

HEMORRHAGIC STROKE PROFILE ON SALATIGA REGIONAL PUBLIC HOSPITAL PATIENTS

Ian A Garudadwiputra¹⁾, Lothar M M V Silalahi²⁾, Widya C Manus³⁾

ABSTRACT

Introduction: There is an increasing number of new hemorrhagic stroke cases from 2017 to 2018 on The Province of Central Java and Salatiga. A study of demographics, laboratory examination, radiology, outcome, risk factor, and clinical presentation on hemorrhagic stroke patients are rarely done at Salatiga Regional Public Hospital.

Purpose: This study aims to describe the hemorrhagic stroke profile on Salatiga Regional Public Hospital patients.

Methods: Hemorrhagic stroke inpatient of Salatiga Regional Public Hospital in the period between October 2018 and October 2019 is studied. Demographic, laboratory examination, radiology, outcome, risk factor, and clinical presentation data are reported.

Results: 47,5% male and 52,5% female with highest age range (55- 64) 33%. The majority of patients came from outside of Salatiga city 71,7%. Patients with blood pressure classification stage 1 11,7%; stage 2 80%. Laboratory examination data shows 52,5% high leucocyte count; normal thrombocyte count; normal lymphocyte count; normal monocyte count; 72,5% high neutrophil count; 71,7% high Neutrophil-Lymphocyte Ratio; 89,2% high ureum level; normal creatine serum; 80% not at risk based on eGFR. Types of hemorrhages are ICH, IVH, and SAH with percentages 68,7%; 25,3%; 6% respectively. Basal Ganglia (48,1%) are the most common location for ICH and lateral ventricle (61,9%) are the highest for IVH.

Conclusion: Hemorrhagic stroke patients at Salatiga Regional Public Hospital are mainly female with the age range of 55-64 are the highest, came from outside of Salatiga city. The most frequent risk factor is hypertension. Most patients have GCS of 14-15 and stage 2 blood pressure classification. Most of the patient have leucocytosis, neutrophillia, high NLR and ureum level. ICH is the highest stroke subtype with the most frequent location of basal ganglia. More patients with good outcomes compared with a bad outcome.

Keywords: Profile, Risk Factor, Hemorrhagic stroke, Salatiga, Outcome

¹⁾ Faculty of Medicine, Duta Wacana Christian University, Yogyakarta
E-mail: kedokteran@ukdw.ac.id

²⁾ Faculty of Medicine, Duta Wacana Christian University, Yogyakarta
E-mail: kedokteran@ukdw.ac.id

³⁾ Faculty of Medicine, Duta Wacana Christian University, Yogyakarta
E-mail: kedokteran@ukdw.ac.id

INTRODUCTION

Non-Communicable Diseases (NCDs) had the highest contribution to the global deaths. Stroke are one of the NCDs. Among Asia, Indonesia has the highest death rate caused by stroke (Venketasubramanian *et al.*, 2017). There is an increase from 2013 to 2018 for stroke prevalence in Indonesia based on diagnosis on population above 15 years old. Stroke (21,1%) became the highest cause of death in Indonesia, followed by cardiovascular disease (Kementerian Kesehatan Republik Indonesia, 2018).

Stroke is a sudden neural disorder caused by cerebrovascular problems. Vascular rupture or blockage disrupted brain blood flow. This disruption will decrease oxygen supply to the brain; therefore, cell death and clinical appearance will occur. Ischemic stroke is a stroke caused by a cerebrovascular blockage. A ruptured cerebrovascular blood vessel will cause a hemorrhagic stroke. Unlike hemorrhagic stroke, mild ischemic stroke shows a good outcome (Khaku, Hegazy and Tadi, 2019).

There is a modifiable and non-modifiable risk factor in hemorrhagic stroke. The modifiable risk factors are smoking, alcohol consumption, drugs, physical activities, diet, stress, and social-economic factor. The non-modifiable factors are sex, age, ethnicity, and genetic. In the process of hemorrhagic stroke, hypertension comes to be the major risk factor (Boehme, Esenwa and Elkind, 2017).

The health profile of The Central Province of Java in 2017 shows 9.993 new stroke cases and 298 new cases in The Salatiga City (Dinas kesehatan, 2017). Compared to the 2018 health profile data, there is an increase in hemorrhagic stroke

incidence for The Province of Central Java and Salatiga City. Data from the health Profile of The Central Province of Java confirms 16.415 new cases of hemorrhagic stroke in The Central Province of Java, 724 new cases in Salatiga City alone (Dinas kesehatan, 2018).

METHODS

The research is conducted at Salatiga Regional Public Hospital from February to April 2020. The purpose of this study is to describe the hemorrhagic stroke profile of Salatiga Regional Public Hospital inpatients, during October 2018 and October 2019. Samples were taken by the total sampling method. The criteria are; medical records of CT scan diagnosed hemorrhagic stroke inpatient with demographic, laboratory test, lipid profile test, kidney function test, risk factors, a clinical presentation that were recorded at admission, and outcome data. Exclusion criteria are medical records that do not add outcome data. Variable used in this study are demographic, laboratory, radiology, outcome, risk factors, and clinical presentation. The data were analyzed using descriptive statistics, then presented as tables, charts, and crosstabs

RESULTS AND DISCUSSION

Of 195 data gathered, 120 meet the criteria. Profile that will be described from the samples is age, sex, domicile, leukocyte, thrombocyte, lymphocyte, monocyte, neutrophil, neutrophil to lymphocyte ratio (NLR), urea, creatinine, glomerular filtration rate, hemorrhage type, hemorrhage location, clinical outcome, hypertension, diabetes mellitus, atrial fibrillation, smoking, Glasgow Coma Scale (GCS) score, systolic blood pressure, and diastolic blood pressure.

Table 1 age frequency distribution of hemorrhagic stroke patients

Age	Frequency	Percentage (%)
20 - 44	8	7
44 - 54	23	19
55 - 64	40	33
65 - 74	33	28
75 - 84	12	10
>85	4	3

The highest average age is the age range 55 to 64 years (33%). Age is directly taking a role in the brain vascular system. Indirectly, age takes part in the hypertension process as the main risk factor of hemorrhagic stroke (Camacho *et al.*,

2015). Age-related vascular dysfunction is considered to be the main cause of the cerebrovascular disease (Izzo *et al.*, 2018).

Table 2 sex frequency distribution of hemorrhagic stroke patients

Sex	Frequency	Percentage (%)
Male	57	47.5
Female	63	52.5
Total	120	100

More female patients compared to the male. Another study has shown the same result as a higher female hemorrhagic stroke patient (56.4%) (Dharmawita, 2015). This result may occur due to fact that the total population and sex ratio at Salatiga

City are higher on the female. Based on the 2018 Salatiga City population data, there are 93.718 (thousand) male and 97.853 (thousand) female. Female sex ratio are also higher on Semarang City and The Central Province of Java (Badan Pusat Statistik Provinsi Jawa Tengah, 2018

Table 3 domicile frequency distribution of hemorrhagic stroke patients

Domicile	Frequency	Percentage (%)
Kec. Argomulyo	8	6.7
Kec. Tingkir	7	5.8
Kec. Sidomukti	6	5.0
Kec. Sidorejo	13	10.8
luar Salatiga	86	71.7
Total	120	100

Kec. = Kecamatan

Most of the patients came from outside of Salatiga City in which Semarang City, Boyolali City, Magelang City, Kulon Progo, Grobogan City, North Halmahera, and Purbalingga City. This condition may occur because of Salatiga City's geographic

location that is surrounded by Semarang districts. Moreover, Salatiga Regional Public Hospital acts as a referral hospital from other hospitals inside and outside Salatiga City. Based on the Communication and Informatics Service of Salatiga City in 2018, Salatiga Regional Public Hospital is a

hospital with the largest number of beds in Salatiga City.

Table 4 blood test frequency distribution of hemorrhagic stroke patients

Type of Blood Test	Frequency	Percentage (%)
Leukocyte		
Normal	57	47.5
High	63	52.5
Thrombocyte		
Normal	109	90.8
High	11	9.2
Lymphocyte		
Normal	118	98.3
High	2	1.7
Monocyte		
Normal	120	100
High	0	0
Neutrophil		
Normal	33	27.5
High	87	72.5
NLR		
Normal	34	28.3
High	86	71.7

NLR = Neutrophil to Lymphocyte Ratio

Laboratory test data were found to have high results are leukocyte, neutrophil, and Neutrophil to Lymphocyte Ratio. There are 52.5% of patients with high leukocyte count. Intracerebral hemorrhage is associated with leukocytosis. Inflammatory response due to leukocytosis takes a role in the severity of intracerebral hemorrhage. Various studies conclude that high leukocyte count is associated with higher severity of intracerebral hemorrhage. Higher severity of intracerebral hemorrhage is indicated by decreased consciousness, hemorrhage volume, and higher incident of intraventricular hemorrhage. Leukocyte takes an important role in the hemostasis process. Acute leukocytosis affects hemostatic balance to trigger coagulation in an effort to stop the bleeding (Morotti *et al.*, 2016).

When intracerebral hemorrhage occurs, the neutrophil is the earliest

inflammatory cell that invades the central nervous system. Neutrophil activation in the hyperacute phase of intracerebral hemorrhage can trigger procoagulant characteristics which can prevent hemorrhage expansion (Morotti *et al.*, 2016). An increase in the Neutrophil to Lymphocyte Ratio indicates an imbalance value between central and peripheral inflammation caused by stroke. Neutrophil to Lymphocyte Ratio number turns out to be a promising value to predict the prognosis of a stroke incident both ischemic and hemorrhagic (Song *et al.*, 2019).

Table 5 kidney function test frequency distribution of hemorrhagic stroke patients

Type of Test	Frequency	Percentage (%)
Ureum		
Normal	13	10.8
High	107	89.2
Creatinine		
Normal	102	85.0
High	18	15.0
GFR		
Not at risk	96	80.0
At risk	24	20.0

GFR = Glomerular Filtration Rate

Kidney function test data that were found to have high results are urea levels. A study conducted at *RSUP Prof. Dr. R. D. Kandou Manado* discovered the average urea levels of 34 hemorrhagic stroke patients is 36.59 (SD 20.59) (Mieke Ahn Kembuan, dr MAJA and Universitas Sam Ratulangi Fakultas Kedokteran, 2012). In

this study, the level of urea is stated high if the value is above 20 mg/dl. High urea levels are due to hypertension progress (Bulpitt and Breckenridge, 1976). A persistent hypertension condition leads to kidney damage (Bidani and Griffin, 2004). A high urea level is a practical marker to predict kidney damage progress (Seki *et al.*, 2019).

Table 6 hemorrhage location frequency distribution of hemorrhagic stroke patients

Type of Hemorrhage	Frequency	Percentage (%)
ICH	114	68.7
IVH	42	25.3
SAH	10	6

ICH = Intracerebral Hemorrhage, IVH = Intraventricular Hemorrhage, SAH = Subarachnoid Hemorrhage

Table 7 multiple hemorrhage location frequency distribution of hemorrhagic stroke patients

Type of multiple hemorrhage	Frequency	Percentage (%)
ICH and IVH	32	26.7
ICH, IVH and SAH	4	3.3
ICH and SAH	4	3.3
SAH and IVH	2	1.7

ICH = Intracerebral Hemorrhage, IVH = Intraventricular Hemorrhage, SAH = Subarachnoid Hemorrhage

Intracerebral Hemorrhage incidents are the highest amongst all types of hemorrhagic stroke. Intracerebral hemorrhage contributes 10% of all stroke incidents (Aguilar and Brott, 2011). The most important risk factor for intracerebral hemorrhage incidents is hypertension and Cerebral Amyloid Angiopathy (CAA). Hypertension-related intracerebral

hemorrhage is more common in deep locations, intracerebral hemorrhage risks are directly proportional with a blood pressure increase (Caceres and Goldstein, 2012). Another study showed location or type of hemorrhage distribution is 23% Subarachnoid Hemorrhage and 77% Intracerebral Hemorrhage (Siwi, Lalenoh and Tambajong, 2016).

Table 8 hemorrhage location frequency distribution based on type of hemorrhage

Type of Hemorrhage	Hemorrhage Location	Frequency	Percentage (%)
ICH	Cerebellum	6	4.6
	Corona Radiata	1	0.8
	Ganglia Basalis	64	48.9
	Hemisfer Dextra	3	2.3
	Lobus Frontalis	5	3.8
	Lobus Occipitaliis	4	3.1
	Lobus Parietalis	24	18.3
	Lobus Temporalis	17	13.0
	Pons	5	3.8
	Substansia Alba	1	0.8
IVH	No Description	1	0.8
	Lateralis	26	61.9
	Panventrikuli	13	31.0
	Quartus	2	4.8
SAH	No Description	1	2.4
	Fisura Sylvii	1	9.1
	Parietalis	2	18.2
	Regio Temporalis	3	27.3
	No Description	5	45.5

ICH = Intracerebral Hemorrhage, IVH = Intraventricular Hemorrhage, SAH = Subarachnoid Hemorrhage

Two out of three intracerebral hemorrhages are in deep location. Deep intracerebral hemorrhage is located in basal ganglia and internal capsule (35%- 70%), brainstem (5%-10%), and cerebellum (5%-10%). Hemorrhage located in lobes 15%-30% (Aguilar and Brott, 2011). Seventy percent of intraventricular hemorrhages are secondary due to hemorrhage in the brain

parenchyma (Hinson, Hanley and Ziai, 2010). Aneurysm rupture brought about 85% of non-traumatic subarachnoid hemorrhage cases. Aneurysm prevalence in the general population is 2% to 5%. Aneurysms are often developed in the cerebral artery branch at the anterior and posterior region (Marcolini and Hine, 2019).

Table 9 clinical outcome frequency distribution of hemorrhagic stroke patients

Clinical Outcome	Frequency	Percentage (%)
Live	87	72.5
Died	33	27.5

The clinical outcomes of stroke patients in Salatiga Regional Public Hospital are more likely to live (72.3%) than died. Contradictory to a study conducted at *RSUD dr. Soebandi Jember*, that discovered a hemorrhagic stroke

mortality rate at 72.3%. The high mortality rate in the previously mentioned study resulted as a consequence of a decreased consciousness when admitted to the emergency (Darotin, Nurdiana and Nasution, 2017).

Table 10 risk factor frequency distribution of hemorrhagic stroke patients

Risk Factor	Frequency	Percentage (%)
Hypertension		
Yes	92	76.7
No	28	23.3
Diabetes Mellitus		
Yes	16	13.3
No	104	86.7
Atrial Fibrillation		
Yes	1	0.8
No	119	99.2
Smoking		
Yes	22	18.3
No	98	81.7

Hypertension is the highest risk factor for hemorrhagic stroke patients at Salatiga Regional Public Hospital. A study gathered 549 hemorrhagic stroke cases. Uncontrolled hypertension is a significant risk factor for hemorrhagic stroke incidents. Uncontrolled

hypertension is frequently discovered and perform an important role in hemorrhagic stroke incidents. The study stated that one-fourth of hemorrhagic stroke events can be prevented if all of the hypertension cases are treated well (Woo *et al.*, 2004).

Table 11 clinical presentation frequency distribution of hemorrhagic stroke patients

GCS score	Frequency	Percentage (%)
3 – 8	24	20
9 – 13	27	22
14 – 15	69	58

GCS = Glasgow Coma Scale

The highest Glasgow Coma Scale score discovered in this study is at the range 14 to 15 (58%). Similar study at *Rumah Sakit Daerah dr. Soebandi Jember* identified a Glasgow Coma Scale score of <8 has the highest percentage (62.4%). The

study mentioned poor GCS scores at admission are a strong predictor of hemorrhagic stroke mortality. Mortality rates at the previously mentioned study are 72.3% (Darotin, Nurdiana and Nasution, 2017).

Table 12 blood pressure frequency distribution of hemorrhagic stroke patients

Blood Pressure Classification (JNC7)	Frequency	Percentage (%)
Normal (sistolik <120, diastolik <80)	4	3.3
Prehypertension (sistolik 120-139, diastolik 80-89)	5	4.2
Stage 1 (sistolik 140-159, diastolik 90-99)	14	11.7
Stage 2 (sistolik >160, diastolik >100)	97	80.8

JNC = Joint National Committee

Hypertension is a foremost modifiable risk factor in stroke. Hypertension treatment can lower stroke risks. This finding shows blood pressure control is important in every individual. Systolic and diastolic blood pressure is an

important risk factor in hemorrhagic stroke. An individual with normal blood pressure also had risks to have a hemorrhagic stroke. Blood pressure changes and episodic hypertension higher stroke risk (Norrving, 2014).

Table 13 hemorrhagic stroke patients crosstab based on clinical outcome (a)

Variable	Live (n=87)				Died (n=33)			
	n	%	mean	SD	n	%	mean	SD
Demographic								
Age	87		62.78	11.267	33		59.61	15.817
Clinical Presentation								
GCS score	87		13.26	3.175	33		9.15	4.063
Systolic BP	87		181.97	32.744	33		188.03	44.720
Diastolic BP	87		105.28	18.345	33		109.39	27.579

BP = Blood Pressure, GCS = Glasgow Coma Scale

Table 14 hemorrhagic stroke patients crosstab based on clinical outcome (b)

Variable	Category	Live (n=87)		Died (n=33)	
		n	%	n	%
Sex	Male	39	44.8	18	54.5
	Female	48	55.2	15	45.5
Laboratory Leukocyte	Normal	51	58.6	6	18.2
	High	36	41.4	27	81.8
Neutrophil	Normal	26	29.9	7	21.2
	High	61	70.1	26	78.8
NLR	Normal	26	29.9	8	24.2
	High	61	70.1	25	75.8
Urea	Normal	11	12.6	2	6.1
	High	76	87.4	31	93.9
Radiology	ICH	60	69.0	14	43.0
	ICH,IVH	20	23.0	12	36.0
	ICH,IVH,SAH	1	1.0	3	9.0
	ICH,SAH	3	4.0	1	3.0
	IVH	2	2.0	2	6.0
	SAH,IVH	1	1.0	1	3.0

NLR = Neutrophil to Lymphocyte Ratio, ICH = Intracerebral Hemorrhage, IVH = Intraventricular Hemorrhage, SAH = Subarachnoid Hemorrhage

The age average with the died outcome is 59.61 and mostly are male patients (54%). A study stated at 3-, 6-, and 12-month intracerebral hemorrhage mortality rates are higher in males. This result is due to neuroprotective effects by female gonadal hormones that slow up intracerebral hemorrhage events. The hormones mentioned earlier acts by lower lipid levels and affect fast vasomotor response on the wall of the blood vessel. The high male mortality of intracerebral hemorrhage is also caused by the high prevalence of smoking, alcohol consumption, and diastolic blood pressure (Xing *et al.*, 2017). An analysis shows that male has higher possibility to experience pneumonia and sepsis. Another analysis on mortality shows male and infection events are describing independent risk factors for death in 90 days (Care *et al.*, 2017).

Died outcome patients have a high value on leukocyte, neutrophil, and NLR. Leukocyte and neutrophil act in the brain tissue secondary damage by several mechanisms such as cellular toxicity, Blood-Brain Barrier (BBB) disruption, and inflammation elevation. When BBB is disrupted, inflammation cells including leukocyte, neutrophil, and monocyte will infiltrate the perihematoma area. Neutrophils are related to vascular damage, BBB disruption, microglial reaction, and neuron apoptosis (Yu *et al.*, 2019). Urea levels on dead patients are high. Ureatoxin accumulation in the blood can induce coagulopathy as the result of a decreased thrombocyte adhesion on the wall of the blood vessel, an elevated thrombocyte turnover, and a decreased thrombocyte count (Brunkhorst, 2014). Intracerebral hemorrhage is the highest type of hemorrhage in patients with the died outcome. In an intracerebral hemorrhage, the perihematoma area can be identified with the presence of oedemas, apoptosis, necrosis, and inflammation cells. Hematomas are causing damage by mechanical disruption

of neurons and glial cells, followed by mechanical deformation that causes an oligemia, neurotransmitter release, mitochondrial dysfunction, and membrane depolarisation (Qureshi, Mendelow and Hanley, 2009).

CONCLUSION

From all the samples gathered and analyzed, can be concluded:

1. Hemorrhagic stroke patients at Salatiga Regional Public Hospital have an average age in the range of 55-64 years (33%). Higher in female than male patients. Mostly came from outside of Salatiga City.
2. Hemorrhagic stroke patients at Salatiga Regional Public Hospital have a high level of leukocyte, neutrophil, NLR, and urea.
3. The Highest hemorrhagic stroke patients at Salatiga Regional Public Hospital type of hemorrhage is intracerebral hemorrhage (68.7%). The highest location of intracerebral hemorrhage is basal ganglia (48.1%). The highest location of intraventricular hemorrhage is the lateral ventricle (61.9%).
4. Hemorrhagic stroke patients at Salatiga Regional Public Hospital patients are more likely to live (72.5%).
5. The highest risk factor of hemorrhagic stroke patients at Salatiga Regional Public Hospital is hypertension (76%).
6. Hemorrhagic stroke patients at Salatiga Regional Public Hospital have the highest GCS score of 14 to 15 (58%) with the highest blood pressure classification of stage 2 (80.8%)

ACKNOWLEDGEMENT

1. dr. The Maria Meiwati Widagdo, Ph. D

2. dr. Lothar Matheus Manson
Vanende Silalahi, Sp.N
3. dr. Widya Christine Manus, M.
Biomed

4. RSUD Salatiga
5. Friends of FK UKDW 2016

REFERENCES

1. Aguilar, M. I. and Brott, T. G. (2011) 'Update in intracerebral hemorrhage.', *TheNeurohospitalist*, 1(3), pp. 148–59. doi: 10.1177/1941875211409050.
2. Badan Pusat Statistik Provinsi Jawa Tengah (2018) BPS Provinsi Jawa Tengah. Available at: <https://jateng.bps.go.id/statistictable/2016/08/19/1257/jumlah-penduduk-dan-rasio-jenis-kelamin-menurut-kabupaten-kota-di-provinsi-jawa-tengah-2018.html> (Accessed: 3 June 2020).
3. Bidani, A. K. and Griffin, K. A. (2004) 'Pathophysiology of hypertensive renal damage: Implications for therapy', *Hypertension*. Lippincott Williams & Wilkins, pp. 595–601. doi: 10.1161/01.HYP.0000145180.38707.84.
4. Boehme, A. K., Esenwa, C. and Elkind, M. S. V. (2017) 'Stroke Risk Factors, Genetics, and Prevention', *Circulation Research*, 120(3), pp. 472–495. doi:10.1161/CIRCRESAHA.116.308398.
5. Brunkhorst, R. (2014) 'Uremia', in *Urology at a Glance*. Springer Berlin Heidelberg, pp. 57–60. doi: 10.1007/978-3-642-54859-8_12.
6. Bulpitt, C. J. and Breckenridge, A. (1976) 'Plasma urea in hypertensive patients', *Heart*, 38(7), pp. 689–694. doi: 10.1136/hrt.38.7.689.
7. Caceres, J. A. and Goldstein, J. N. (2012) 'Intracranial Hemorrhage', *Emergency Medicine Clinics of North America*. W.B. Saunders, pp. 771–794. doi: 10.1016/j.emc.2012.06.003.
8. Camacho, E. et al. (2015) 'The role of age in intracerebral hemorrhages', *Journal of Clinical Neuroscience*. Churchill Livingstone, pp. 1867–1870. doi:10.1016/j.jocn.2015.04.020.
9. Care, N. et al. (2017) 'Men Experience Higher Risk of Pneumonia and Death After Intracerebral Hemorrhage', *Neurocritical Care*. doi: 10.1007/s12028-017-0431-6.
10. Darotin, R., Nurdiana and Nasution, T. H. (2017) 'Analisis Faktor Prediktor Mortalitas Stroke Hemoragik di Rumah Sakit Daerah dr Soebandi Jember', *NurseLine Journal*, 2(2), p. 9.
11. Dharmawita (2015) 'Angka Kejadian Stroke Berdasarkan Usia Dan Jenis Kelamin Pada Stoke', *Angka Kejadian Stroke Berdasarkan Usia Dan Jenis Kelamin Pada Stroke Hemoragik dan Non-Hemoragik di Instalasi Rawat Inap Neurologi*, 2(4), pp. 157-163
12. Dinas kesehatan (2017) Profil Kesehatan Provinsi Jawa Tengah Tahun 2017. Available at: http://www.depkes.go.id/resources/download/profil/PROFIL_KES_PROVINSI_2017/13_Jateng_2017.pdf (Accessed: 13 September 2019).
13. Dinas kesehatan (2018) Profil Kesehatan Provinsi Jawa Tengah Tahun 2018. Available at: http://dinkesjatengprov.go.id/v2018/dokumen/profil_2018/mobile/index.html (Accessed: 3 October 2019).
14. Hinson, H. E., Hanley, D. F. and Ziai, W. C. (2010) 'Management of intraventricular hemorrhage', *Current Neurology and Neuroscience Reports*.

- NIH Public Access, pp. 73–82. doi: 10.1007/s11910-010-0086-6.
15. Izzo, C. et al. (2018) 'The impact of aging on cardio and cerebrovascular diseases', *International Journal of Molecular Sciences*. MDPI AG. doi: 10.3390/ijms19020481.
 16. Kementerian Kesehatan Republik Indonesia (2018). Available at: <http://www.depkes.go.id/article/view/18052800008/rokok-akar-masalah-jantung-dan-melukai-hati-keluarga.html> (Accessed: 10 September 2019).
 17. Khaku, A. S., Hegazy, M. and Tadi, P. (2019) *Cerebrovascular Disease (Stroke)*, StatPearls. StatPearls Publishing. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/28613677> (Accessed: 19 September 2019).
 18. Marcolini, E. and Hine, J. (2019) 'Approach to the diagnosis and management of subarachnoid hemorrhage', *Western Journal of Emergency Medicine*. eScholarship, pp. 203–211. doi: 10.5811/westjem.2019.1.37352.
 19. Mieke Ahn Kembuan, D., dr MAJA, S. P. and Universitas Sam Ratulangi Fakultas Kedokteran, S. (2012) STATUS GAGAL GINJAL KRONIK PADA PENDERITA STROKE DI RSUP Prof. Dr. R. D. KANDOU MANADO.
 20. Morotti, A. et al. (2016) 'Leukocyte Count and Intracerebral Hemorrhage Expansion.', *Stroke*, 47(6), pp. 1473–8. doi: 10.1161/STROKEAHA.116.013176.
 21. Norrving, B. (ed.) (2014) *Oxford Textbook of Stroke and Cerebrovascular Disease*. Oxford University Press. doi: 10.1093/med/9780199641208.001.0001.
 22. Qureshi, A. I., Mendelow, A. D. and Hanley, D. F. (2009) 'Intracerebral haemorrhage', *The Lancet*. NIH Public Access, pp. 1632–1644. doi: 10.1016/S0140-6736(09)60371-8.
 23. Seki, M. et al. (2019) 'Blood urea nitrogen is independently associated with renal outcomes in Japanese patients with stage 3–5 chronic kidney disease: a prospective observational study', *BMC Nephrology*, 20(1), p. 115. doi: 10.1186/s12882-019-1306-1.
 24. Siwi, M., Lalenoh, D. and Tambajong, H. (2016) 'Profil Pasien Stroke Hemoragik yang Dirawat di ICU RSUP Prof. Dr. R.D. Kandou Manado Periode Desember 2014 sampai November 2015', *e-CliniC*, 4(1). Available at: <https://ejournal.unsrat.ac.id/index.php/eclinic/article/view/11015/10604> (Accessed: 13 September 2019)
 25. Song, S. Y. et al. (2019) 'Clinical Significance of Baseline Neutrophil-to-Lymphocyte Ratio in Patients With Ischemic Stroke or Hemorrhagic Stroke: An Updated Meta-Analysis', *Frontiers in Neurology*. Frontiers Media S.A. doi: 10.3389/fneur.2019.01032.
 26. Venketasubramanian, N. et al. (2017) 'Stroke Epidemiology in South, East, and South-East Asia: A Review.', *Journal of stroke*, 19(3), pp. 286–294. doi: 10.5853/jos.2017.00234.
 27. Woo, D. et al. (2004) 'Effect of untreated hypertension on hemorrhagic stroke', *Stroke*, 35(7), pp. 1703–1708. doi: 10.1161/01.STR.0000130855.70683.c8.
 28. Xing, Y. et al. (2017) 'Sex differences in the clinical features, risk factors, and outcomes of intracerebral

hemorrhage: A large hospital-based stroke registry in China', *Scientific Reports*, 7(1). doi: 10.1038/s41598-017-00383-6.