HHS Public Access

Author manuscript

Neurocrit Care. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

Neurocrit Care. 2017 April ; 26(2): 160–166. doi:10.1007/s12028-016-0367-2.

Lymphopenia, Infectious Complications, and Outcome in Spontaneous Intracerebral Hemorrhage

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Abstract

Background—Lymphopenia is increasingly recognized as a consequence of acute illness and may predispose to infections. We investigated whether admission lymphopenia (AL) is associated with increased risk of infectious complications and poor outcome in patients with spontaneous intracerebral hemorrhage (ICH).

Methods—We retrospectively analyzed a prospectively collected cohort of ICH patients ascertained between 1994 and 2015. We identified subjects with lymphocyte count obtained within 24 h from onset, and AL was defined as lymphocyte count < 1000/μL. Infectious complications were assessed through retrospective chart review. Association between AL, infections, and mortality was investigated using multivariable logistic regression.

Results—Of the 2014 patients meeting inclusion criteria, 548 (27.2%) had AL and 605 (30.0%) developed an infectious complication. Case-fatality at 90 days was 36.9%. Patients with AL had larger hematoma volumes, higher frequency of intraventricular hemorrhage, and lower Glasgow Coma Scale score on presentation (all $p < 0.001$). AL was independently associated with increased risk of pneumonia [odds ratio (OR) 1.97, 95% confidence interval (CI) 1.50–2.58, $p < 0.001$] and multiple infections (OR 1.84, 95% CI 1.24–2.71, $p = 0.003$). AL was also an independent predictor of 90-day mortality (OR 1.55, 95% CI 1.18–2.04, $p = 0.002$) after adjusting for confounders.

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Compliance with Ethical Standards

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest Andrea Morotti, Sandro Marini, Michael Jessel, Kristin Schwab, Christina Kourkoulis, Alison M. Ayres, M. Edip Gurol, and Steven M. Greenberg report no disclosures

Conclusions—AL is common in ICH patients and independently associated with increased risk of infectious complications and poor outcome. Further studies will be needed to determine whether prophylactic antibiotics in ICH patients with AL can improve outcome.

Keywords

Stroke; Cerebral hemorrhage; Cerebrovascular disorders; Lymphopenia; Infection; Pneumonia

Introduction

Intracerebral hemorrhage (ICH) is still the deadliest type of stroke, with lack of an acute phase treatment proven to reduce mortality and improve functional outcome [1]. Inflammation and lymphocyte migration into the brain appear to play a key role in secondary brain damage and clinical deterioration following acute ICH [2]. Clinical trials of fingolimod in ICH have, therefore, been guided by the theory that lymphocyte depletion may improve outcome reducing edema and inflammation-mediated tissue damage [3]. Prior studies, however, suggest that hemorrhagic stroke, like ischemic stroke or other acute severe illnesses can be accompanied by immunodepression, manifested by lymphopenia [4–6]. Lymphopenia, in turn, may predispose to the development of infections [7, 8]. The role of lymphopenia in ICH, and in particular, whether it predisposes to infectious complications (IC) during the acute course is poorly understood and may have implications for the design of future clinical trials of immunomodulation in ICH. In this study we investigated the frequency and determinants of lymphopenia in subjects with ICH and whether it was associated with increased risk of IC and poor outcome.

Methods

Study Design and Patient Selection

All aspects of the study were approved by the Institutional Review Board (IRB). Informed written or verbal consent was obtained by patients or family members or waived by the IRB.

We retrospectively analyzed an ongoing prospective cohort of patients with spontaneous ICH collected at a single academic hospital from January 1994 to April 2015 [9, 10]. The inclusion criteria for the present study were: (1) diagnosis of spontaneous ICH on non-contrast CT scan (2) complete white blood cell count obtained within 24 h from stroke onset. Subjects were excluded if there was evidence of (1) traumatic intracranial bleeding, (2) intracranial tumor, aneurysm, or other vascular malformation presumed to be the cause of the hemorrhage, (3) hemorrhagic conversion of acute brain infarction, (4) missing data on infectious complications, and (5) missing follow-up data on mortality at 90 days.

Image Acquisition and Analysis

All images were analyzed by study staff blinded to all clinical and laboratory variables. Non-contrast CT images were acquired with an axial technique and 5-mm-thickness slices, 120–140 kVp, 10–500 mA and reviewed for determination of ICH location and the presence of intraventricular extension of the hematoma (IVH). Hematoma volume was calculated with semi-automated computer-assisted technique (Analyze Direct 11.0 software).

Clinical Variables

Demographic and clinical data were systematically collected through patient and family members' interviews and retrospective review of hospital charts. We assessed the presence of medical history of hypertension, diabetes mellitus, hypercholesterolemia, antiplatelet therapy, and oral anticoagulant treatment (OAT) as previously described in detail [10]. We also collected data on pre-stroke functional status, and functional dependence was defined as requiring assistance in at least one instrumental activity of daily living before the index ICH [11].

Because previous reports have demonstrated that the relationship between total lymphocyte count and susceptibility to infections is not linear and that the odds of experiencing an IC increase only when the lymphocyte count drops below a critical threshold [7, 12], we analyzed admission lymphopenia (AL) defined as absolute lymphocyte count < 1000/μL [7, 13]. We also collected data on admission leukopenia (absolute leukocyte count < 4000/μL), admission neutropenia (absolute neutrophil count < 1500/μL), and admission monocytopenia (absolute monocyte count < 200/μL) [14, 15].

Infectious Complications and Mortality

IC were identified through a retrospective review of hospital charts, discharge reports, laboratory, and radiological tests. The presence of an IC during the hospital stay was established according to previously published criteria [16–18] by two investigators (AM, SM), blinded to the presence of AL. In particular, we looked for evidence of the following infections during the hospital stay: pneumonia, urinary tract infections, and sepsis. The diagnosis of pneumonia was based on the combination of typical clinical presentation with confirmatory chest X-ray changes [16]. A positive urine culture was required for the diagnosis of urinary tract infection [17]. Sepsis was diagnosed in case of documented source of infection associated with evidence of acute organ dysfunction [18]. Mucocutaneous infections, gastrointestinal infections, and meningoencephalitis were grouped in the category "other infections." The case-fatality rate at 90 days was assessed via telephone interviews and querying of the Social Security Death Index (SSDI) national database as previously described [10].

Statistical Analysis

Categorical variables were expressed as count (%) while continuous variables as median (interquartile range, IQR). Differences between patients with and without AL and with and without infections were examined using the χ^2 test or Mann–Whitney U test as appropriate.

The association between AL and infectious complications was investigated with a multivariable logistic regression analysis, adjusted for predictors of infections [19, 20]. All the variables with p value <0.1 in univariate analysis were included in the regression model. The relationship between AL and 90-day mortality was investigated with a multivariable logistic regression, accounting for known predictors of outcome in ICH patients (age, ICH volume, admission Glasgow Coma Scale score, presence on IVH, and infratentorial location) [21]. p values <0.05 were considered statistically significant. All analyses were performed using the statistical package SPSS v. 21, 2012 (www.spss.com).

Results

A total of 2403 patients with ICH were screened and 2014 met the eligibility criteria for the present analysis. The frequency of AL was 27.2% and a total of 605 (30.0%) patients experienced an infection during the hospital stay. Overall mortality at three months was 36.9%. A total of 351 subjects were excluded because of lack of lymphocyte count, and 38 patients were excluded because of missing clinical or demographic data. Compared to the study population, patients excluded from the analysis were older, more likely to be on antiplatelet treatment, and less likely to have a medical history of hypertension, diabetes mellitus, and hypercholesterolemia. The remaining demographic and clinical characteristics were similar between the two groups (all p values >0.05).

Factors Associated with Admission Lymphopenia

Patients with AL were older and had larger baseline hematoma volume and higher frequency of intraventricular extension of the hemorrhage (Table 1). In addition, AL was associated with infratentorial location of the hematoma and lower admission Glasgow Coma Scale score.

Infectious Complications

The presence of AL was significantly higher in patients with IC (31.6 vs 25.3%, $p = 0.004$) whereas the frequency of leukopenia, neutropenia, and monocytopenia was similar between the two groups (Table 2).

After adjustment for potential confounders in multivariable regression, AL was independently associated with increased risk of pneumonia, and multiple infections, but not with urinary tract infection and sepsis (Table 3).

Mortality

AL was independently associated with increased case-fatality at 90 days (odds ratio 1.55, 95% CI 1.18–2.04, $p = 0.002$) after accounting for known predictors of mortality in ICH (age, admission GCS, presence of IVH, infratentorial location of the hematoma and baseline ICH volume) [21]. Figure 1 shows the adjusted survival analysis stratified by presence of AL.

Duration of hospitalization was longer in patients experiencing at least one IC (11 vs 5 days, $p < 0.001$). While patients with IC had lower mortality in univariate analysis, their mortality rate was significantly higher when the analysis was restricted to subjects surviving longer than 72 h (mortality at 90 days: 27.0 vs 21.4%, $p = 0.022$), consistent with the presence of survival bias underlying the unrestricted assessment of mortality [22].

All results were unchanged when pre-stroke functional status was also included in the multivariate analysis (OR for infectious complications 1.46, 95% CI 1.44–1.87, $p = 0.002$; OR for 90 days mortality 1.48, 95% CI 1.09–2.00, $p = 0.011$).

Discussion

We found that lymphopenia on admission is frequent in ICH patients and is independently associated with increased risk of IC and long-term mortality. In particular, AL was an independent predictor of pulmonary infections and multiple infections during the hospital stay.

While it remains to be determined whether the immunosuppression manifested by lymphopenia precedes the ICH or is an acute consequence of it, accumulating data suggest that brain injury can influence the physiologic interplay between the central nervous system and the immune system, leading to the onset of a systemic immunodepressive syndrome [5, 23, 24]. This immunodepressive state is characterized by the acute secretion of several stress mediators, with secondary apoptotic loss of circulating lymphocytes that appears to be proportional to the severity and extension of brain damage [5, 6, 23]. Indeed, in our study, AL was associated with ICH of higher severity. Patients with AL had larger ICH volumes, lower GCS, and higher frequency of IVH, and AL could theoretically be just a marker of ICH severity. Pre-stroke functional status may also be an important confounder and the presence of lymphopenia could simply reflect the degree of disability prior to the index ICH.

However, the association between lymphopenia, infections, and outcome remained significant after adjusting for multiple potential confounders such as pre-stroke disability and measures of ICH severity. In agreement with previous studies on stroke-associated immunodepression [4–6, 8], our results suggest that the presence of lymphopenia correlates with stroke severity but plays an independent role in predisposing to infections and unfavorable outcome.

Consistent with prior studies [13], we also demonstrated that AL is an independent predictor of poor outcome. Our results offer evidence for a mechanism through which AL may be operating. Infections are indeed a major cause of mortality in stroke patients [19, 25–27], and AL was associated with an increased risk of pneumonia and multiple infections in our study.

In this regard, we observed a higher mortality in subjects with infectious complications only restricting the analysis to patients surviving the first three days after stroke. One possible explanation is the influence of survival bias. Multiple previous studies showed that hematoma expansion, intraventricular bleeding, and limitation of care are the main determinants of early mortality after ICH [28, 29]. Conversely, infections have a negative influence on stroke outcome especially in the subacute phase, and therefore, patients that did not experience early clinical deterioration and death are at higher risk of developing a nosocomial infection [28, 29]. In line with this Katzan and Colleagues showed that stroke-associated pneumonia increased mortality after exclusion of patients dying or receiving withdrawal of care within 72 h from onset [30], again suggesting that infections have a greater influence on late rather than early mortality after stroke.

It appears, therefore, plausible that an increased susceptibility to IC may be the link between AL and worse outcome in patients hospitalized for ICH.

The association between systemic inflammation, leukocyte activation, and ICH is complex [9, 31, 32]. Our findings suggest that lymphocytes play a key role in protection against infections in ICH patients, which may have important implications for future studies. Several neuroprotective strategies targeting inflammation and leukocyte activation are currently under investigation in stroke and ICH [3, 33]. However, the results of our analysis raise the hypothesis that acute inflammation and lymphocyte activation in the acute phase of ICH may play a beneficial role, decreasing the propensity to develop an IC. This hypothesis is indirectly supported by several reports describing an increased risk of infections in patients treated with immunomodulatory drugs that reduce lymphocyte count and function [34–38].

Clinical trials targeting inflammation in stroke patients should therefore balance the possible benefits of immunomodulation against a potential increased susceptibility to infections. From a clinical standpoint, infections are a leading cause of mortality in stroke patients, and therefore, prevention of such complications is an appealing therapeutic strategy [8]. However, prophylactic antibiotic treatment to prevent infections in stroke patients did not lead to improved long-term outcome in two large randomized clinical trials [39, 40]. One possible explanation is the inclusion of patients irrespective of their probability of experiencing an IC. The presence of AL may be a useful biomarker to identify patients at increased risk of IC and, therefore, more likely to benefit from intensification of preventive measures [41] or prophylactic antibiotic administration.

Lymphocyte count is a widely available and inexpensive biomarker that may be used to stratify the risk of IC also in clinical practice. Finally, discussion of goals of care and palliative treatments is a key aspect of ICH care [1], and an accurate estimation of ICH prognosis is still an unmet need [42]. AL may provide additional value in predicting the prognosis of ICH patients.

Some limits of our study should be acknowledged. First, our results derive from a single center, retrospective analysis and should be validated in prospective studies. Second, the long recruitment period may have influenced our results since several changes in ICH management occurred in this time frame. Finally, pre-ICH lymphocyte count was not available in our dataset, and therefore, we were not able to exclude the influence of potential confounders like inflammatory, infectious, and autoimmune disorders preceding the admission for ICH.

Conclusions

AL is common in ICH patients and independently associated with increased risk of infections and mortality. This highlights a possible beneficial role of lymphocytes activation in ICH morbidity and may offer a therapeutic opportunity for prevention of infections in clinical practice or in the setting of clinical trials.

Acknowledgments

This study was supported by the following awards from the NINDS: 5R01NS073344, K23AG02872605, K23 NS086873, R01NS059727. None of the funding entities had any involvement in study design; data collection, analysis, and interpretation; writing of the manuscript; or decision to submit the study for publication.

Anand Viswanathan, Christopher D. Anderson, Jonathan Rosand, and Joshua N. Goldstein report research funding from NIH; Joshua N. Goldstein reports research funding from Boehringer Ingelheim, Pfizer, and Portola; and consulting from Bristol Myers Squibb.

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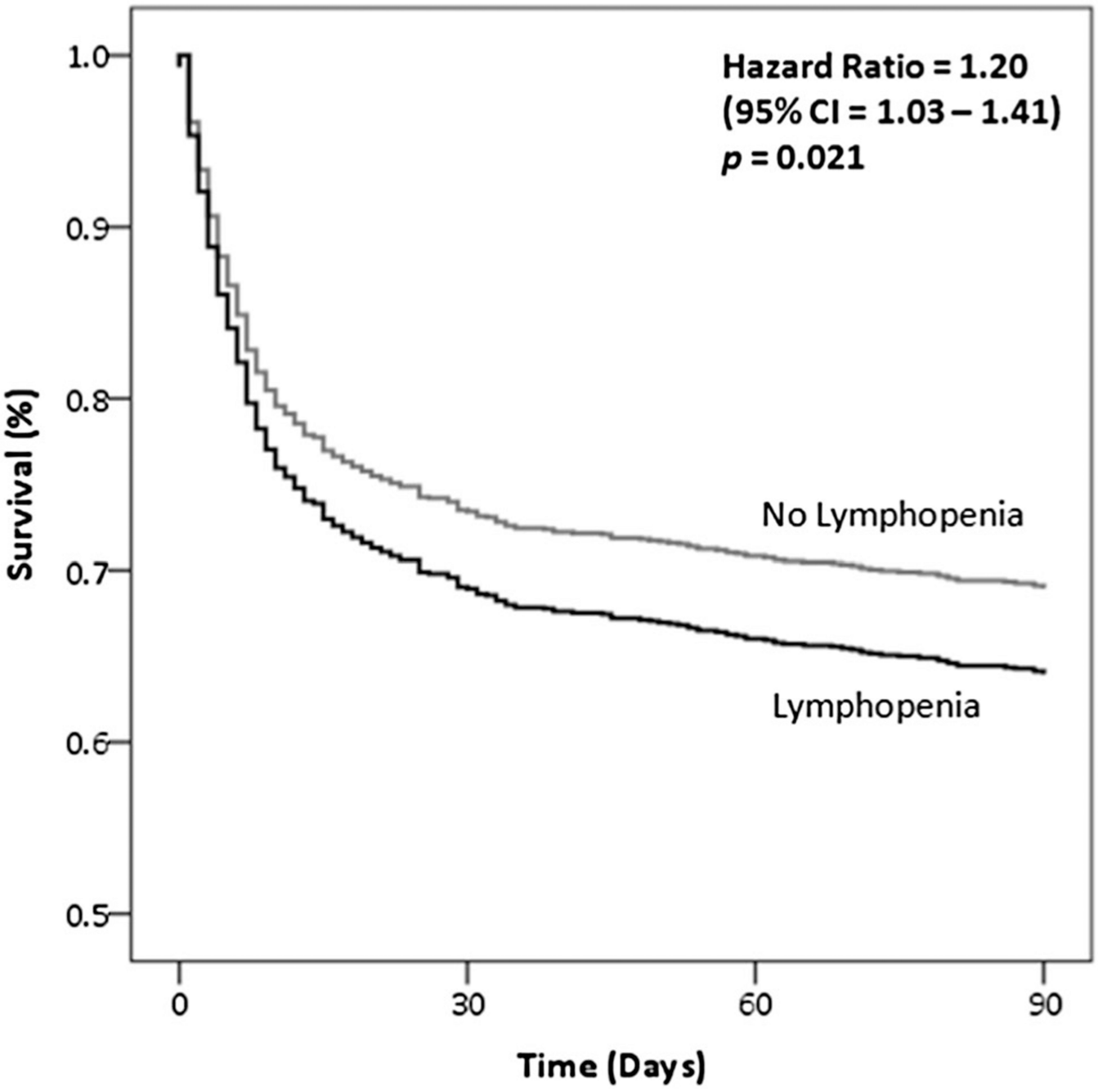

Fig. 1.

Adjusted survival curve, stratified by admission lymphopenia. Hazard Ratio (HR) was obtained with a Cox proportional hazard model, adjusted for age, admission GCS, baseline ICH volume, presence of IVH, intubation, infratentorial location. *ICH* intracerebral hemorrhage, *GCS* Glasgow Coma Scale, *IVH* intraventricular hemorrhage

Table 1

Comparison between patients with and without admission lymphopenia (n = 2014)

Variable	Lymphopenia		*p* value
	No (n = 1466)	Yes (n = 548)	
Age, median (IQR), year	74 (63–82)	76 (66–83)	0.003
Sex, male, *n* (%)	785 (53.5)	303 (55.3)	0.484
History of hypertension, *n* (%)	1144 (78.0)	435 (79.4)	0.377
History of diabetes, *n* (%)	323 (22.0)	113 (20.6)	0.790
History of hypercholesterolemia, *n* (%)	565 (38.5)	202 (36.9)	0.732
Antiplatelet treatment, *n* (%)	695 (47.4)	261 (47.6)	0.986
Warfarin treatment, *n* (%)	272 (18.6)	151 (27.6)	<0.001
Pre-stroke dependence, *n* (%)	194/1332 (14.6)	77/501 (15.4)	0.665
Baseline ICH volume, median (IQR), mL	16 (5–40)	23 (6–57)	<0.001
Admission GCS, median (IQR)	14 (8–15)	12 (6–15)	<0.001
Infratentorial location, *n* (%)	147 (10.0)	87 (15.9)	<0.001
IVH presence, *n* (%)	666 (45.4)	331 (60.4)	<0.001
Intubation, *n* (%)	458 (31.2)	251 (45.8)	<0.001
Surgery, *n* (%)	68 (5.9)	45 (8.2)	0.156
Any infectious complication, *n* (%)	414 (28.2)	191 (34.9)	0.004
Pneumonia, *n* (%)	233 (15.9)	138 (25.2)	<0.001
Urinary tract infection, *n* (%)	223 (15.2)	83 (15.1)	0.971
Sepsis, *n* (%)	32 (2.2)	16 (2.9)	0.335
Other infection, *n* (%)	20 (1.4)	6 (1.1)	0.634
Multiple infections, *n* (%)	88 (6.0)	49 (8.9)	0.020
Length of hospital stay, median (IQR), days	6 (3–11)	6 (3–12)	0.954
90-day mortality, *n* (%)	474 (32.3)	269 (49.1)	<0.001

IQR interquartile range, *ICH* intracerebral hemorrhage, *GCS* Glasgow Coma Scale, *IVH* intraventricular hemorrhage

Table 2

Comparison between patients with and without infectious complications (n = 2014)

Variable	Infectious complications		*p* value
	No (n = 1409)	Yes (n = 605)	
Age, median (IQR), year	75 (63–82)	74 (64–83)	0.457
Sex, male, n (%)	768 (54.5)	320 (52.9)	0.505
History of hypertension, n (%)	1089 (77.3)	490 (81.0)	0.143
History of diabetes, n (%)	300 (21.3)	136 (22.5)	0.813
History of hypercholesterolemia, n (%)	541 (38.4)	226 (37.4)	0.854
Antiplatelet treatment, n (%)	670 (47.6)	286 (47.3)	0.833
Warfarin treatment, n (%)	302 (21.4)	121 (20.0)	0.594
Pre-stroke dependence, n (%)	168/1279 (13.9)	103/554 (18.6)	0.003
Baseline ICH volume, median (IQR), mL	17 (5–60)	16 (5–40)	0.137
Admission GCS, median (IQR)	14 (7–15)	13 (8–15)	0.427
Infratentorial location, n (%)	173 (12.3)	61 (10.1)	0.189
IVH presence, n (%)	676 (48.0)	321 (53.1)	0.094
Intubation, n (%)	485 (34.4)	224 (37.0)	0.388
Surgery, n (%)	81 (5.7)	50 (8.3)	0.097
Leukopenia, n (%)	13 (0.9)	7 (1.2)	0.627
Neutropenia, n (%)	1 (0.1)	2 (0.3)	0.167
Monocytopenia, n (%)	62 (4.4)	25 (4.1)	0.786
Lymphopenia, n (%)	357 (25.3)	191 (31.6)	0.004
Length of hospital stay, median (IQR), days	5 (2–8)	11 (6–19)	<0.001
90-day mortality, n (%)	560 (39.7)	183 (30.2)	<0.001

IQR interquartile range, *ICH* intracerebral hemorrhage, *GCS* Glasgow Coma Scale, *IVH* intraventricular hemorrhage

Table 3

Association between lymphopenia and infectious complications

Type of infectious complication	OR (95% CI)	*p* value
Any infection *	1.49 (1.18–1.89)	0.001
Pneumonia	1.97 (1.50–2.58)	<0.001
Urinary tract infection	1.11 (0.83–1.48)	0.495
Sepsis	1.89 (0.97–3.61)	0.055
Other infection	1.01 (0.36–2.82)	0.987
Multiple infections	1.84 (1.24–2.71)	0.003

ICH intracerebral hemorrhage, *GCS* Glasgow Coma Scale, *IVH* intraventricular hemorrhage, *OR* odds ratio, *CI* confidence interval

* Adjusted for age, admission GCS, baseline ICH volume, presence of IVH, intubation, infratentorial location, warfarin treatment, and length of hospital stay