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ARTICLE

CHALLENGES IN THE DIGANOSIS AND MANAGEMENT OF INTRACRANIAL ABSCESS IN DEVELOPING COUNTRIES: A RETROSPECTIVE STUDY FROM A TERTIARY HOSPITAL IN INDONESIA

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ABSTRACT

Despite progressive development of antibiotics and surgical approaches, outcomes in patients with intracranial abscess remained far from ideal. This paper aimed to describe challenges in the diagnosis and treatment of intracranial abscess in developing countries based on study from a tertiary hospital in Indonesia. A retrospective study was performed and included patients who were suspected of intracranial abscess at a tertiary referral hospital in Indonesia between January 1, 2012 and January 1, 2020. Clinical, radiological and laboratory characteristics were analyzed. Two-hundred-and-seventy-seven patients were initially enrolled. Age (p = 0.001), GCS at admission (p = 0.009), comorbidity with hypoalbuminemia (p = 0.003) and hydrocephalus (p = 0.009) are significantly associated with patients' GCS when discharged. Results from culture and resistance tests could only be retrieved from 66 patients, with 33 (50%) obtained negative results, while the other 33 (50%) results were positive, consisted of 20 (60.6%) were of gram-negative bacteria and 13 (39.4%) were of gram-positive bacteria. Treatments that are directed to hypoalbuminemia and hydrocephalus should also be prioritized when any of these comorbidities exist.

Keywords: Intracranial abscess, Diagnosis, Management, Developing countries

АБСТРАКТ

Несмотря на прогрессивное развитие антибиотиков и хирургических подходов, результаты лечения пациентов с внутричерепным абсцессом по-прежнему далеки от идеальных. Цель данной работы - описать проблемы диагностики и лечения внутричерепного абсцесса в развивающихся странах на основе исследования, проведенного в одном из третичных госпиталей Индонезии. В ретроспективное исследование были включены пациенты с подозрением на внутричерепной абсцесс, находившиеся в третичном реферативном госпитале в Индонезии в период с 1 января 2012 года по 1 января 2020 года. Анализировались клинические, рентгенологические и лабораторные характеристики. Первоначально в исследование было включено двести семьдесят семь пациентов. Возраст (p = 0,001), ГКС при поступлении (p = 0,009), коморбидность с гипоальбуминемией (p = 0,003) и гидроцефалией (p = 0,009) достоверно связаны с ГКС пациентов при выписке. Результаты культуральных исследований и тестов на резистентность удалось получить только у 66 пациентов, причем у 33 (50%) они были отрицательными, а у остальных 33 (50%) - положительными, причем у 20 (60,6%) - грамотрицательными, а у 13 (39,4%) - грамположительными бактериями. Лечение, направленное на устранение гипоальбуминемии и гидроцефалии, также должно быть приоритетным при наличии любого из этих сопутствующих заболеваний.

Ключевые слова: Внутричерепной абсцесс, диагностика, лечение, развивающиеся страны

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INTRODUCTION

Intracranial abscess is not rare in low- and middle-income countries. Recent data concluded that the prevalence of intracranial abscess in southeast Asia is higher compared to any other CNS infections, reaching as high as 49 cases/100,000 people. This finding suggests that the incidence of intracranial abscess is significantly affected by demographic factors.[1] Thus, studies on intracranial abscess from different parts of the world are essential to extend the knowledge on this devastating disease. Unfortunately, despite the need and potentially-higher number of patients compared to developed countries, high quality data that are sufficient for peer-reviewed publications limited the number of studies on intracranial abscess in developing countries. Consequently, even the accurate number of intracranial abscess incidence from many countries are yet to be available.[2]

Despite the advent of antibiotic and surgical therapy has gradually improved the prognosis of patients with brain abscess, its rates of morbidity and mortality remained unideal.[2] Until now, many factors have been suspected of having strong association with the incidence and outcome of intracranial abscess. Since CNS infection is strongly associated with the status of immune system, comorbidity with other conditions that hinder immunity, such as human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and chronic consumption of immunosuppressive agents would increase the susceptibility to intracranial abscess.[3,4] Based on its pathogenesis, meningitis, congenital heart disease, chronic otitis, mastoiditis and periodontitis have also been considered as predisposing factors of intracranial abscess.[5,6,7,8] Despite their clear associations with the incidence of intracranial abscess, the effect of comorbidity on patients outcome remained unclear, suggesting the presence of other influential factors. In one study, male patients who were presented at higher Glasgow Coma Scale (GCS), with no other septic complication, or had gram positive coci grown in abscess culture are likely to acquire more favorable outcomes. In the same study, focal neurological deficit, seizure and treatment modalities were not significantly associated with patients' outcomes.[9] Contrary to this study, another study suggested that focal neurological deficit and seizure were independently associated with worse clinical outcomes.[10] These contradicting conclusions suggest that factors that affect prognosis of patients with intracranial abscess might vary between different populations. Lately, the complexity of treatment in patients with intracranial abscess is even worsened with the advent of microbial resistance.[11-12] More studies on intracranial abscess, particularly from countries with expectedly higher number of patients will be pivotal to improve prognosis of intracranial abscess patients.

This study aimed to describe the effort and highlights the challenges that are faced by researchers when performing study on intracranial abscess at a tertiary hospital in Indonesia. To do so, clinical, radiological and laboratory characteristics of patients who were diagnosed with intracranial abscess were collected, then analysis on the association between variables that represent patients' clinical characteristics and patients' GCS when discharged was performed. Afterwards, challenges that are faced during data collection and analysis are discussed.

MATERIAL AND METHODS

This was a retrospective study conducted in Dr. Hasan Sadikin General Hospital, between January 1, 2012 – January 1, 2020. Ethical clearance was granted by the ethical committee of Dr. Hasan Sadikin general hospital. Patients were included if they met the following criteria: (1) Presented with history of classic symptoms of cerebritis, including headache, fever and decreased consciousness; (2) Head computed tomography (CT) or magnetic resonance imaging (MRI) results suspected the diagnosis of intracranial abscess. As many as 277 patients were enrolled in this study. Patient's epidemiological, clinical and laboratory

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characteristics, including gender, age, GCS at admission, diagnosis, comorbidities, therapy, GCS when discharged, results from culture and resistance tests were retrieved. Re-evaluation of head CT or MRI was performed to the number and location of abscess. Since patient's medical record that contained patient's clinical history after admittance until discharge was only kept for 5 years, only medical records from 2017 onward could be re-evaluated. Thus, outcome from only 121 patients could be analyzed further. Results from microbial resistance tests could only be obtained from 66 patients.

Data analysis on the distribution of patients who were suspected of intracranial abscess was based on gender, age, GCS at admission, number and location of lesion, and therapy was performed to obtain the epidemiological data. Association between gender, age, GCS at admission, diagnosis, number and location of abscess, therapy and microbiological characteristics with outcomes were evaluated independently. To analyze the possible association of every variable with patient's outcome that was represented with patient's GCS at discharge, every variable was first subcategorized. Patient's age was subcategorized into ≤ 1-year-old, 1- to 5-year-old, 6- to 10-year-old, 11- to 17-year-old 18- to 40-year-old, 41- to 60-year-old and > 61-year-old. Both patient's GCS when admitted and at discharge were subcategorized into GCS ≤ 8, GCS 9-13 and GCS 14-15. Fifteen comorbidities were acknowledged, including diabetes mellitus, sepsis, malnourishment, electrolyte imbalance, hypoalbuminemia (intravascular albumin level of <3.5 g/dL), human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), hydrocephalus, meningitis, mastoiditis, chronic otitis, tuberculosis, syanotic cardiac disease, periodontitis, pulmonary atresia and epilepsy. After re-examining the head CT/MRI results, the number of lesions was subcategorized into single and multiple lesions, while the location of lesion was subgrouped into supratentorial, infratentorial, extraaxial and any possible combination of 2 between these 3 subgroups. Both epidural and subdural empyema were included in the subgroups of extraaxial lesion. Six types of treatment were performed in our patients, including burrhole aspiration, abscess resection, craniotomy debridement, CSF diversion, craniotomy debridement with CSF diversion, and conservative.

To calculate the association of patients' gender with patients' GCS when discharged, Mann-Whitney U test was used. Meanwhile, to evaluate the association of age and GCS at admission with outcomes, the Goodman-Kruskal Gamma test was applied. Analysis between every comorbidity and patients' outcome was performed by one-sample binomial test. Association of abscess number, location and therapy with outcomes were independently evaluated by Kruskall-Wallis H test. Descriptive summary and data analysis were performed using. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, IBM Corporation.

RESULT

Two-hundred-and-seventy-seven patients were initially included in this study, including 156 males (56.3%) and 121 females (43.7%) (p = 0.041). Based on patient's age, 30 patients (10.8%) were ≤ 1-year-old, 38 patients (13.7%) were aged 1- to 5-year-old, 42 patients (15.1%) were of 6- to 10-year-old, 21 patients (7.5%) were aged 11- to 17-year-old, 93 patients (33.5%) were of 18- to 40-year-old, 46 patients (16.6%) were aged 41- to 60-year-old and 7 patients (2.5%) were aged > 60-year-old (p = 0.0001). Based on the level of consciousness at admission, 18 patients (6.5%) had GCS ≤ 8, 98 patients (35.4%) were admitted with GCS 9-13, and 161 patients (58.1%) had GCS 13-15 (p = 0.11) (p = 0.11). Based on the number of lesions, 162 patients (58.5%) were diagnosed with single lesion, while 115 patients (41.5%) were diagnosed of having multiple lesions (p = 0.005). As many as 184 patients (66.4%) suspected of cerebral abscess at supratentorial locations, while only 47 patients (17%) had lesion located at the infratentorial regions, and 29 patients (10.4%)

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had extraaxial lesion. Lastly, seventeen patients (6.1%) had lesions at both supratentorial and infratentorial locations (p = 0001). To evaluate the impact of patients' characteristics on patients' outcome that was represented by patients' GCS when discharged, statistical analysis to evaluate the association between every variable and patients' GCS when discharged was performed. Despite differences on the number of patients in every subgroup, gender (p = 0.184), number of lesion (p = 0.204), location of lesion (p = 0.698) and therapy (p =0.868) are not significantly associated with patients' outcome. Furthermore, majority of comorbidities, including diabetes mellitus (p = 0.074), sepsis (0.661), malnourishment (p = 0.487), electrolyte imbalance (p = 0.115), HIV/AIDS (p = 0.609), mastoiditis (p = 0.573), chronic otitis (p = 0.314), tuberculosis (p = 0.845), syanotic cardiac disease (p = 0.424), periodontitis (p = 0.266), pulmonary atresia (p = 0.790) and epilepsy (p = 0.245) are not significantly associated with patients' GCS when discharged. Conversely, patients' age has significant association with patients' GCS when discharged (p = 0.001), with the highest rate of worse GCS at discharge (GCS ≤ 8) in a subgroup was featured in patients aged 1- to 5-year-old (7/18 (38.9%)). As expected, patients' GCS at admission is also significantly associated with patients' GCS when discharged (p = 0.009), with the highest rate of patients that had GCS ≤ 8 when discharged was acknowledged in the subgroup of patients who were admitted with GCS 9-12 (12/43 (27.9%)). Two comorbidities were identified to have significantly affected patients' GCS at discharge, including hypoalbuminemia (p = 0.003) and hydrocephalus (p = 0.009), with the rates of patients with GCS ≤ 8 when discharged in both groups were 57% (4/7) and 33.3% (7/21), respectively.

Culture and resistance tests were only performed on pus that was collected from burrhole aspiration, abscess resection, and craniotomy debridement surgeries. Of 135 patients, results from 66 patients were available, thus evaluated further. As many as 33 specimens (50%) were found negative of any bacteria, while another 33 (50%) had bacterial growth. Of all patients who had microbial growth, as many as 13 specimens (19.7%) were identified as gram-positive bacteria, while 20 specimens (30.3%) were identified as gram-negative bacteria (Table 2). The most common gram-positive bacterium in our patients is *Staphylococcus haemolyticus* (6/66 (9%)), followed by *Staphylococcus epidermidis* (4/66 (6%)), *Staphylococcus hominis.* (2/66 (3%)), *Staphylococcus aureus* (1/66 (1.5%)). Meanwhile, *Acinetobacter baumanii* (4/66 (6%)) and *Klebsiela pneumonia* (4/66 (6%)) are the most common gram-negative species, followed by *Proteus mirabilis* (3/66 (4.5%)), *Escherichia coli* (2/66 (3%)), *Acinetobacter iwoffii* (1/66 (1.5%)), *Enterobacter aerogenes* (1/66 (1.5%)), *Enterobacter cloacae* (1/66 (1.5%)), *Pseudomonas aeruginosa* (1/66 (1.5%)), *Salmonela spp* (1/66 (1.5%)).

Profiles of antibiotic resistance were collected from every specimen that had microbial growth. Following the advent of antibiotic resistance, the sets of antibiotics that were used to in antibiotic resistance test are growing each year, thus samples from different years were subjected to different sets of antibiotics in their resistance tests. Nonetheless, of the examined samples, the highest rates of antibiotic resistance are against Cephalotin (13/14 (92.9%)), Cefuroxime (13/14 (92.9%)), Cefoperazone (13/14 (92.9%)) and Cefixime (13/14 (92.9%)). On the other hand, the highest rate of antibiotic sensitity is against Vancomycin (14/14 (100%)).

DISCUSSION

At its early stages, majority of intracranial Abscesses are controllable. However, they are typically underdiagnosed and cause late emergencies because to their damage to cerebral tissue and ongoing expansion, which causes mass effect and increasing intracranial pressure. A quick brain abscess diagnosis is difficult. Patients often experience unspecific symptoms including headache, fever, and

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malaise at the start. If brain abscess is not diagnosed early, symptoms increase and lesion grows. A 2008–2014 US hospital research found 17.5% morbidity and 4.0% mortality in otogenic brain abscess patients.13 Another US hospital study found increased morbidity and mortality in children with intracerebral abscess. According to the same study, early diagnosis, especially in children with predisposing circumstances, may enhance patient outcomes.14 In addition, initial GCS and comorbidities may predict brain abscess outcome.[15]

Southeast Asia has the most intracranial abscesses, according to a meta-analysis.1 High prevalence and limited CT-scan and MRI facilities make brain abscess management difficult in many southeast Asian nations. The study was expected to offer a unique look of brain abscess in southeast Asia's most populated nation. The study covered 277 suspected cerebral abscess patients from January 1, 2012 to January 1, 2020. Patient admission data from the department was used for these statistics. Like prior epidemiological research, our investigation found a small male predominance with a male/female ratio of 1.29:1 (156:121) (Table 1).16,17 Since innate and adaptive immunity are thought to be greatly influenced by age, younger and older patients were first believed to be more prevalent.18,19 Interestingly, 18-to-40-year-olds had the most patients (n = 93, 33.6%). This study cannot determine the sensitivity of this age group to cerebral abscess, but this data suggests that additional factors contribute to human vulnerability. Most patients in this study had initial GCS 13-15 (n = 161, 58.1%), at least one supratentorial lesion (n = 162, 58.5%). Most patients had high initial GCS, therefore treatment for their brain abscess should improve them. Despite 58.5% of patients having one lesion, 41.5% had numerous abscesses. The significant proportion of patients with many abscesses makes surgical planning problematic, especially whether to target all lesions or just the one most likely to produce neurological symptoms. The lesion suspected of causing neurological symptoms was our major focus, and we expected antibiotic treatment to significantly improve all other lesions. Paper medical records were only kept for 5 years, and electronic medical records were only used since 2020, so only medical records from patients admitted in 2017 onwards could be retrieved for further investigation into their clinical progress during hospitalisation and discharge outcomes. Only 121 patients could be analysed for their association with outcomes since some patients' families declined treatment. After carefully reviewing hospitalised patients' clinical histories, we found that 156 refused part or all of the prescribed treatment. Only 121 participants' outcomes were dependable enough for analysis (Table 2). GCS at discharge was not linked with gender (p = 0.184). Discharged patients with GCS ≤ 8 were most likely to be aged 1- to 5-year-old (n = 7/18, 38.9%), indicating a significant correlation (p = 0.001). As expected, admission GCS is highly linked with discharge GCS (p = 0.009). GCS ≤ 8 discharge rates were highest for patients admitted with GCS 9-12 (n = 12/43, 27.9%), followed by GCS ≤ 8 (n = 1/5, 20%) and GCS 13-15 (n = 13/73, 17.8%). Unexpectedly, those discharged with GCS 13-15 were mostly from those hospitalised with GCS ≤ 8 (n = 4/5, 80%). The statistical analysis revealed a substantial link between this variable and patients' GCS at discharge. However, only 5 patients were admitted with GCS ≤ 8, therefore bias cannot be ruled out. However, this may suggest other factors that affect patient outcomes. Additional research with additional patients admitted with GCS ≤ 8 is needed to confirm this result..

To investigate the presence of any other diseases than the abscess itself that might have affected patients' GCS when discharged, we identified the possible presence of 15 different comorbidities (Table 2). Interestingly, only 2 comorbidities showed significant association with patients' GCS when discharged, including hypoalbuminemia (p = 0.003) and hydrocephalus (p = 0.009) (See Table 2). Albumin has been used as a marker of nutritional status, hence hypoalbuminemia

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could be concluded as poor nutritional status. In patients with intracranial abscess, decreased albumin in serum might be caused by low intake and the increase of proinflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).[20] Release of these proinflammatory cytokines inhibits albumin production and increase vascular permeability that leads to albumin leakage through the capillaries.[21,22] Whether hypoalbuminemia only serves as an indicator of poorer prognosis in patients, or if it predisposes other condition that worsen patient's condition, is a question that remains unanswered. Future trials of albumin infusion in intracranial abscess patients who are also diagnosed with hypoalbuminemia would shed light to this potentially-prognosis-improving treatment. On this case, we speculate if albumin infusion in hypoalbuminemia patients does not associate with improved patient's outcome, then albumin depletion in these patients only represents the severity of the disease, thus could only be used in predicting patient's prognosis. Conversely, if albumin infusion improves patient's outcome, then hypoalbuminemia in these patients is likely to predispose other condition that worsen patient's outcome. If the latter is proven, then treatment of hypoalbuminemia in patients with intracranial abscess would be essential to improve their outcomes. Another comorbidity that has a signification with patient's GCS when discharged is hydrocephalus. Hydrocephalus has been reported as a complication of brain abscess due to its infectious nature and/or location. Similar with causes of hydrocephalus in our patients, previous study reported the incidence of meningitis, ventriculitis, ventricular rupture and cerebellar location of the abscess that eventually led to the incidence of hydrocephalus in brain abscess patients.[23] Rarely, the cause of hydrocephalus could also be the occurrence of primary intraventricular brain abscess.[24] Regardless of the cause, the occurrence of hydrocephalus in brain abscess patients adds another complexity to its treatment. As we know, acute hydrocephalus is a neurosurgical emergency that requires immediate CSF diversion. In our cases, CSF diversion followed by intravenous antibiotic administration was proven suffice for majority of brain abscess patients who were also diagnosed with hydrocephalus (n = 10/17, 58.8%).

Culture test results from 66 intracranial abscess patients were acquired by using pus or CSF specimens that were obtained during surgery. As many as 33 specimens gave no microbial growth, while 13 gave growth to gram-positive bacteria, and another 20 gave growth to gram-negative bacteria (Table 3). To explain the negative results, we understand that many pitfalls might play roles. Regardless, negative results from culture tests on pus that were isolated from brain abscess have been reported in previous literatures.[25-27] Furthermore, compared to gram-positive bacteria, gram-negative bacteria have also been suspected to be significantly associated with worse patient's outcome.[26] In our study, even though the number of specimens with the growth of gram-negative bacteria was found higher than those that had gram-positive bacteria grew in it, the highest number of patient was identified in the group that had the growth of *Staphylococcus haemolyticus* (n = 6, 9%), a normal skin flora in humans and part of member of the coagulase-negative staphylococci (CoNS) with high level of antibiotic resistances.[28] Thus, we then looked into the patterns of antimicrobial sensitivities and resistances. Based on the sensitivity and resistance tests from 33 specimens who resulted on the previously mentioned microbial growth, Vancomycin and Amikacin are the antibiotics that have the highest rates of sensitivity, thus lowest resistance rates (See Table 4). Unfortunately, since not all resistance and sensitivity test results were conclusive, further statistical analysis failed to show any significant association of the pattern of antibiotic sensitivity and resistance with patient's outcome. Nevertheless, it is logical to consider this data when administering empirical antibiotic treatment for patients with intracranial abscess who undergo non-

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surgical treatment or still waiting for sensitivity and resistance test.

Based on the difficulties that were faced along the course of this study, we suggested some challenges that prevented us from collecting the intended data that might be valuable to extend our knowledge on the diagnosis and treatment of intracranial abscess, including low education level among patients and their families that made them hard to understand the necessity of treatment and slow conversion into electronic medical system.

CONCLUSION

At its early stages, majority of intracranial abscess are manageable. Yet, they are often underdiagnosed and cause late emergency due to its insult on cerebral tissue, along with its continuous expansion, causing mass effect that eventually leads to increased intracranial pressure. Regrettably, the prompt identification of brain abscess in patients frequently poses a difficult task. During the early stages, patients typically exhibit nonspecific clinical symptoms, including headache, fever, and malaise. Untimely diagnosis of cerebral abscess leads to worsening of symptoms and significant expansion of lesion. Recent study concluded that morbidity and mortality in patients with otogenic brain abscess for years 2008 to 2014 at a hospital in the United States were as high as 17.5% and 4.0%, respectively.[13] Other study from another hospital in the United States also acknowledged high rates of morbidity and mortality in children who were diagnosed with intracerebral abscess. In line with the previous statement, the same study also suggested that early detection, particularly in children with predisposing factors, might be key to improve patient's outcome.[14] Furthermore, initial GCS and comorbidities have been suspected to have prognostic values in brain abscess.[15]

The findings of a recent meta-analysis indicate that the combined occurrence of intracranial abscess in southeast Asia was the greatest when compared to all other locations worldwide. One The prevalence of cerebral abscess in many countries in southeast Asia is considerable, however there is a scarcity of healthcare institutions equipped with CT-scan and/or MRI. This situation poses distinctive obstacles in managing intracranial abscess in these countries. Therefore, it was anticipated that the findings of this study would provide a distinctive perspective on cerebral abscesses in the highly populous country of Southeast Asia. As many as 277 patients who were suspected of intracranial abscess from January 1, 2012 until January 1, 2020 were included in this study. These data were based on the department's database on patients at their time of admittance. In line with previous epidemiology studies, slight male predominance was also identified in our study, with male/female ratio was 1.29:1 (156:121) (Table 1).[16,17]

Table 1 Patients' Characteristics Based on Clinical and Radiological Findings

Variable	Frequency (%)	p-value
Gender		0.041
Male	156 (56.3)	
Female	121 (43.7)	
Age		
≤ 1 year old	30 (10.8)	
1 to 5 year old	38 (13.7)	
6 to 10 year old	42 (15.2)	
11 to 17 year old	21 (7.6)	
18 to 40 year old	93 (33.6)	
41 to 60 year old	46 (16.6)	
> 61 year old	7 (2.5)	
GCS at admission		0.11
GCS ≤ 8	18 (6.5)	
GCS 9-12	98 (35.4)	
GCS 13-15	161 (58.1)	
Number of lesion		0.005
Single lesion	162 (58.5)	
Multiple lesion	115 (41.5)	
Location of lesion		0.0001
Supratentorial	184 (66.4)	
Infratentorial	47 (17)	
Extraaxial	29 (10.4)	
Supratentorial + Infratentorial	17 (6.1)	

Given that both innate and adaptive immunity are believed to be strongly influenced by age, it was initially anticipated that a greater proportion of patients would be

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observed in the youngest and oldest age categories.The user's input consists of the numbers 18 and 19.The group of 18- to 40-year-olds had the highest number of patients, with a total of 93, accounting for 33.6% of the total. Examining the susceptibility of this particular age group to cerebral abscess is not within the scope of this study. However, this discovery suggests that other factors significantly contribute to the vulnerability of humans to intracranial abscess. Majority of patients in this study was presented with initial GCS 13-15 (n = 161, 58.1%), single lesion (n = 162, 58.5%) at supratentorial locations (n = 184, 66.4%). Since initial GCS in majority of patients were relatively high, it is logical to expect an optimal improvement after treatment for their cerebral abscess. Even though 58.5% of patients were diagnosed with having a single lesion, as high as 41.5% of patients were identified of having multiple abscess. The high number of patients with multiple abscess indicate the difficulties when planning surgery in these patients, particularly on whether to target all lesions or only the lesion that was most likely caused neurological symptoms. The suspected lesion that was responsible for the neurological symptoms was the primary focus of our attention, and we anticipated that antibiotic therapy would result in a significant response from all of the other suspect lesions. Furthermore, because the families of some patients declined therapy, there were only 121 patients eligible for further study evaluating their association with outcomes. This was due to the fact that some relatives of patients refused treatment. Following a comprehensive review of the patient's clinical history upon admission to the hospital, it was discovered that a total of 156 patients denied either some or all of the treatment choices that were given to them. It was determined that only the findings from 121 patients were reliable enough to be included in the subsequent study (Table 2). According to the findings of the study, there was not a statistically significant link between the gender of patients and their Glasgow Coma Scale (GCS) at the time of discharge (p = 0.184). On the other hand, there is a statistically significant correlation between the Glasgow Coma Scale (GCS) of patients following discharge and their age (p = 0.001). With seven out of eighteen children (38.9%) having a GCS score of eight or lower at the time of discharge, the age group range of one to five years old had the highest proportion of patients with such a score. There is a significant correlation between the Glasgow Coma Scale (GCS) score of patients at the time of admission and their GCS score at the time of discharge (p = 0.009). This is something that can be observed and understood. The patients who were initially admitted with a Glasgow Coma Scale (GCS) score of 9-12 had the highest rate of discharges with a GCS score of 8 or lower (n = 12/43, 27.9%). This was one of the patients who had the highest number of discharges. Following this were patients who were initially admitted with a GCS score of 8 or below (n = 1/5, 20%) and those with a GCS score of 13-15 (n = 13/73, 17.8%). These patients were the next group to be evaluated. Surprisingly, the group of patients who were discharged while having a Glasgow Coma Scale (GCS) score of 8 or lower had the highest percentage of patients who were discharged with a GCS score of 13 to 15. This fraction was responsible for eighty percent of the patients in this group (n = four out of five). According to the findings of the statistical study, there is a strong correlation between this variable and the Glasgow Coma Scale (GCS) of patients at the time that they were discharged from the hospital. It is crucial to note that only five patients were admitted with a Glasgow Coma Scale (GCS) score of eight or lower, which may have introduced bias. However, this may indicate that more primary factors affect patient outcomes. To confirm this study's findings, more patients with a Glasgow Coma Scale (GCS) score of 8 or below must be studied.

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Table 2 Analyses on the Association of Patients' Characteristics with Patients' GCS when Discharged

Variables	GCS when discharged (frequency, %)			p-value
	≤ 8	9-12	13-15	
Gender				0.184
Male	11	7	44	
Female	15	9	35	
Age				0.001
≤ 1 year old	3	6	8	
1 to 5 year old	7	4	7	
6 to 10 year old	3	2	12	
11 to 17 year old	2	1	4	
18 to 40 year old	8	2	24	
41 to 60 year old	3	1	22	
> 61 year old	0	0	2	
GCS at admission				0.009
GCS ≤ 8	1	0	4	
GCS 9-12	12	12	19	
GCS 13-15	13	4	56	
Comorbidity				
Diabetes Melitus	0	0	6	0.074
Sepsis	0	0	1	0.661
Malnourished	2	1	9	0.487
Electrolyte imbalance	10	3	16	0.115
Hypoalbuminemia	4	2	1	0.003
HIV/AIDS	1	0	1	0.609
Hydrocephalus	7	6	8	0.009
Meningitis	4	0	7	0.645
Mastoiditis	1	0	4	0.573
Chronic otitis	2	0	9	0.314
Tuberculosis	5	2	15	0.845
Syatonic cardiac disease	5	0	16	0.424
Periodontitis	0	1	5	0.266
Pulmonary atresia	1	0	3	0.790
Epilepsy	5	1	7	0.245
Number of Lesion				0.204
Single lesion	12	8	47	
Multiple lesion	14	8	32	
Location of Lesion				0.698
Supratentorial	20	12	55	
Infratentorial	3	0	9	
Extraaxial	1	3	11	
Supratentorial + Infratentorial	2	1	4	
Therapy				0.868
Burrhole aspiration	10	4	22	
Abscess resection	1	1	6	
Crainotomy debridement	2	0	4	
CSF diversion	2	4	10	
Conservative	10	8	37	

To investigate the presence of any other diseases than the abscess itself that might have affected patients' GCS when discharged, we identified the possible presence of 15 different comorbidities (Table 2). Interestingly, only 2 comorbidities showed significant association with patients' GCS when discharged, including hypoalbuminemia ($p = 0.003$) and hydrocephalus ($p = 0.009$) (See Table 2). Albumin has been used as a marker of nutritional status, hence hypoalbuminemia could be concluded as poor nutritional status.

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In patients with intracranial abscess, decreased albumin in serum might be caused by low intake and the increase of proinflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).[20] Release of these proinflammatory cytokines inhibits albumin production and increase vascular permeability that leads to albumin leakage through the capillaries.[21,22] Whether hypoalbuminemia only serves as an indicator of poorer prognosis in patients, or if it predisposes other condition that worsen patient's condition, is a question that remains unanswered. Future trials of albumin infusion in intracranial abscess patients who are also diagnosed with hypoalbuminemia would shed light to this potentially-prognosis-improving treatment. On this case, we speculate if albumin infusion in hypoalbuminemia patients does not associate with improved patient's outcome, then albumin depletion in these patients only represents the severity of the disease, thus could only be used in predicting patient's prognosis. Conversely, if albumin infusion improves patient's outcome, then hypoalbuminemia in these patients is likely to predispose other condition that worsen patient's outcome. If the latter is proven, then treatment of hypoalbuminemia in patients with intracranial abscess would be essential to improve their outcomes. Another comorbidity that has a signification with patient's GCS when discharged is hydrocephalus.

Hydrocephalus has been reported as a complication of brain abscess due to its infectious nature and/or location. Similar with causes of hydrocephalus in our patients, previous study reported the incidence of meningitis, ventriculitis, ventricular rupture and cerebellar location of the abscess that eventually led to the incidence of hydrocephalus in brain abscess patients.[23] Rarely, the cause of hydrocephalus could also be the occurrence of primary intraventricular brain abscess.[24] Regardless of the cause, the occurrence of hydrocephalus in brain abscess patients adds another complexity to its treatment. As we know, acute hydrocephalus is a neurosurgical emergency that requires immediate CSF diversion. In our cases, CSF diversion followed by intravenous antibiotic administration was proven suffice for majority of brain abscess patients who were also diagnosed with hydrocephalus (n = 10/17, 58.8%).

Results of culture tests from 66 individuals with cerebral abscesses were obtained using pus or cerebrospinal fluid specimens collected during surgery. 33 specimens showed no microbial growth, 13 showed growth of gram-positive bacteria, and 20 showed growth of gram-negative bacteria (Table 3). To elucidate the bad outcomes, we acknowledge that several pitfalls may be contributing factors. However, earlier literature has revealed negative results from culture tests on pus isolated from brain abscesses.[25] Furthermore, compared to gram-positive bacteria, gram-negative bacteria have also been suspected to be significantly associated with worse patient's outcome.[26] In our study, even though the number of specimens with the growth of gram-negative bacteria was found higher than those that had gram-positive bacteria grew in it, the highest number of patient was identified in the group that had the growth of *Staphylococcus haemolyticus* (n = 6, 9%), a normal skin flora in humans and part of member of the coagulase-negative staphylococci (CoNS) with high level of antibiotic resistances.[28] Thus, we then looked into the patterns of antimicrobial sensitivities and resistances. Based on the sensitivity and resistance tests from 33 specimens who resulted on the previously mentioned microbial growth, Vancomycin and Amikacin are the antibiotics that have the highest rates of sensitivity, thus lowest resistance rates (See Table 4). Unfortunately, since not all resistance and sensitivity test results were conclusive, further statistical analysis failed to show any significant association of the pattern of antibiotic sensitivity and resistance with patient's outcome. Nevertheless, it is logical to consider this data when administering empirical antibiotic treatment for patients with intracranial abscess who undergo non-

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surgical treatment or still waiting for sensitivity and resistance test.

Table 3. Results of Culture Tests from Pus that were Isolated from Intracranial Abscess

Results of Culture Test	Number if cases (%) (n=66)
Negative	33 (50)
Positive	33 (50)
Gram-positive	13 (19.7)
Staphylococcus aureus	1 (1.5)
Staphylococcus epidermidis	4 (6)
Staphylococcus haemolyticus	6 (9)
Staphylococcus hominis	2 (3)
Gram-negative	20 (30.3)
Acinetobacter baumanii	4 (6)
Acinetobacter iwofii	1 (1.5)
Enterobacter aerogenes	1 (1.5)
Enterobacter cloacae	1 (1.5)
Eschericia coli	2 (3)
Klebsiela pneumonia	4 (6)
Proteus mirabilis	3 (4.5)
Pseudomonas aeruginosa	1 (1.5)
Salmonela spp	1 (1.5)

Table 4. Antibiotic Resistances and Sensitivities of Abscess-Causing-Bacteria that were Isolated from Intracranial Abscess

Antibiotic	Resistance	Sensitive
Amikacin	3	21
Ampicilin sulbactam	25	12
Amoxicillin + clavulanic acid	12	2
Aztreonam	6	8
Cephalotin	13	1
Cefuroxime	13	1
Cefoperazone	13	1
Cefixime	13	1
Cefotaxime	18	7
Ceftazidime	24	15
Ceftriaxone	28	11
Cefazoline	28	2
Cefepime	20	18
Ciprofloxacine	26	12
Cotrimoxazole	19	18
Ertapenem	1	13
Gentamycin	21	18
Levofloxacin	10	4
Meropenem	8	18
Moxifloxacin	10	4
Piperacilin / tazobacta,	18	10
Tigecycline	6	33
Vancomycin	0	14

Based on the difficulties that were faced along the course of this study, we suggested some challenges that prevented us collecting the intended data that might be valuable to

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extend our knowledge on the diagnosis and treatment of intracranial abscess, including low education level among patients and their families that made them hard to understand the necessity of treatment and slow conversion into electronic medical system. The results from this study showed that intracranial abscess patient's age, GCS at admission, the presence of other comorbidities, including hypoalbuminemia and hydrocephalus are significantly associated with patient's GCS when discharged.

CONCLUSION

Intracranial abscess patient's age, GCS at admission, the presence of other comorbidities, including hypoalbuminemia and hydrocephalus are significantly associated with patient's GCS when discharged. Developing countries, such as Indonesia, have some unique challenges that prevented the retrieval of high-quality data for studies on intracranial abscess.

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DECLARATIONS

Author contributions to the study and the manuscript preparation. Conception and design All; Methodology **Akhmad Imron**; Formal Analysis **Akhmad Imron[1], Dewi Kartika Turbawaty[2]**; Writing - Original Draft All; Writing - Review and Editing All; Supervision All.

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