial inflammatory responses in patients with aSAH (14).

Considering these overlapping pathophysiological features, we hypothesized that in aSAH patients the development of sepsis and DCI might be associated and may have an additive effect resulting in poor functional outcome. However, current data on the relation of sepsis and DCI in patients with aSAH are limited and inconclusive (11). Although nosocomial infection was independently associated with DCI in an exploratory analysis (11), two preceding studies did not find an association between sepsis and DCI (7, 15). These studies were, however, performed before 2016 (7, 15) and did not use the updated sepsis definition (sepsis-3), which focuses on septic organ dysfunction (16). Thus, we performed a comprehensive retrospective, single-center cohort study to investigate the association between sepsis and DCI and their potential cumulative effect on functional outcome in aSAH patients using current sepsis definition.
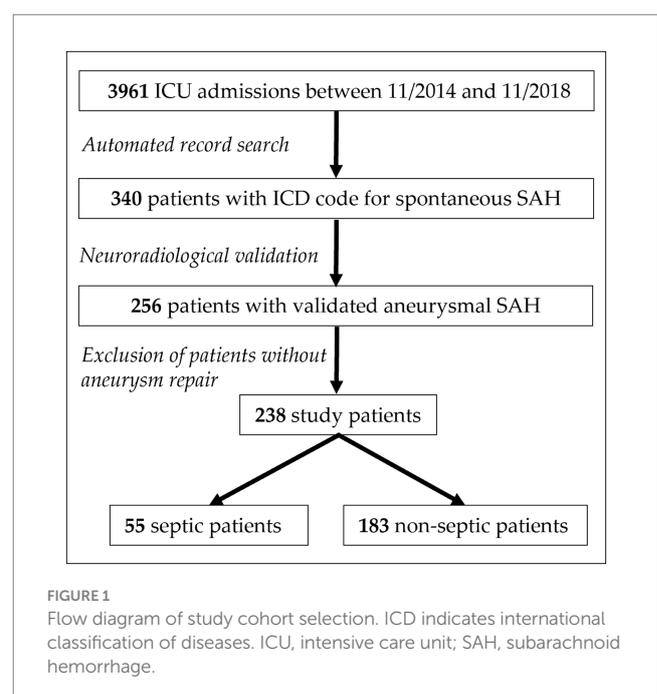
2 Materials and methods

2.1 Study design, setting and patient selection

This single-center retrospective cohort study was conducted at the 25-bed intensive care unit (ICU) of the Department of Anesthesiology, Surgical Intensive Care Medicine and Pain Medicine at the University Medical Center Mannheim, Germany, where aSAH patients were treated and managed in close collaboration with the Department of Neurosurgery. The Medical Ethics Commission II of Medical Faculty Mannheim, University of Heidelberg, approved the study design as well as reanalysis of neuroradiological reports and imaging data (reference number: 2019-1096R, 2017-825R-MA and 2017-828R-MA; date of approval: 01/10/2019). The need for informed consent was waived because of the retrospective nature of the study. Study design and reporting adhered to the STROBE guidelines [STrengthening the Reporting of OBservational studies in Epidemiology; (17)]. The study was registered at the German Clinical Trials Register (ID: DRKS00030748).

Data on all patients (age ≥ 18 years) treated in our ICU between 11/2014 and 11/2018 were extracted from an electronic health record database (Figure 1). Of 3,961 patients, 340 (8.6%) patients were preselected via ICD codes for spontaneous subarachnoid hemorrhage (code I60*). For 256 patients, aneurysmal subarachnoid hemorrhage on initial computed tomography (CT) scan was verified by an experienced neuroradiologist (H.W.). In a further step, 18 (7.0%) patients who did not receive aneurysm repair because of disease severity were excluded, resulting in 238 patients as final study cohort (Figure 1; Supplementary Table S1).

FIGURE 1
Flow diagram of study cohort selection. ICD indicates international classification of diseases. ICU, intensive care unit; SAH, subarachnoid hemorrhage.

2.2 Clinical assessment and management

All patients were screened for healthcare-associated infections according to center for disease control (CDC) criteria (18). For all patients who developed an infection, sequential organ failure assessment (SOFA) scores (19) were determined for 24-h periods by intensive care physicians. To ensure comparability of sepsis criteria application with the original approach of sepsis-3 definition (16), sepsis-3 criteria were applied using an automated algorithm as previously described (20). Baseline characteristics (age, sex, length of stay (LOS) in ICU and in-hospital mortality) were extracted from the electronic health records. Clinical parameters were extracted and verified by intensive care physicians: pre-existing illnesses, World Federation of Neurological Surgeons SAH grading scale (WFNS) at admission, placement of an external ventricular drainage (EVD), type of aneurysm repair and modified Rankin Scale (mRS) at hospital discharge. DCI as primary endpoint was defined as proposed by Vergouwen et al. (13) based on neuroimaging of cerebral infarction from DCI. Clinical management was performed as described in the Supplementary Text S1 and the procedures followed were in accordance with institutional guidelines (21). Since January 2016, an updated protocol for standardized detection and management of DCI was implemented by the Department of Neurosurgery in line with our previous studies (22, 23). We adjusted for these changes in DCI treatment protocol during all our analyses by incorporating a binary (yes/no) factor variable (DCI protocol). Patients with infections and sepsis were treated in accordance with current recommendations (24, 25). For enhanced hemodynamic and fluid management central venous access, PiCCO catheter (Pulsion Medical Systems, Munich, Germany) and foley catheter placement were routinely performed in all study patients.

2.3 Statistical analysis

Normally distributed variables were described using their means and standard deviations (SD), non-normally distributed variables with their medians, lower and upper quartile (LQ-UQ), while proportions were shown for categorical variables. All analyses were performed with the R statistics program™ (v.4.3.2, R Core Team 2023, Vienna Austria; RStudio IDE v. 2023.12.0 Build 554, Boston, MA, United States). Statistical analyses and their results were reported in accordance with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines (26).

The main research question, and explanatory variable of interest, was the effect of sepsis on the development of DCI. Therefore, we first performed propensity score matching (PSM) to adjust for potential confounders between subgroups of sepsis positive and negative patients (27). Matching weights for sepsis-3 ($n_{yes\_sepsis-3} = 55$) subgroups were calculated using (the default settings of the matchit package) 1:1 nearest neighbor approach ($N_{total} = 238$; $N_{matched} = 110$) without replacement based on propensity score distance estimated with logistic regression including the following covariates: age, sex, WFNS grading scale, intraventricular hemorrhage (IVH), DCI protocol and smoking status as well as presence of arterial hypertension. The target estimand was calculated based on the average treatment effect of the treated (ATT). Second, we applied an exploratory modeling approach using standard generalized linear models (base glm) on the original cohort (28, 29). For this, the primary and secondary endpoint variables were the development of DCI (yes vs. no) and functional outcome at hospital discharge (mRS 0–3 vs. 4–6), respectively. These endpoints were modeled by multivariable logistic regression (LR) adjusted for sepsis, age, smoking status, WFNS grading scale, EVD-placement and type of aneurysm repair. The target explanatory variable of interest was sepsis based on sepsis-3 criteria. As sensitivity analyses, interaction terms were added to the multivariable LR model to investigate if the main- and combination effects of DCI and sepsis stayed consistent within mRS outcomes. Data regarding the time-dependency of these research questions were lacking in the literature. Thus, the distributions of time of occurrences of sepsis and DCI were described using median, LQ-UQ. Between group comparisons of un- and matched PSM cohorts were performed using Chi-squared test for categorical variables (with continuity correction) and two-group t-test. In case of potentially non-normally distributed continuous variables (e.g., ICU days), the Kruskal–Wallis (global test) or for two-groups the Wilcoxon-Mann–Whitney tests whereas for categorical variables with small cell counts the Fisher's exact test were used (30, 31). Due to the limited number of cases, it was not possible to evaluate complex multivariable models in time-varying regression frameworks (32). Additionally, *post hoc* power calculations were performed for 2×2 contingency tables with independent samples to estimate the power of our analyses given the proportion of good functional outcome at discharge in septic (yes vs. no) and DCI (yes vs. no) cohorts using two-sided $\alpha = 0.05$ thresholds (power.exact.test function, Exact package). Figures were created using the ggplot2 grammar of graphics. $p < 0.05$ were considered significant. Due to the explorative nature of our analyses, *p*-values were not adjusted for multiple testing (31).

3 Results

3.1 Cohort characteristics

The 238 patients with aSAH had a median age of 56 years (Q1-Q3: 50–64; Table 1) and 69.7% (166/238) were female. 116 (48.7%) patients developed any infection. When applying sepsis-3 criteria, 55 patients were diagnosed as septic, resulting in a sepsis frequency of 47.4% (55/116) in patients with an infection and 23.1% (55/238) in relation to the total cohort. This resulted in a mortality rate of 14.5% (8/55) within the septic subpopulation. Of all patients 31.1% (74/238) developed DCI, while 47.3% (26/55) with sepsis also developed DCI. The diagnosis of sepsis preceded the diagnosis of DCI in 65.4% (17/26) by a median of 43 h. A total of 129 patients (54.2%) had a poor functional outcome at hospital discharge (mRS >3) and the overall in-hospital mortality was 14.7% (35/238, Table 1).

3.2 Propensity score matching

PSM was performed for the development of sepsis. Variables included established risk factors for DCI (33, 34) such as smoking, sex, diabetes and arterial hypertension. Unmatched control cases were excluded from univariate analyses ($n = 128$).

Before PSM ($n = 238$, Table 2) diabetes, modified Fisher, IVH, EVD-placement, DCI, infection, functional outcome and ICU LOS

TABLE 1 Clinical and treatment characteristics of the total cohort with aneurysmal subarachnoid hemorrhage (N = 238).

Variable	N (%)
Median age (Q1-Q3 [years])	56 (50–64)
Female	166 (69.7)
Arterial hypertension	133 (55.9)
Diabetes mellitus	16 (6.7)
Smoking history	90 (37.8)
WFNS grade I	82 (34.5)
II	59 (24.8)
III	11 (4.6)
IV	41 (17.2)
V	45 (18.9)
Modified Fisher scale 0	5 (2.1)
1	15 (6.3)
2	14 (5.9)
3	74 (31.1)
4	130 (54.6)
Intraventricular hemorrhage (IVH)	143 (60.1)
EVD-placement	184 (77.3)
Coiling/Clipping	125 (52.5) / 113 (47.5)
Angiographic vasospasm	103 (43.3)
Delayed Cerebral Ischemia (DCI)	74 (31.1)
Infection	116 (48.7)
Sepsis	55 (23.1)
mRS at discharge 0	15 (6.3)
1	37 (15.5)
2	35 (14.7)
3	22 (9.2)
4	28 (11.8)
5	66 (27.7)
6	35 (14.7)
Median ICU LOS (Q1-Q3 [days])	14 (9–21)
In-hospital mortality	35 (14.7)

Data presented as number (percentage) or median (interquartile range). EVD, external ventricular drainage; ICU, intensive care unit; LOS, length of stay; mRS, modified Rankin Scale; Q1, lower quartile; Q3, upper quartile; WFNS, World Federation of Neurological Surgeons SAH grading scale.

were significantly different between septic and non-septic patients. After propensity score matching ($n = 110$), infection ($p < 0.01$) and ICU LOS ($p = 0.046$) remained significant and among the 55 matched patients without sepsis, 27 (49.1%) had poor functional outcomes, contrasting with 43 patients (78.2%) who developed sepsis ($p < 0.01$, Table 2).

3.3 Association between sepsis and DCI

In multivariable LR fitted on complete cases ($n = 238$, Table 1) of the original cohort, sepsis demonstrated an independent association with the occurrence of DCI (adjusted odds ratio (aOR) = 2.46, 95%CI:

1.28–4.72, $p = 0.007$; Table 3; Figure 2A). The history of smoking slightly missed statistical significance with DCI ($p = 0.054$; Figure 2A).

To further scrutinize the link between DCI and sepsis, we performed three sensitivity analyses. First, we excluded patients who developed sepsis after DCI ($n = 9$) from the cohort, only focusing on cases in whom sepsis preceded DCI. This LR model indicated a trend towards increased odds of DCI if sepsis was diagnosed (aOR = 1.59, 95%CI: 0.78–3.24, $p = 0.21$; Table 3). Second, patients who developed sepsis before DCI ($n = 17$) were excluded, focusing on cases in whom DCI preceded sepsis. In this LR analysis, there was no apparent association between DCI and sepsis (aOR = 0.85, 95%CI: 0.37–1.95, $p = 0.70$; Supplementary Table S2). Third, to differentiate whether a change in vital parameters was due to neuroinflammation caused by the SAH ictus (10) or sepsis, sepsis as variable of interest in the primary multivariable model (Figure 2A; Table 3) was replaced with quick SOFA (qSOFA) independent from the infectious status. There was no association between qSOFA and DCI when applied independently from an infection (aOR = 0.85, 95%CI: 0.43–1.68, $p = 0.65$; Supplementary Figure S1; Supplementary Table S3).

3.4 Association between sepsis and DCI with functional outcome

In multivariable LR models containing all cases ($n = 238$) of the original cohort, sepsis was independently associated with poor functional outcome (mRS >3) at hospital discharge with an aOR = 2.85 (95%CI: 1.23–6.63, $p = 0.02$; Figure 2B; Supplementary Table S4). Age (aOR = 1.84, 95%CI: 1.29–2.62, $p < 0.01$), EVD-placement (aOR = 21.87, 95%CI: 6.76–70.77, $p < 0.01$) and DCI (aOR = 2.45, 95%CI: 1.18–5.07, $p = 0.02$) were additional predictors of poor functional outcome.

Furthermore, we evaluated the effects of potential interactions between sepsis and DCI regarding functional outcome (Supplementary Table S5). Sepsis showed an interaction with DCI (aOR = 11.05, 95%CI: 1.31–93.27, $p = 0.03$) and neither of these variables remained independently associated ($p = 0.53$ for sepsis and $p = 0.27$ for DCI) in the interaction model (Supplementary Table S5). Thus, indicating that the main effect of sepsis and DCI on functional outcome could not be independently interpreted from each other.

The proportion of patients with good functional outcome (mRS 0–3) gradually decreased in subgroups of patients from 56.3% (76/135) in those with neither sepsis nor DCI, to 43.8% (21/48) in those with no sepsis but DCI, to 34.5% (10/29) in patients with sepsis but no DCI and to 7.7% (2/26) in those with both sepsis and DCI. To quantify the potential effect of small numbers of patients in some subgroups of the latter results, we performed *post hoc* power analyses. If identical proportions (i.e., probabilities) of poor outcome (mRS 4–6) were assumed for a study between non-septic ($p_1 = 0.46$, $n_1 = 183$) and septic ($p_2 = 0.78$, $n_2 = 55$) patients using two-sided $\alpha = 0.05$, this would result in a power of 99.0%. Additionally, ±10–20% variations of the above proportions (p_1 vs. p_2) within the identically sized two groups for 0.46 versus 0.68 and 0.36 versus 0.58 resulted both in a power of 79.9%, respectively.

4 Discussion

The primary aim of the present study was to investigate the association between sepsis and DCI and a potential cumulative effect of

TABLE 2 Clinical and treatment characteristics before and after propensity score matching (PSM) for cases with sepsis.

	Before PSM			After PSM		
	Not septic N = 183	Septic N = 55	p-value	Not septic N = 55	Septic N = 55	p-value
Age [years]	55 (50–63)	58 (52–69)	0.09	60 (55–70)	58 (52–69)	0.37
Female	127 (69.4)	39 (70.9)	0.96	41 (74.5)	39 (70.9)	0.83
Arterial hypertension	98 (53.6)	35 (63.6)	0.24	40 (72.7)	35 (63.6)	0.41
Diabetes mellitus	8 (4.4)	8 (14.5)	**0.02**	4 (7.3)	8 (14.5)	0.36
Smoking history	74 (40.4)	16 (29.1)	0.17	17 (30.9)	16 (29.1)	1.0
WFNS grade I	68 (37.2)	14 (25.5)	0.29	17 (30.9)	14 (25.5)	0.83
II	47 (25.7)	12 (21.8)		15 (27.3)	12 (21.8)	
III	7 (3.8)	4 (7.3)		3 (5.5)	4 (7.3)	
IV	30 (16.4)	11 (20.0)		10 (18.2)	11 (20.0)	
V	31 (16.9)	14 (25.5)		10 (18.2)	14 (25.5)	
Modified Fisher scale 0	5 (2.7)	0 (0.0)	**0.03**	1 (1.8)	0 (0.0)	0.86
1	12 (6.6)	3 (5.5)		3 (5.5)	3 (5.5)	
2	11 (6.0)	3 (5.5)		3 (5.5)	3 (5.5)	
3	65 (35.5)	9 (16.4)		11 (20.0)	9 (16.4)	
4	90 (49.2)	40 (72.7)		37 (67.3)	40 (72.7)	
IVH	101 (55.2)	42 (76.4)	**<0.01**	40 (72.7)	42 (76.4)	0.83
EVD-placement	134 (73.2)	50 (90.9)	**0.01**	44 (80.0)	50 (90.9)	0.18
Clipping	89 (48.6)	24 (43.6)	0.62	24 (43.6)	24 (43.6)	1.0
DCI	48 (26.2)	26 (47.3)	**0.01**	16 (29.1)	26 (47.3)	0.08
Updated DCI protocol	134 (73.2)	41 (74.5)	0.98	41 (74.5)	41 (74.5)	1.0
Infection	67 (36.6)	55 (100)	**<0.01**	24 (43.6)	55 (100.0)	**<0.01**
mRS at discharge 0	15 (8.2)	0 (0.0)	**<0.01**	4 (7.3)	0 (0.0)	**<0.01**
1	29 (15.8)	8 (14.5)		7 (12.7)	8 (14.5)	
2	32 (17.5)	3 (5.5)		11 (20.0)	3 (5.5)	
3	21 (11.5)	1 (1.8)		6 (10.9)	1 (1.8)	
4	19 (10.4)	9 (16.4)		4 (7.3)	9 (16.4)	
5	40 (21.9)	26 (47.3)		15 (27.3)	26 (47.3)	
6	27 (14.8)	8 (14.5)	1.00	8 (14.5)	8 (14.5)	
mRS 4–6	86 (47.0)	43 (78.2)	**<0.01**	27 (49.1)	43 (78.2)	**<0.01**
ICU LOS [days]	13 (9–20)	18 (13–27)	**<0.01**	15 (10–21)	18 (13–27)	**0.046**
In-hospital mortality	27 (14.8)	8 (14.5)	1.00	8 (14.5)	8 (14.5)	1.0

Data presented as number (percentage) or median (interquartile range). Propensity score distance was estimated with logistic regression including covariates age, sex, WFNS grading scale, IVH, DCI protocol, smoking history, and arterial hypertension. Bold p-values indicate statistical significance at < 0.05-level. For multi-level factor variables (e.g., WFNS grade, modified Fisher, mRS) only the results of the respective global test are shown. DCI, delayed cerebral ischemia; EVD, external ventricular drainage; ICU, intensive care unit; IVH, intraventricular hemorrhage; LOS, length of stay; mRS, modified Rankin Scale; WFNS, World Federation of Neurological Surgeons SAH grading scale.

sepsis and DCI on functional outcome in a cohort of patients with aSAH using current sepsis definition. Because of overlapping pathophysiological features, we hypothesized that sepsis and DCI might be associated and have a cumulative effect on poor functional outcome. In our cohort of aSAH patients, sepsis was independently associated with DCI. However, when patients that developed sepsis before or after DCI were excluded, this association did not remain. If sepsis preceded DCI, we found a trend towards a higher probability of developing DCI, which was probably limited by the sample size. Nonetheless, sepsis was confirmed as an independent risk factor for poor functional outcome in patients with aSAH. The worst functional outcome was observed in patients who suffered from both sepsis and DCI.

Robust data on the association between sepsis and DCI in patients with aSAH are limited and inconclusive (11). A previous study by Foreman et al. described an independent association between nosocomial infection and DCI (11). However, in their study no differentiation between localized and systemic infection was made (11). Jeon et al. reported that sepsis was neither associated with DCI nor with mRS > 3 at 3 months after SAH (15). In a relatively small cohort of 98 aSAH patients, Budohosky et al. found a trend towards increased odds of DCI in patients with sepsis (OR = 4.4, 95%CI: 0.08–25.2; p = 0.095) (7). Although the used sepsis operationalization was shown to be important in studies on sepsis-associated outcomes in critically ill patients in general (20, 35) and

in patients with aSAH specifically (2, 36), neither of the aforementioned studies included details about the utilized sepsis definition. Additionally, both studies were performed before 2016 (7, 15) and did not apply the updated sepsis-3 definition that focuses on septic organ dysfunction (16). To our knowledge, this is the first study evaluating sepsis-3 criteria for the association between sepsis and DCI in patients with aSAH.

We observed a strong association between sepsis and DCI in the total cohort. When patients who developed sepsis after DCI were excluded from the analysis, thereby focusing on the effect of sepsis

preceding DCI, the association between sepsis and DCI was no longer statistically significant but indicated a potential trend towards a positive association with DCI. Thus, we assume that a larger, potentially multi-centric cohort could improve statistical power and underscore their temporal association. This notion was also supported by the sensitivity analysis focusing on patients who developed sepsis after DCI, in which no relevant association between sepsis and DCI could be identified. These findings hint to a rather complex interplay between sepsis and DCI.
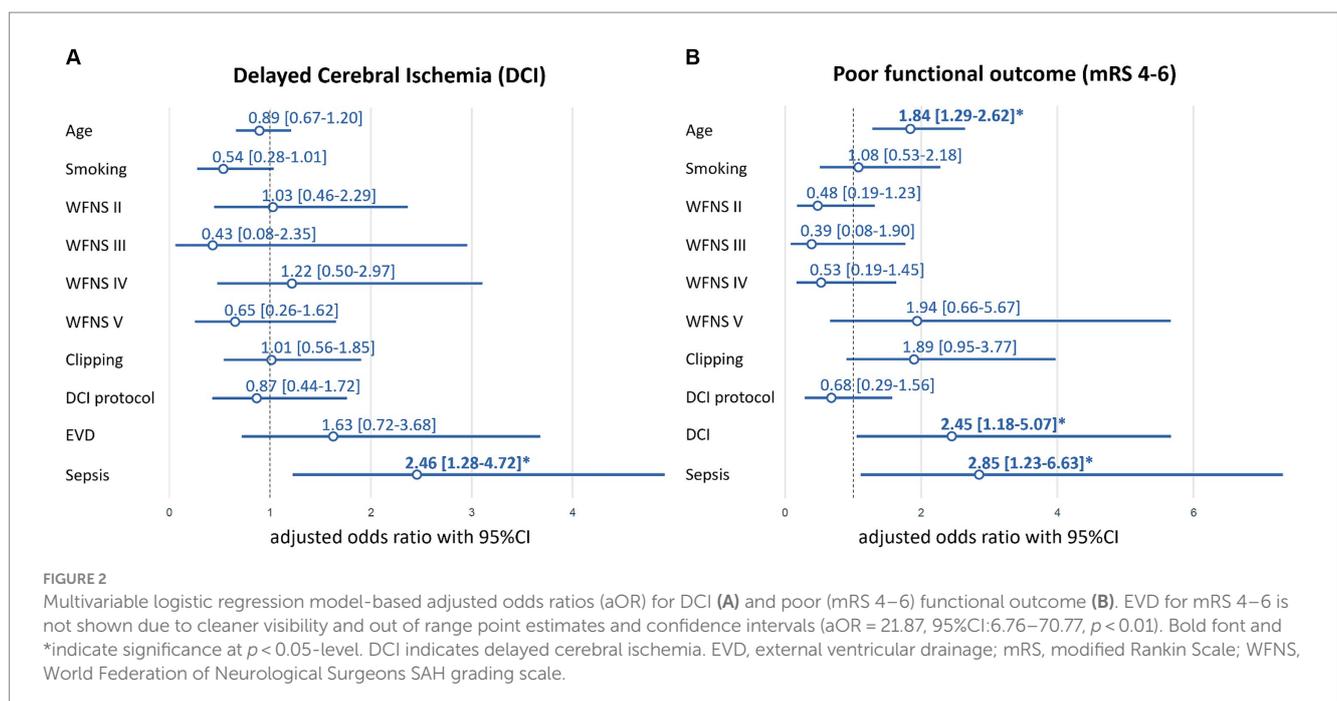
The observed association between sepsis and DCI in the present study might be explained by overlapping pathophysiological effects of sepsis in the brain and DCI. Both conditions are characterized by vascular dysfunction including dysregulation of cerebral vascular tone and impairment of vascular autoregulation (3, 7, 36). While DCI can occur independently from cerebral vasospasm, there is still a strong association between angiographic vasospasm with neurological worsening, cerebral infarction, and poor outcome (12). Simultaneously, in contrast to systemic vasodilation in early sepsis, vasoconstriction of the resistance arterioles in the brain occurs in patients with sepsis-associated encephalopathy (37). It is noteworthy that the titration of the systemic circulation to a specific blood pressure target with vasopressors will not automatically restore cerebral perfusion in septic patients (38). In recent years, new evidence has been established for both sepsis-associated encephalopathy and DCI that factors beyond a disturbed macrocirculation of cerebral blood vessels play an important role in the pathophysiology including microcirculatory disturbances due to endothelial dysfunction, neuroinflammation and microthrombosis with consecutive disruption of the blood–brain barrier and cellular injury (9, 10, 39, 40).

While DCI is defined as cerebral ischemia due to sequelae of SAH (13), sepsis can cause cerebral ischemia via the multifactorial pathophysiological processes described above (5, 6, 39). Hence, both sepsis and DCI are associated with derangements of vascular tone and integrity, microthrombosis formation and neuroinflammation

TABLE 3 Multivariable logistic regression models including sensitivity analysis for the primary endpoint delayed cerebral ischemia (DCI).

Variable	Total cohort (N_{total} = 238) aOR [95%CI]; p-value	Patients with sepsis after DCI excluded (N_{sens} = 229; $N_{excluded}$ = 9) aOR [95%CI]; p-value
Age	0.89 [0.67–1.20]; 0.45	0.86 [0.17–4.38]; 0.85
Smoking	0.54 [0.28–1.01]; 0.054	0.98 [0.96–1.01]; 0.25
WFNS grade II	1.03 [0.46–2.29]; 0.95	0.97 [0.42–2.21]; 0.94
III	0.43 [0.08–2.35]; 0.33	0.53 [0.10–2.83]; 0.46
IV	1.22 [0.50–2.97]; 0.67	1.33 [0.54–3.30]; 0.53
V	0.65 [0.26–1.62]; 0.36	0.61 [0.23–1.60]; 0.32
Clipping	1.01 [0.56–1.85]; 0.96	1.00 [0.54–1.85]; 1.00
EVD placement	1.63 [0.72–3.68]; 0.24	1.54 [0.68–3.50]; 0.30
DCI protocol	0.87 [0.44–1.72]; 0.68	0.92 [0.45–1.87]; 0.81
Sepsis	**2.46 [1.28–4.72]; 0.007**	1.59 [0.78–3.24]; 0.21

Bold text indicates statistical significance at $p < 0.05$ level. aOR, adjusted odds ratio; DCI, delayed cerebral ischemia; EVD, external ventricular drainage; WFNS, World Federation of Neurological Surgeons SAH grading scale.

FIGURE 2
Multivariable logistic regression model-based adjusted odds ratios (aOR) for DCI **(A)** and poor (mRS 4–6) functional outcome **(B)**. EVD for mRS 4–6 is not shown due to cleaner visibility and out of range point estimates and confidence intervals (aOR = 21.87, 95%CI:6.76–70.77, $p < 0.01$). Bold font and *indicate significance at $p < 0.05$-level. DCI indicates delayed cerebral ischemia. EVD, external ventricular drainage; mRS, modified Rankin Scale; WFNS, World Federation of Neurological Surgeons SAH grading scale.

resulting in cerebral ischemia (4, 6, 9, 10, 39). These pathophysiological effects are concordant with the results of the present study in that both sepsis and DCI were independent risk factors for poor functional outcome in our cohort of aSAH patients. Sepsis is known to be independently associated with persistent new cognitive impairment and functional disability among survivors in general populations (41) and might contribute to brain dysfunction after SAH as a second hit to an already vulnerable brain (1). Accordingly, the relevance of sepsis on the functional outcome in patients with aSAH was shown before (1, 42, 43) and confirmed in the present study. Interestingly, our analysis revealed a significant interaction between sepsis and DCI and showed that their effects on functional outcome could not be interpreted independently from each other. Furthermore, sensitivity analyses suggested that temporal characteristics of sepsis and DCI occurrence are of relevance. In line with this, we observed a gradual decrease of the proportion of patients with good functional outcome in the presence of DCI and sepsis. Only 7.7% of patients who suffered from sepsis and DCI achieved an mRS 0–3 outcome, which underlines a cumulative effect that warrants further research. In this context, it has been recently shown that systemic infection can increase intracranial inflammatory responses in patients with aSAH (14), which might be a promising approach to explore the here established associations between sepsis, DCI and functional outcome. Further investigating the temporal course of sepsis, the systemic immune response and the development of DCI could be helpful to better define the relationship (11).

4.1 Limitations

Our study has several limitations: The data are derived from a single-center retrospective cohort study. However, the retrospective nature permitted the inclusion of all available information independent from temporal occurrence and for the comprehensive description of infectious complications. Concurrently, the retrospective design prevented conclusions about cause–effect inferences. Our analyses are based on a cohort, which was extracted up to 11/2018. This was due to a data lockdown within the research project Scientific Computing for Improved Detection and Therapy of Sepsis (SCIDATOS (44, 45), funded by the Klaus Tschira Foundation, grant number 00.277.2015) and a consecutive elaborate data annotation and validation process by several experts from multiple medical disciplines. Nonetheless, this is, to our knowledge, among the largest cohorts in that the association between sepsis and DCI in aSAH patients was analyzed (7, 11, 15). Functional outcome at hospital discharge, as the endpoint of this study, cannot capture long-term outcomes. As demonstrated in a previous study of SAH patients, sepsis was identified as an independent risk factor for both poor functional outcome at hospital discharge and in the long term (1). It is tempting to speculate that the here established association between sepsis and DCI may also be relevant for long-term functional outcome, warranting investigation in future studies.

5 Conclusion

In conclusion, the present study is, to our knowledge, the first to demonstrate a significant association between sepsis and DCI in

aSAH patients and indicate the relevance of their temporal association. Sepsis was confirmed as an independent risk factor for poor functional outcome at hospital discharge. Furthermore, the co-occurrence of sepsis and DCI led to a cumulative effect towards poor functional outcome. Our analyses highlight the significant impact of sepsis on the disease course of aSAH patients suggesting a complex interplay between sepsis and DCI, which warrants further research on this topic.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Medical Ethics Commission II of the Medical Faculty Mannheim, University of Heidelberg. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin due to the observational and retrospective nature of the study.

Author contributions

F-SC: Writing – original draft, Validation, Project administration, Methodology, Investigation, Data curation, Conceptualization. HW: Writing – review & editing, Validation, Resources, Investigation, Data curation. MO: Writing – review & editing, Validation, Software, Resources, Formal analysis, Data curation. F-JD: Writing – review & editing, Investigation. JS-S: Writing – review & editing, Investigation. TP: Writing – review & editing, Investigation. JS: Writing – review & editing, Investigation. BH: Writing – review & editing, Software, Formal analysis, Data curation. AA: Writing – review & editing, Investigation. KH: Writing – review & editing, Investigation. CG: Writing – review & editing, Resources. JK: Writing – review & editing, Validation, Resources. MT: Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition. NE: Writing – review & editing, Validation, Resources. MM: Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation.

Funding

Acknowledgments

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1393989/full#supplementary-material

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