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Pathogenic organism and risk factors of infection after acute ischemic stroke during the COVID-19 pandemic

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ABSTRACT

This study aims to determine the pathogen organisms' profile and risk factors for infection after acute ischemic stroke (AIS) during the COVID-19 pandemic because of few studies. We conducted a retrospective cross-sectional study using the medical records of AIS inpatients at the National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono, Jakarta, Indonesia, from 2020-2021. We found the species of pathogen organisms based on the positive growth of microbiological cultures of various specimens. Among 479 AIS patients, the infection prevalence was 12.3%. This study found the common pathogenic organisms were Gram-negative bacteria, and there were drug-resistant strains in *S. aureus, S. epidermidis, K. pneumoniae,* and *E. coli.* The risk factors for infection in COVID-19-infected patients were pneumonia (OR 6.89, 95% CI 1.49-31.79, $p = 0.013$) and intensive care stay (OR 0.13, 95% CI 0.05-0.36, $p < 0.001$); meanwhile, in non-COVID-19 patients were HIV comorbidity (OR 1.55, 95% CI 1.18-2.06, $p = 0.002$), leukocytosis (OR 0.07, 95% CI 0.01-0.43, $p = 0.004$), use of CVC (OR 0.29, 95% CI 0.12-0.68, $p = 0.005$), use of steroids (OR 0.21, 95% CI 0.06-0.70, $p = 0.011$), and tracheostomy (OR 0.17, 95% CI 0.05-0.62, $p = 0.007$). To sum up, the growth of pathogenic organisms indicated that the prevalence of infections after AIS during the COVID-19 pandemic did not increase. The risk factor for infections depends on the characteristics of patients, whether they have COVID-19 or have not been infected.

Keywords: COVID-19, culture, infection, ischemic stroke, prevalence, risk factor

INTRODUCTION

A new coronavirus was finally found to be the reason for a spate of pneumonia cases that the Wuhan Municipal Health Commission in China reported in Wuhan, Hubei Province, on December 31, 2019. On March 02, 2020, it was confirmed to have expanded to Indonesia. The World Health Organization (WHO) determined that the concerning rates of severity, inactivity, and spread of coronavirus disease 2019 (COVID-19) warranted the classification of the illness as a pandemic [1]. The COVID-19 pandemic has had an impact on healthcare and the general functioning of populations all over the world [2]. The COVID-19 epidemic appears to have had an impact on stroke patients' admission and care worldwide. Stroke admission rates decreased during the COVID-19 pandemic, but the severity of the stroke upon admission and inpatient mortality increased [3].

In most previous studies, infection complications can affect stroke outcomes that are often encountered in the care of acute stroke patients [4]. Prior research showed that anatomical, clinical, and iatrogenic factors could influence infection after stroke [5-7]. A meta-analysis showed that it was expected to give empiric treatment for bacterial secondary infections in hospitalized COVID-19 patients in the early COVID-19 pandemic. Improper administration of antibiotics will increase mortality due to antibiotic resistance [8]. Although the trend of the outcomes of acute ischemic stroke (AIS) has been discussed elsewhere, little research has been reported on infection complications in AIS patients throughout the COVID-19 outbreak.

The primary objectives of this study were to determine the prevalence and profile of microbiological culture of infection in AIS during the COVID-19 pandemic. The secondary objective was to determine whether certain variables are associated with microbiological cultures of COVID-19 and non-COVID-19 patients separately.

MATERIALS AND METHODS

Study Design and Participants

This retrospective cross-sectional study was single-center and conducted at the National Brain Center Hospital (NBC) Prof. Dr. dr. Mahar Mardjono, Jakarta, Indonesia. As a public tertiary neurology teaching and referral hospital, NBC Hospital has a wide range of neurological health services, with 253

inpatient services, including in intensive care wards, which consist of 12 intensive care units (ICUs), eight high care units (HCUs), and ten stroke care units (SCUs).

We used secondary data from medical records of hospitalized patients during the COVID-19 pandemic between January 01, 2020, and December 31, 2021. We enrolled patients with the inclusion criteria, as follows:

(1) adult patients more than 18 years old,

(2) diagnosed with AIS, and

(3) performed microbiological culture.

We excluded patients with ischemic stroke more than seven days after stroke onset.

Definitions

AIS is a stroke caused by sudden arterial occlusion due to thrombosis or embolism that occurs within a week of stroke onset [9]. Any infection that manifests itself during the acute phase of an ischemic stroke is referred to as infection after AIS [10]. Based on centers for disease control and prevention standards, pneumonia [11] and urinary tract infection [12] were diagnosed, while sepsis was determined using the Sepsis-3 criteria [13] or a procalcitonin test result of greater than 0.5 ng/mL [14]. The chemiluminescent assay's sandwich principle (Elecsys BRAHMS PCT, Cobas®, Roche Diagnostics GmBH, Mannheim) was used to quantify procalcitonin as it was operating in Cobas® c501 clinical chemistry analyzer (Roche Diagnostics GmBH, Mannheim) [14].

The basis for the microbiological profile was microbiological culture using the Vitek 2 Compact platform (BioMerieux, Lyon) [15], which allows the identification of the causative agents by multiplying microbial organisms from infected tissue or body fluid specimens [16]. Positive culture was defined as microorganism growth in the specimen culture. Nevertheless, it was defined as a negative culture. Specimen collection from sterile and non-sterile sites proceeded microbiological culture using previously described methods to determine microorganisms [17]. The prevalence of infection after AIS was based on the percentage of positive growth in microbiological cultures divided by the total number of subjects tested in microbiological cultures.

The risk factors included were, as follows:

(1) anatomical factors, such as the number of the infarct location,

(2) clinical factors, such as age of more than 60 years, sex, diabetes mellitus (DM), Human Immunodeficiency Virus (HIV), and dysphagia, and

(3) Iatrogenic factors, such as ventilator, urinary catheter, central or peripheral vein use [5-7].

We also covered procedures like tracheostomy, digital subtraction angiography (DSA), and head surgery like craniectomy or craniotomy, in addition to treatments like antibiotics, steroids, total parenteral nutrition (TPN), and transfusion.

A plasma glucose level measured during fasting that was greater than 126 mg/dL (7.0 mm/L) was considered type 2 DM [18]. The sandwich principle of the chemiluminescent test (GLUC3, Cobas®, Roche Diagnostics GmBH, Mannheim) was being used to measure blood glucose in Cobas® c501 clinical chemistry analyzer application (Roche Diagnostics GmBH, Mannheim) [19].

Using three consecutive reactive HIV rapid diagnostic tests, HIV infection was identified in accordance with the WHO HIV strategy. Reactive on all three assays was the definition of HIV positive [20]. Assay-1, assay-2, and assay-3 used INDEC® HIV ½ & Syphilis Combo (Indec Diagnostics, Jakarta) [21], Standard™ Q HIV ½ Ab 3-Line (SD Biosensor, Chungcheongbuk-do) [22], and Rapidan® Testes Anti-HIV ½ Test (TurkLab, Izmir) [23], respectively.

The automated hematology analyzer Sysmex XN-1000 was utilized to perform a leukocyte count. (Sysmex Indonesia, Jakarta). The reference range of leukocyte count was 5,000 – 10,000/μL. leukocyte count of more than 10,000/μL was defined as leukocytosis, whereas less than 5,000/μL was defined as leukopenia [24]. The polymerase chain reaction assay (Real-Q 2019-nCoV detection kit, BioSewoom, Seoul) for the severe acute respiratory syndrome coronavirus 2 positive assay confirmed COVID-19 [25, 26]. According to the culture results, we defined positive and negative culture subgroups for COVID-19 and non-COVID-19 AIS patient groups.

Data Analysis

The medical records provided demographic information, possible risk factors based on prior research, and other examination data. Descriptive information is provided on the subjects' characteristics. In order to display the categorical data, n (%) was utilized as the frequency. Kolmogorov-Smirnov test was used to analyze the normality of the distribution of continuous variables and reported as mean with standard deviation (SD) if normally distributed; otherwise, medians with interquartile range (IQR). To compare characteristics by culture and COVID-19 status, we used Chi-square analysis when comparing categorical variables [27]. Identify risk factors based on bivariate analysis. *p*-values were from 2-sided tests, and $p < 0.25$ were included in multivariate logistic regression analysis [28]. To control for numerous confounders simultaneously, we used the multivariate logistic regression model [29]. Complete modeling includes main variables and confounding variables. Interaction variables were removed one by one according to the most significant *p*-value. The confounding variable was assessed based on changes in the main factor's odds ratio (OR), and a change in OR > 10% was the mean that the variable was confounding. *p*-values were from 2-sided tests, and $P<0.05$ was considered statistically significant. Analyses were performed using the statistical package for the social sciences (IBM® SPSS® Statistics) version 26.

RESULTS

According to medical records of hospitalized patients between January 01, 2020, and December 31, 2021, there were 8,569 cases of ischemic stroke. Out of these, 886 underwent specimen cultures. We have excluded 407 patients who were diagnosed with non-AIS (ischemic stroke > 7 days). Eventually, we have enrolled 479 patients who have met the inclusion criteria, including 171 in 2020 and 308 in 2021 (**Figure 1**).

This study revealed that the median age of patients was 60.0 (14.0) years old, and in groups of ages less than and at least 60 years, the numbers and proportions are almost the same. Male and female patients accounted for 66.8% (320) and 33.2% (159). Nearly 70% of patients did not need intensive care. The majority of main diagnoses and infection symptoms (41.5%) were pneumonia, with sepsis coming in second (39.2%).

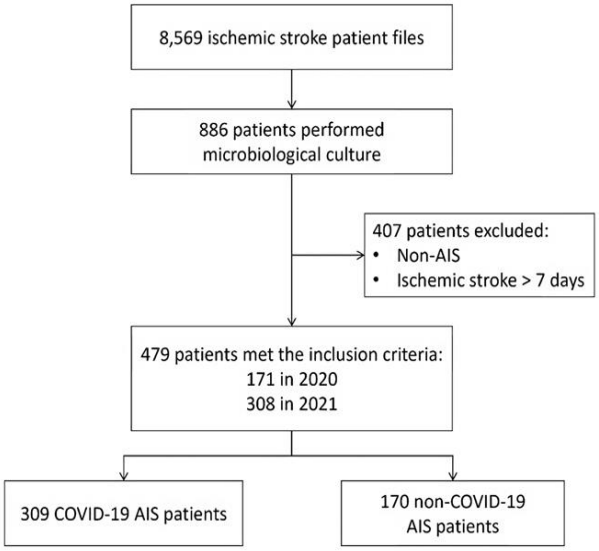

Figure 1. Flowchart of study participants (Source: Authors' own elaboration)

Table 1. Subject characteristics

	Total		COVID-19		Non-COVID-19		*p*
	n	(%)	n	(%)	n	(%)	
Subject	479	(100)	309	(64.5)	170	(35.5)	
Age, median (IQR)	60.0 (14.0)		60.0 (14.0)		60.0 (15.0)		-
Age group, years, n (%)							
<60	226	(47.2)	146	47.2	80	47.1	0.374
≥60	253	(52.8)	163	52.8	90	52.9	
Sex, n (%)							
Male	320	66.8	198	64.1	122	71.8	0.087
Female	159	33.2	111	35.9	48	28.2	-
Clinical manifestation of infection, n (%)							
Fever	111	23.2	68	22.0	43	25.3	0.415
Sepsis	188	39.2	116	37.5	72	42.4	0.302
Meningitis/ encephalitis	14	2.9	6	1.9	8	4.7	0.429
Pneumonia	199	41.5	118	38.2	81	47.6	0.044*
Infected wound	7	1.5	5	1.6	2	1.2	1.000
UTI	4	0.8	4	1.3	-	-	-
Care unit, n (%)							
Intensive	140	29.2	57	18.4	83	48.8	<0.001*
Non-intensive	339	70.8	252	81.6	87.0	51.2	-
Comorbidity, n (%)							
DM	141	29.4	86	27.8	55	32.4	0.299
HIV	21	4.4	12	3.9	9	5.3	0.471
Leukocyte/mL, n (%)	11.8	7.0	11	6.9	12.8	7.5	<0.001*
>10,000	304	63.5	179	57.9	125	73.5	0.001*
5,000-10,000	161	33.6	120	38.8	41	24.1	0.001*
<5,000	14	2.9	10	3.2	4	2.4	0.583
Number infarct location, n (%)							
1	59	12.3	40	12.9	19	11.2	0.727
2	52	10.9	32	10.4	20	11.8	0.593
3	45	9.4	25	8.1	20	11.8	0.203
4	32	6.7	21	6.8	11	6.5	0.981
5	12	2.5	8	2.8	4	2.4	0.928
6	8	1.7	6	1.9	2	1.2	0.574
7	4	0.8	2	0.6	2	1.2	0.521
9	1	0.2	1	0.3	-	-	0.468
Medical device, n (%)							
Ventilator	43	9.0	17	5.5	26	15.3	<0.001*
CVC	116	24.2	57	18.4	59	34.7	<0.001*
NGT	32	6.7	19	6.1	13	7.6	0.530
Urinary catheter	19	4.0	14	4.5	5	2.9	0.394
Treatment, n (%)							
Antibiotic	305	63.7	200	64.7	105	61.8	0.519
Steroid	34	7.1	16	5.2	18	10.6	0.027*
TPN	23	4.8	9	2.9	14	8.2	0.009*
Transfusion	21	4.4	9	2.9	12	7.1	0.034
Procedure, n (%)							
Tracheostomy	22	4.6	6	1.9	16	9.4	<0.001*
DSA	3	0.6	1	0.3	2	1.2	0.258
Head surgery	7	1.5	-	-	7	4.1	<0.001*
Microbiological culture result, n (%)							
Positive	59	12.3	20	6.5	39	22.9	<0.001*
Bacteria	51	10.6	18	5.8	33	19.4	-
Fungi	8	1.7	2	0.6	6	3.5	-
Negative	420	87.7	289	93.5	131	77.1	-

Note. *p<0.05; COVID: Coronavirus disease; CVC: Central venous catheter; DM: Diabetes mellitus; DSA: Digital subtraction angiography; HIV: Human immunodeficiency virus; IQR: Interquartile range; NGT: Nasogastric tube; TPN: Total parenteral nutrition; & UTI: Urinary tract infection

Additionally, the study discovered that whereas 29.4% (141) of patients reported having DM, 64.5% (309) of patients with AIS tested positive for COVID-19. Almost a quarter of patients utilized CVC, whereas approximately one-third of patients applied NGT, which is usually used by patients who experience dysphagia. More than half of patients have used antibiotics previously. Although the proportion is small, tracheostomy is the most frequently performed procedure (4.6% of all procedures). A summary of subject characteristics is listed in **Table 1**.

Microbiological Culture Results

COVID-19 AIS patients were more likely to have negative microbiological results, with the difference in positive microbiological results being 6.5 vs. 22.9%, p < 0.001. Among specimens, blood was the largest proportion of specimens to be tested (90.9 vs. 69.4%), followed by sputum (4.2 vs. 23.5%) (**Table 2**).

Microorganism growth had a predominance of bacterial than fungal (10.6 vs 1.7%, p < 0.001). Among positive microbiological results, Gram-positive and Gram-negative bacteria and fungi were 35.3%, 64.7%, and 1.7%, respectively. The three most common Gram-positive bacteria were *Staphylococcus aureus* (15.6%), *S. epidermidis* (7.8%), and *S. haemolyticus* (3.9%). *S. aureus* and *S. epidermidis* were found in both groups, whereas *S. haemolyticus* was only found in non-COVID-19 AIS patients. The three most common Gram-negative bacteria were *Klebsiella pneumoniae* (27.3%), *Escherichia coli* (18.2%), and *Acinetobacter baumannii* (9.8%). *A. baumannii* was the most common Gram-negative bacteria in COVID-19 AIS patients, whereas *K. pneumoniae* was found dominantly in non-COVID-19 AIS patients. Fungal microbiological culture results were dominated by *Candida albicans* (87.5%) and also in both groups (**Figure 2**, **Figure 3**, and **Figure 4**).

This study found that there were drug-resistant bacteria during the COVID-19 pandemic, which were methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae*. The most ecumenical drug-resistant bacteria was ESBL-producing *E. coli*.

Table 2. Positive and negative culture in COVID-19 and non-COVID-19 AIS patients based on the specimens

	Total			COVID-19						Non-COVID-19					
				Total		Positive		Negative		Total		Positive		Negative	
	n	%	*p*	n	%	n	%	n	%	n	%	n	%	n	%
LCS	14	2.9	0.429	6	1.9	1	5.0	5	1.7	8	4.7	-	-	8	6.1
Blood	399	83.3	0.033	281	90.9	4	20.0	277	95.8	118	69.4	6	15.4	112	85.5
Bronchial lavage	1	0.2	-	-	-	-	-	-	-	1	0.6	-	-	1	0.8
Sputum	53	11.1	0.305	13	4.2	12	60.0	1	0.3	40	23.5	32	82.1	20	15.3
Pleural fluid	1	0.2	-	-	-	-	-	-	-	1	0.6	-	-	1	0.8
Pus	7	1.5	1.000	5	1.6	2	10.0	3	1.0	2	1.2	1	2.6	1	0.8
Urine	4	0.8	-	4	1.3	1	5.0	3	1.0	-	-	-	-	-	-

Note. *p<0.05; COVID: Coronavirus disease; & LCS: Liquor cerebrospinal

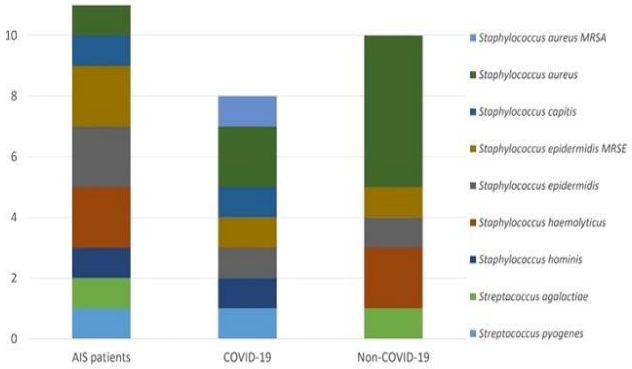

Figure 2. Gram-positive bacteria of positive culture results (Source: Authors' own elaboration)

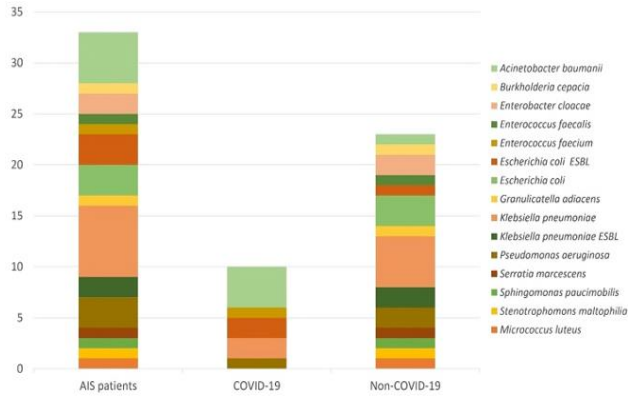

Figure 3. Gram-negative bacteria of positive culture results (Source: Authors' own elaboration)

Characteristics of Culture Groups of COVID-19 and Non-COVID-19 Acute Ischemic Stroke Patients

The differences between COVID-19 and non-COVID-19 AIS patients by bivariate analysis were shown that COVID-19 AIS patients had less pneumonia as manifestations of infection (38.2 vs. 47.6%, p = 0.044), more normal leukocyte count (38.8 vs. 24.1%, p = 0.001), less leukocytosis (57.9 vs. 73.5%, p = 0.001). They were also less in the intensive care ward (18.4 vs. 48.8%, p < 0.001). Therefore, they used not only fewer medical devices, such as ventilator (5.5 vs. 15.3%, p < 0.001) and CVC (18.4 vs. 34.7%, p = 0.001), but also steroid (5.2 vs. 10.6%, p = 0.027), total parenteral nutrition (TPN) (2.9 vs. 8.2%, p = 0.009), transfusion (2.9 vs. 7.1%, p = 0.034), and procedures such as tracheostomy (1.9 vs. 9.4%, p < 0.001), and head surgery (0.0 vs. 4.1%, p = 0.002). A detailed description of the characteristics of COVID-19 and non-COVID-19 AIS patients is shown in **Table 1**.

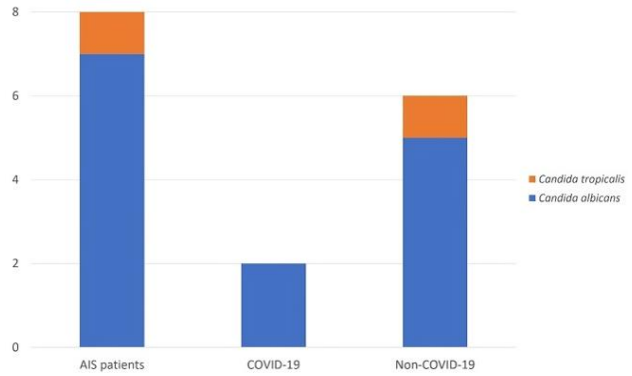

Figure 4. Fungi of positive culture results (Source: Authors' own elaboration)

There were no differences in age groups, sex, and comorbidities in positive and negative culture groups of COVID-19 AIS patients. Moreover, there were no differences in the leukocyte count in laboratory tests and the number of lesion locations in the radiology examination. Presenting manifestations of infection were somewhat similar among COVID-19 AIS patients, but positive culture groups of COVID-19 AIS patients had fewer pneumonia cases (10.0 vs. 40.1%, p = 0.008 and more in intensive care ward (60.0 vs. 15.6%, p < 0.001). Therefore, they used more medical devices, such as CVC (35.0 vs. 17.3%, p = 0.048), urinary catheters (20.0 vs. 3.5%, p = 0.008), and ventilators, even though not statistically significant (10.0 vs. 5.2%, p = 0.303).

In positive and negative culture groups of non-COVID-19 AIS patients, there were no differences in age groups, sex, diabetes mellitus comorbidities, manifestations of infection, and number of infarct locations in the brain. There were differences in HIV comorbidities (17.9 vs. 1.5%, p < 0.001) and leukocyte count in laboratory tests. The positive culture groups of non-COVID-19 AIS patients had an increase in leukocyte count (92.3 vs. 67.9%, p = 0.002), whereas the negative culture groups of non-COVID-19 AIS patients had normal leukocyte count (7.7 vs. 29.0%, p = 0.005).

The positive culture groups of non-COVID-19 AIS patients were not only more in the intensive care ward (76.9 vs. 40.5%, p < 0.001) and using more ventilators (35.9 vs. 9.2%, p < 0.001) or CVC (56.4 vs. 28.2%, p < 0.001) but also had more steroid (20.5 vs. 7.6%, p = 0.022) and TPN (17.9 vs. 5.3%, p = 0.012). Comparing procedures between groups of non-COVID-19 AIS patients, there were differences in tracheostomy (25.6 vs. 4.6%, p < 0.001) and head surgery (12.8 vs. 1.5%, p = 0.002). Details of the culture groups of COVID-19 and non-COVID-19 AIS patients are listed in **Table 3**.

Table 3. Culture groups characteristics of COVID-19 and non-COVID-19 AIS patients

	COVID-19							Non-COVID-19						
	Total		Positive		Negative		*p*	Total		Positive		Negative		*p*
	n	%	n	%	n	%		n	%	n	%	n	%	
Subject	309	(64.5)	20	(6.5)	289	(93.5)	-	170	(35.5)	39	(22.9)	131	(77.1)	-
Age, median (IQR)	60.0 (14.0)		56.0 (9.0)		60.0 (14.0)		0.005*	60.0 (15.0)		59.0 (20.0)		60.0 (45.8)		-
Age group, years, n (%)														
<60	146	(47.2)	13	(65.0)	133	(46.0)	0.100	80	(47.1)	20	(51.3)	60	(45.8)	0.542
≥60	163	(52.8)	7	(35.0)	156	(54.0)		90	(52.9)	19	(48.7)	71	(54.2)	
Sex, n (%)														
Male	198	(64.1)	12	(60.0)	186	(64.4)	0.694	122	(71.8)	30	(76.9)	92	(70.2)	0.415
Female	111	(35.9)	8	(40.0)	103	(35.6)	-	48	(28.2)	9	(23.1)	8.0	(29.8)	-
Clinical manifestation of infection, n (%)														
Fever	68	(22.0)	2	(10.0)	66	(22.8)	0.265	43	(25.3)	6	(15.4)	37	(28.2)	0.105
Sepsis	116	(37.5)	9	(45.0)	107	(37.0)	0.476	72	(42.4)	13	(33.3)	59	(45.0)	0.194
Meningitis/encephalitis	6	(1.9)	1	(5.0)	5	(1.7)	1.000	8	(4.7)	-	-	8	(6.1)	1.000
Pneumonia	118	(38.2)	2	(10.0)	116	(40.1)	0.008*	81	(47.6)	18	(46.2)	63	(48.1)	0.832
Infected wound	5	(1.6)	2	(10.0)	3	(1.0)	1.000	2	(1.2)	1	(2.6)	1	(0.8)	0.809
UTI	4	(1.3)	1	(5.0)	3	(1.0)	1.000	-	-	-	-	-	-	-
Care unit, n (%)														
Intensive	57	(18.4)	12	(60.0)	45	(15.6)	<0.001*	83	(48.8)	30	(76.9)	53	(40.5)	<0.001*
Non-intensive	252	(81.6)	8	(40.0)	244	(84.4)	-	87	(51.2)	9	(23.1)	78	(59.5)	-
Comorbidity, n (%)														
DM	86	(27.8)	4	(20.0)	82	(28.4)	0.607	55	(32.4)	14	(35.9)	41	(31.3)	0.590
HIV	12	(3.9)	1	(5.0)	11	(3.8)	0.559	9	(5.3)	7	(17.9)	2	(1.5)	<0.001*
Leukocyte count/mL, median (IQR)	11.0 (6.9)		12.0 (10.1)		11.0 (6.8)		0.685	12.8 (7.5)		15.5 (6.8)		12.4 (9.5)		-
Leukocyte count/mL, n (%)														
>10,000	179	(57.9)	16	(80.0)	163	(56.4)	0.059	125	(73.5)	36	(92.3)	89	(67.9)	0.002*
5,000-10,000	120	(38.8)	4	(20.0)	116	(40.1)	0.097	41	(24.1)	3	(7.7)	38	(29.0)	0.005*
<5,000	10	(3.2)	-	-	10	(3.5)	1.000	4	(2.4)	-	-	4	(3.1)	0.575
Number infarct location, n (%)														
1	40	(12.9)	1	(5.0)	39	(13.5)	0.489	19	(11.2)	6	(15.4)	13	(9.9)	0.342
2	32	(10.4)	1	(5.0)	31	(10.7)	0.706	20	(11.8)	6	(15.4)	14	(10.7)	0.424
3	25	(8.1)	2	(10.0)	23	(8.0)	0.670	20	(11.8)	2	(5.1)	18	(13.7)	0.169
4	21	(6.8)	-	-	21	(7.3)	0.379	11	(6.5)	1	(2.6)	-	-	0.259
5	8	(2.8)	-	-	8	(2.8)	1.000	4	(2.4)	1	(2.6)	3	(2.3)	0.921
6	6	(1.9)	-	-	6	(2.1)	1.000	2	(1.2)	0	(0.0)	2	(1.5)	0.438
7	2	(0.6)	-	-	2	(0.7)	1.000	2	(1.2)	0	(0.0)	2	(1.5)	1.000
9	1	(0.3)	-	-	1	(0.3)	1.000	-	-	-	-	-	-	-
Medical device, n (%)														
Ventilator	17	(5.5)	2	(10.0)	5	(5.2)	0.303	26	(15.3)	14	(35.9)	12	(9.2)	<0.001*
CVC	57	(18.4)	7	(35.0)	50	(17.3)	0.048*	59	(34.7)	22	(56.4)	37	(28.2)	0.001*
NGT	19	(6.1)	3	(15.0)	16	(5.5)	0.115	13	(7.6)	4	(10.3)	9	(6.9)	0.485
Urinary catheter	14	(4.5)	4	(20.0)	10	(3.5)	0.008	5	(2.9)	1	(2.6)	4	(3.1)	0.874
Treatment, n (%)														
Antibiotic	200	(64.7)	9	(45.0)	191	(66.1)	0.056	105	(61.8)	25	(64.1)	80	(61.1)	0.732
Steroid	16	(5.2)	1	(5.0)	15	(5.2)	1.000	18	(10.6)	8	(20.5)	10	(7.6)	0.022*
TPN	9	(2.9)	2	(10.0)	7	(2.4)	0.109	14	(8.2)	7	(17.9)	7	(5.3)	0.012*
Transfusion	9	(2.9)	1	(5.0)	8	(2.8)	0.457	12	(7.1)	4	(10.3)	8	(6.1)	0.374
Procedure, n (%)														
Tracheostomy	6	(1.9)	2	(10.0)	4	(1.4)	0.051	16	(9.4)	10	(25.6)	6	(4.6)	<0.001*
DSA	1	(0.3)	-	-	1	(0.3)	1.000	2	(1.2)	-	-	2	(1.5)	0.438
Head surgery	-	-	-	-	-	-	-	7	(4.1)	5	(12.8)	2	(1.5)	0.002

Note. *p<0.05; COVID: Coronavirus disease; CVC: Central venous catheter; DM: Diabetes mellitus; DSA: Digital subtraction angiography; HIV: Human immunodeficiency virus; IQR: Interquartile range; NGT: Nasogastric tube; TPN: Total parenteral nutrition; & UTI: Urinary tract infection

Risk Factors of Infection After Acute Ischemic Stroke

Bivariate analysis determined that some risk factors were significantly different between groups. Using the significance level of $p < 0.25$ in bivariate analysis, the risk factors for infection after AIS in COVID-19 patients were at least 60 years of age groups, pneumonia, intensive care stay, leukocytosis, normal leukocyte count, use of CVC, NGT, and urinary catheter, use of antibiotic, and tracheostomy. Multivariate logistic regression analysis also demonstrated that the risk factors for infection after AIS in COVID-19 AIS patients were pneumonia (OR 6.89, 95% CI 1.49-31.79, $p = 0.013$) and intensive care stay (OR 0.13, 95% CI 0.05-0.36, $p < 0.001$).

In comparison, the risk factors for infection after AIS in non-COVID-19 AIS patients were fever, sepsis, intensive care stay, HIV comorbidity, leukocytosis, normal leukocyte count, 3 locations of brain infarct, use of a ventilator and CVC, use of steroids and TPN, tracheostomy and head surgery. The risk factors associated with infection after AIS in non-COVID-19 patients were HIV comorbidity (OR 1.55, 95% CI 1.18-2.06, $p = 0.002$), leukocytosis (OR 0.07, 95% CI 0.01-0.43, $p = 0.004$), use of CVC (OR 0.29, 95% CI 0.12-0.68, $p = 0.005$), use of steroids (OR

Table 4. Multivariate analysis of risk factors of infection after AIS

	Initial model			Final model		
	OR	**(95% CI)**	***p***	**OR**	**(95% CI)**	***p***
COVID-19 patients						
Age (>60 years)	0.84	(0.65-1.09)	0.186	-	-	-
Pneumonia	5.44	(1.06-27.93)	0.043	6.89	(1.49-31.79)	0.013
Intensive care	0.15	(0.05-0.45)	0.001	0.13	(0.05-0.36)	<0.001
Leukocytosis	-	-	0.999	-	-	-
Normal leukocyte count	-	-	0.999	-	-	-
CVC	1.00	(0.31-3.25)	0.997	-	-	-
NGT	1.04	(0.81-1.32)	0.785	-	-	-
Urinary catheter	1.17	(0.93-1.47)	0.182	-	-	-
Antibiotic	0.96	(0.84-1.09)	0.536	-	-	-
Tracheostomy	1.36	(0.17-10.98)	0.772	-	-	-
Non-COVID-19 patients						
Fever	0.98	(0.83-1.14)	0.785	-	-	-
Sepsis	0.94	(0.83-1.05)	0.274	-	-	-
Intensive care	0.64	(0.20-1.99)	0.438	-	-	-
Comorbidity (HIV)	1.47	(1.10-1.95)	0.008	1.55	(1.18-2.06)	0.002
Leukocytosis	-	-	0.999	0.07	(0.01-0.43)	0.004
Normal leukocyte count	-	-	0.999	-	-	-
Number of infarct locations (3)	0.99	(0.97-1.01)	0.327	-	-	-
Ventilator	0.71	(0.15-3.29)	0.661	-	-	-
CVC	0.46	(0.16-1.31)	0.145	0.29	(0.12-0.68)	0.005
Steroid	0.24	(0.06-1.02)	0.053	0.21	(0.06-0.70)	0.011
TPN	0.57	(0.09-3.29)	0.529	-	-	-
Tracheostomy	0.22	(0.06-0.85)	0.028	0.17	(0.05-0.62)	0.007
Head surgery	0.22	(0.03-1.67)	0.143	-	-	-

Note. *p<0.05; COVID: Coronavirus disease; CVC: Central venous catheter; HIV: Human immunodeficiency virus; NGT: Nasogastric tube; & TPN: Total parenteral nutrition

0.21, 95% CI 0.06-0.70, p = 0.011), and tracheostomy (OR 0.17, 95% CI 0.05-0.62, p = 0.007). The risk factors of infection after AIS are listed in **Table 4**.

DISCUSSION

Compared to other research, the median age in this study was lower (60.0 [14.0] years old) [30-33]. Consistent with previous research, more male patients were in this study (66.8%) [31-33]. After a stroke, the patient is susceptible to several health complications that have been associated with poor clinical outcomes. These complications account for 60% of all stroke cases, primarily in instances where the stroke is severe [34]. The prevalence of infection after AIS in this study was 12.3% based on the pathogen organisms' growth in microbiological culture. In addition, there was a difference between COVID-19 and non-COVID-19 AIS patients. In COVID-19 AIS patients, the prevalence of infection after AIS was 6.5%, whereas in non-COVID-19 AIS patients was 22.9%. The prevalence of infection after AIS in this study was in the same range as in those previous studies, which showed a range of infection rates after stroke from 5-65% [10, 35-37]. Nonetheless, the prevalence in this study was lower than the pooled overall infection rate, which indicated that the pooled overall infection rate was 30% based on the meta-analysis [10, 35-38]. The reason for the lower prevalence in this study compared to the pooled overall infection rate is likely that we not only included AIS patients whose ischemic stroke events occurred within a week of the stroke onset but also based the infection prevalence on positive culture results, which is the gold standard for diagnosing infections. In microbiological culture, we could only report bacterial and fungal growth.

With a frequency of 1.7%, this study suggested that fungal infections due to *Candida albicans* and *Candida tropicalis* were only a modest cause of infection following AIS. In this study, bacteria were the most prevalent source of infection. Gram-negative bacteria such as *A. baumannii* in COVID-19 AIS patients and *K. pneumoniae* in non-COVID-19 AIS patients were the majority causes. These pathogens are closely associated with nosocomial infection and remain a primary concern owing to the rapid development of resistance to various antimicrobials. We found that *S. aureus* was the most prevailing cause of Gram-positive bacteria in both groups. This finding is in accordance with earlier studies that show infection caused by Gram-negative bacteria and *S. aureus* is frequently observed in the context of hospital settings [10].

The drug-resistant bacteria during the COVID-19 pandemic were found in this study, for example, MRSA, MRSE, ESBL-producing *E. coli,* and ESBL-producing *K. pneumoniae,* possibly because of antibiotics in advance. In a previous large, multicenter cohort study of patients hospitalized with COVID-19, even though there were worries that COVID-19 patients would be more susceptible to bacterial coinfections, over half of them received early empirical antibiotic treatment; nonetheless, only roughly three percent of COVID-19 patients had community-onset bacterial coinfections. Diagnostic uncertainty caused by delays in the turnaround time for COVID-19 PCR testing may have contributed to antibiotic use [39]. According to a meta-analysis, more than 70% of patients were prescribed antibiotics, most of which were broad-spectrum medications, including third-generation cephalosporins and fluoroquinolones [40]. Antibiotic resistance will rise as a result of improper antibiotic administration, raising the mortality rate of COVID-19 patients.

Since sepsis was the most prevailing clinical manifestation of infection following pneumonia, blood specimens were the

most ecumenical microbiological culture specimens. The majority of COVID-19-infected patients show no or mild symptoms, while others may present with symptoms of either moderate, severe, or critical disease. The disease can be complicated by sepsis, septic shock, and multi-organ failure, among others [41].

Sputum was the most specimens to be tested following blood due to pneumonia as the most common infection manifestation in COVID-19 and non-COVID-19 AIS patients. Research conducted in both intensive care and general wards has shown that pneumonia is primarily identified in the early days following a stroke, and this study validates the 1-33% pneumonia infection incidence found in other studies [10]. Pneumonia increased the risk of infection after AIS in COVID-19 AIS patients 6.89 times in this study. Pneumonia is indicative of moderate or severe COVID-19 [42]. Moreover, pneumonia caused by that bacteria usually results from the aspiration of endogenous matter from the colonized oropharynx [10]. A study conducted earlier revealed that a substantial proportion of stroke patients who develop dysphagia within the first 72 hours following the event will be at risk of pulmonary aspiration, which is likely to develop pneumonia that can significantly increase the risk of mortality [43]. The incidence of dysphagia in this study, shown by the incidence of NGT use in AIS patients, was lower than the incidence of pneumonia. This suggests that pneumonia in this study may not be only caused by aspiration and confirms the implication of the possibility that there are other mechanisms involved in pneumonia events. The positivity of cultures in COVID-19 AIS patients was not very high in patients with pneumonia, maybe either because of difficulties in the collection of specimens in stroke patients due to neurologic deficits or non-infectious aspiration pneumonitis. In some cases, the infection could be caused by anaerobic bacteria that require special culture techniques [10]. This study also found that intensive care stays decreased the risk of infection after AIS in COVID-19 AIS patients by 13.0%. Prioritizing patients with COVID-19 for care in a professional medical facility, especially in the intensive care ward, may help reduce the mortality rate in the COVID-19 epidemic [44].

In this study, leukocytosis decreased the risk of infection after AIS in non-COVID-19 AIS patients by 6.0%, whereas HIV comorbidity increased the risk by 1.519 times. Infection also can occur in HIV patients, although the lymphocyte count has not decreased, possibly because of defects in both cell-mediated and humoral immunity. These defects include decreases in specific antibody responses of B cells that occur at earlier stages of HIV infection, as well as impairment of phagocyte function that becomes more evident as T-lymphocyte (CD4) decline [45]. HIV patients frequently face multiple morbidities and may be at heightened risk for complications. In this study, HIV comorbidity was not a risk factor for infection after stroke in COVID-19 AIS patients. A previous study found that HIV was not associated with COVID-19. The majority of literature reflects COVID-19 symptoms in HIV patients to be minimal or nonexistent, particularly in those with advanced HIV illness. In addition, few studies discovered an unexpectedly high percentage of recovery in these individuals following COVID-19 infection, defying the conventional wisdom that immunocompromised people had a greater risk of morbidity and mortality [46].

Steroid use decreased the risk of infection after AIS in non-COVID-19 AIS patients by 14.3%. Corticosteroids have been shown *in vivo* to reduce inflammation associated with a dysregulated immune response. The proposed benefit of introducing corticosteroids during the COVID-19 pandemic was the ability of systemic steroids to modulate the immune response when used appropriately [47]. CVC and tracheostomy decreased the risk of infection after AIS in non-COVID-19 AIS patients by 29.0% and 17.0%, respectively. During the pandemic, there was a lack of health care for people with various illnesses besides COVID-19. Patients were more inclined to prioritize avoiding exposure to COVID-19 and disregard symptoms that may have previously led to a hospital visit [48]. Among non-COVID-19 patients, stroke patients visited the hospital to seek timely treatment and were often more severe, hence those needing procedures like tracheostomy or the use of CVC. Throughout the COVID-19 pandemic, infection control procedures have been under strain. Healthcare workers were advised to use personal protective equipment and hand hygiene as these measures may decrease infection and cross-contamination.

This study has several drawbacks. First, because patient and microbiological culture data have been obtained retrospectively, it may be prone to missing data, resulting in less reliability than information obtained prospectively. Furthermore, our findings merely represent correlations; causation must be inferred through a prospective study. Second, this study was done at a single institution, which is a major neurological referral medical center. Therefore, the findings may not apply to other settings. Lastly, due to equipment limitations, microbiological culture was done only for bacterial and fungi detections. However, this study is the largest one, using clinical variables to compare the differences between culture-positive and culture-negative AIS patients and including patients presenting in a pandemic setting.

CONCLUSIONS

The prevalence of infections after AIS during the COVID-19 pandemic did not increase. Besides being different from stroke patients either in general or non-pandemic settings, the risk factor for infections depended on the characteristics of patients, whether they had COVID-19 infection or had not been infected. The risk factors of infection after AIS in COVID-19-infected patients were pneumonia and intensive care stay; meanwhile, in non-COVID-19 patients were HIV comorbidity, leukocytosis, use of CVC, use of steroids, and tracheostomy. Future research to understand potential underlying mechanisms among AIS is warranted.

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Ethical statement: The authors stated that this retrospective study was approved by the Research Ethics Committee of the National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono, Jakarta, approval number DP.04.03/D.XXIII.9/132/2023, October 16, 2023. The requirement for participants' informed permission was waived due to the use of anonymous medical record data for research purposes and the negligible risks to those individuals. The authors further stated that

the National Health Research and Development Ethics Guidelines and Standards of the National Health Research and Development Ethics Committee, Ministry of Health of the Republic of Indonesia (2021) on the implementation of the International Ethical Guidelines for Health-related Research Involving Humans of the Council for International Organizations of Medical Sciences in collaboration with the World Health Organization (CIOMS–WHO) (2016), were followed in accordance with all pertinent requirements and guidelines for all study methods.

Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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