Admission Neutrophil-to-Lymphocyte Ratio as a Predictive Factor in the Outcome of Acute Spontaneous Intracerebral Hemorrhage

Edrome F. Hernandez, MD,[1] Chris Jordan T. Go, MD[1] and Ma. Epifania V. Collantes, MD[1,2]

[1]*Department of Internal Medicine, Manila Doctors Hospital, Manila, Philippines*
[2]*Department of Neurosciences, Philippine General Hospital, University of the Philippines Manila, Manila, Philippines*

ABSTRACT

Background and Objective. A growing body of evidence supports that inflammatory mechanisms are involved in secondary brain injury after intracerebral hemorrhage (ICH) which has implications on the morbidity and mortality of stroke patients. Neutrophil-to-lymphocyte ratio (NLR) is a comprehensive index marker of inflammation and immune status of a patient. The prognostic value of NLR in predicting in-hospital mortality and functional outcome of patients with spontaneous intracerebral hemorrhage will be assessed in this study.

Methods. We retrospectively selected 151 hemorrhagic stroke patients, and demographic and clinical characteristics were collected and computed for NLR. Receiver operating characteristic analysis using Youden's index was utilized to determine the NLR cut-off value with the best sensitivity and specificity. The association of NLR with the in-hospital mortality and functional outcome was assessed using Logistic regression analysis. Pearson Product Model Correlation was employed to evaluate the correlation of NLR with ICH volume.

Results. Admission NLR >7 showed a significant association (p=<0.001 OR 7.99) with in-hospital mortality with a sensitivity of 70.83% and specificity of 72.82%. Furthermore, computed NLR of more than 6.4 showed significant association (p=0.040 OR 2.92) with poor functional outcome. However, our study revealed that admission NLR showed a low level of correlation (r=0.2968, p=0.002) with the volume of ICH.

Conclusion. This study demonstrated that ICH patients with an elevated NLR is associated with increased in-hospital mortality and poor functional outcome and that NLR can be used to predict clinical outcome among patients with spontaneous ICH.

Keywords: neutrophil-to-lymphocyte ratio, intracerebral hemorrhage, in-hospital mortality, functional outcome

INTRODUCTION

Based from the 1998 and 2005 health statistics from the Philippine Department of Health (DOH), cerebrovascular disease (CVD) was the second leading cause of mortality. It has a worldwide incidence that ranges from 10-20 cases per 100,000 population and is relatively higher in Asia when compared to the West.[1] In spite of the availability of more aggressive stroke care, hemorrhagic stroke still represents the most serious type of stroke with high morbidity and mortality. Recently, a growing body of evidence supports that the inflammatory mechanisms are involved in brain injury after ICH which may have implications on the neurologic outcome and mortality of stroke patients.[2]

Oral Presentation – Asia Pacific Stroke Conference 2019, October 2, 2019, SMX Convention Center, Manila, Philippines.

Poster Presentation – 12th Congress of the Asian-Pacific Society of Atherosclerosis and Vascular Diseases, September 21, 2019, Chang Yung-Fa Foundation International Convention Center, Taipei, Taiwan.

Poster Presentation – XXIV World Congress of Neurology, October 27, 2019, Dubai World Trade Center, United Arab Emirates.

eISSN 2094-9278 (Online)
Published: August 30, 2024
https://doi.org/10.47895/amp.vi0.7456

Corresponding author: Edrome F. Hernandez, MD
Department of Internal Medicine
Manila Doctors Hospital
667 United Nations Avenue, Ermita, Manila 1000, Philippines
Email: hernandezedrome@gmail.com
ORCiD: https://orcid.org/0000-0003-2208-2732

Neutrophil-to-lymphocyte ratio (NLR) is a widely available inflammatory marker and is considered to be a comprehensive index that reflects the degree of inflammation and immune status of a patient. It has proven its usefulness in the stratification of mortality in major cardiac events, as a strong prognostic factor in different type of cancers or as a predictor and marker of inflammatory or infectious pathologies. However, studies are lacking that support the prognostic value of NLR in intracerebral hemorrhage.[2,3]

The development of secondary brain injury after stroke is mainly attributed to inflammation. A study by Ye et al. was able to demonstrate a correlation between a higher NLR with 90-day poor outcomes after the intracerebral hemorrhage.[3] These findings were comparable by the study of Tao et al. which identified NLR of more than 6.62 and 6.28 were determined to be a critical threshold for mortality and poor outcome, respectively.[4]

Furthermore, the volume of the hematoma is considered as an independent predictor for clinical outcomes in ICH, and one study was able to demonstrate that patients with higher admission NLR had larger hematoma volumes and higher NIHSS scores. The mechanism is most likely related to a stress-induced response or an inflammatory response in modulating the coagulation cascade after ICH.[2]

This study aims to evaluate the association of admission neutrophil-to-lymphocyte ratio (NLR) with in-hospital mortality and functional outcome of adult Filipinos with spontaneous hemorrhagic stroke. Furthermore, this study will provide insights regarding the correlation of NLR with the volume of intracerebral hematomas.

METHODS

Study design and patient enrollment

This retrospective cohort study included all adult patients 18 years old and above with acute spontaneous intracerebral hemorrhage within 24 hours from the onset of symptoms admitted from January 1, 2014 to September 30, 2018 at our hospital's Stroke Unit. Patients included in the study were retrospectively selected using the Hospital Monthly Census and charts of all ICH patients were retrieved and subsequently reviewed. Patients with myeloproliferative diseases, concurrent infection, coagulation disorders, history of head trauma, immunocompromised state, autoimmune disorders, heart failure, use of anticoagulant, liver cirrhosis and renal dysfunction (GFR < 30 ml/min/1.73 m^2) were excluded from the study as these conditions may have some effect on the NLR. Patients which developed critical care complications during the course of admission like acute coronary syndrome, nosocomial infection, and kidney failure were likewise excluded. Those patients with secondary causes of ICH like arteriovenous malformations (AVM) and ruptured aneurysms documented by computed tomography (CT) angiogram were not included in the study (Figure 1).

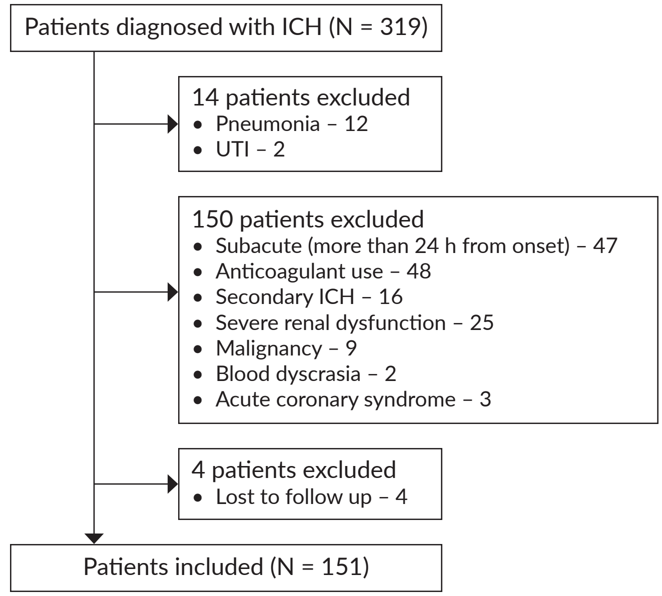

Figure 1. Flowchart of patient enrollment.

ICH: Intracranial hemorrhage; UTI: Urinary tract infection

Data Collection

Demographic and clinical characteristics on admission were retrospectively collected which include age, gender, alcohol use, smoking history, comorbidities, use of antiplatelet or anticoagulant, and the baseline blood pressure on admission. The baseline neurologic status of the patient was assessed using the Glasgow Coma Score (GCS) and the National Institutes of Health Stroke Scale score (NIHSS). Baseline complete blood count extracted on the day of admission was recorded and used to compute for the neutrophil-to-lymphocyte ratio. Neutrophil-lymphocyte ratio was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count from a complete blood count with differential. Radiologic parameters were recorded on the same day of admission including the volume of intracerebral hemorrhage, presence of subarachnoid hemorrhage, and intraventricular hemorrhage (IVH). The volume of intracerebral hemorrhage within 24 hours from the onset of symptoms excluding the IVH volume was measured using the ABC/2 (Kothari) Method. Patients who underwent brain decompression surgery were noted. Receiver operating characteristic analysis using the Youden's index was utilized to determine the NLR cut-off value with the best sensitivity and specificity for mortality and poor functional outcome. The functional outcome of each patient was graded using the Modified Rankin Scale for neurologic disability on day of discharge.[5] A modified Rankin Scale (mRS) of ≥3 was classified as poor outcome, and a mRS <3 was considered favorable outcome (Appendix).

Data Analysis

Data Analysis was performed in Stata SE Version 13. Quantitative variables were summarized as mean and standard deviations while the qualitative variables as frequency and percentage. Accuracy of NLR above the cut-off value in predicting mortality and poor functional outcome among patients with hemorrhagic stroke was computed in terms of its sensitivity, specificity, positive predictive value (PPV), and negative predictive value. Association of NLR with the mortality and functional outcome in ICH was analyzed using the logistic regression analysis. The correlation of NLR with the intracerebral hematoma volume was analyzed using the Pearson Product-Moment Correlation. The level of significance was set at 5%.

Ethical considerations

This research protocol was submitted and approved by the Institutional Review Board of Manila Doctors Hospital (R_MDH IRB 2018-013) to ensure confidentiality of the patient's information. A request for waiver of informed consent was done because of the retrospective nature of the study.

RESULTS

A total of 151 patients with spontaneous ICH were included in our study. Majority of our study population were male (74.1%), hypertensive (78.1%), and almost one third was diabetic (27.1%). Most of the studied patients were alcohol beverage drinker (44.3%) and smoker (39.7%). The total in-hospital mortality was 48 (31.8%), 58 patients (38.4%) had poor outcome and 45 (29.8%) had good functional outcome. Only 16 patients (10.6%) underwent surgical evacuation. Clinical variables which showed significant correlation for both in-hospital mortality and functional outcome were baseline GCS (p=<0.001), baseline NIHSS (p=<0.001), presence of IVH (p=<0.001), and the volume of intracranial bleed (p=<0.001). Presence of SAH (p=<0.001) and baseline SBP (p=0.001) showed significant correlation with in-hospital mortality. Interestingly, hypertension is inversely associated with mortality which is counterintuitive in ICH and can likely be explained by underreporting of those patients who are truly hypertensive (Table 1).

Receiver operating characteristics yielded a cut-off of 7 for NLR (AUC 0.7570) with a sensitivity of 70.83% and specificity of 72.82% in predicting in-hospital mortality. It has positive predictive value of 58.65% and negative predictive value of 84.9% which implies that patients with NLR less than 7 are more likely to survive than those patients with NLR >7 (Figure 2).

Admission NLR > 7 showed a significant association with in-hospital mortality (p=<0.001 OR= 7.99). The majority of patients who died in the study had NLR >7 while most of the patients who survived had NLR of less than 7 (Table 2).

Furthermore, mean NLR of 6.4 was significantly associated with poor functional outcome among ICH patients (p=0.040 OR=2.92), while patients with good functional outcome have generally lower mean NLR of 3.8 (Table 3).

Baseline NIHSS and ICH volume showed signification association with in-hospital mortality, however, baseline GCS was counterintuitive with mortality. This can likely be explained by the fact that only admission GCS was used to analyze association with mortality and did not take into account changes in GCS along the course of admission (Table 4).

Table 1. Baseline Clinical Profile, Radiological Characteristics and Admission NLR in Patients with Spontaneous Intracerebral Hemorrhage (ICH)

Variables	Mean ± SD or n (%)	Died (n=48)	Alive (n=103)	*P* value	Poor outcome (n=58)	Favorable outcome (n=45)	*P* value
Demographic data							
Age (yrs) (mean ± SD range)	54.9 ± 13.2	57.7 ± 15.6	53.5 ± 11.8	0.071	53.7±12.5	53.4±10.9	0.898
Men (n[%])	112 (74.1%)	34 (70.8)	78 (75.7)	0.523	43 (74.14)	35 (77.78)	0.669
Clinical Data							
Hypertension (n[%])	118 (78.1%)	32 (66.67)	86 (83.5)	**0.022**	47 (81.03)	39 (86.67)	0.447
Diabetes Mellitus (n[%])	41 (27.1%)	12 (25%)	29 (28.16)	0.685	19 (32.76)	10 (22.22)	0.241
Drinking (n[%])	67 (44.3%)	19 (39.6)	48 (46.6)	0.419	26 (44.83)	22 (48.89)	0.682
Smoking (n[%])	60 (39.7%)	20 (41.7)	40 (38.8)	0.741	26 (44.83)	14 (31.11)	0.158
Systolic blood pressure (SBP) in mmHg (mean ± SD range)	178.4 ± 31.8	192.1 ± 33.0	172.0 ± 29.3	**0.001**	175±30.7	168.22±27.2	0.245
Diastolic Blood Pressure (DBP) in mmHg (mean ± SD range)	101.6 ± 19.3	104.17 ± 24.7	100.4 ± 16.3	0.265	101.2±15.7	99.3±17.1	0.561
Baseline GCS score (mean ± SD range)	11.5 ±4.1	6.9 ± 3.4	13.7 ± 2.1	**<0.001**	12.9±2.4	14.8±0.9	**0.001**
Baseline NIHSS score (mean ± SD range)	15.9 ±14.0	27.2 ± 8.1	10.6 ± 12.8	**<0.001**	15.6±15.0	4.2±4.2	**<0.001**
Radiologic data							
Presence of SAH (n[%])	26 (17.22%)	20 (41.7)	6 (5.8)	**<0.001**	4 (6.9)	2 (4.44)	0.601
Presence of IVH (n[%])	59 (39.07%)	37 (77.1)	22 (21.4)	**<0.001**	17 (29.31)	5 (11.11)	**0.031**
ICH volume (average)	32.01 ± 41.6	66.8 ± 54.3	15.8 ± 18.92	**<0.001**	22.7± 22.01	7.0±7.4	**<0.001**

Table 2. Association of NLR >7 with In-hospital Mortality in ICH using the Logistic Regression Analysis

	Died (n=48)	Alive (n=103)	Odds Ratio	*P*-value
NLR ≥7	34 (70.8%)	24 (23.3%)	7.99	<0.001
NLR <7	14 (29.2%)	79 (76.7%)		

Table 3. Association of NLR with Poor Functional Outcome in ICH using the Logistic Regression Analysis

	Poor functional outcome (n=58)	Good functional outcome (n=45)	Odds Ratio	*P*-value
NLR	6.4 ± 5.05	3.8 ± 3.0	2.92	0.040

Table 4. Association of Different Clinical Factors and NLR with In-hospital Mortality

	OR (95% CI)	*P*- value
Baseline GCS	0.52 (0.41-0.64)	<0.001
Baseline NIHSS	1.14 (1.09-1.19)	<0.001
ICH volume	1.04 (1.03-1.07)	<0.001

However, admission NLR showed a low level of correlation with ICH volume using the Pearson Product Model Correlation (r=0.2968, p=0.002) (Figure 3).

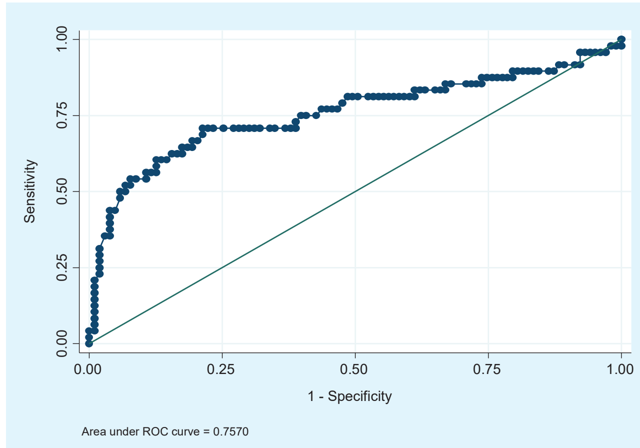

Figure 2. Receiver operating characteristics curve for in-hospital mortality prediction with NLR >7.

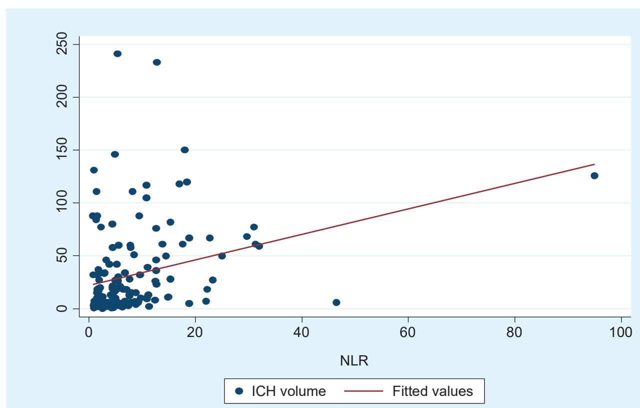

Figure 3. Correlation of NLR and ICH Volume using the Pearson Product Model Correlation.

DISCUSSION

Major findings of this study revealed that ICH patients with an elevated NLR were significantly correlated with increased in-hospital mortality (NLR >7) and poor functional outcome (NLR >6.4). However, admission NLR showed a poor correlation with the volume of ICH. The morbidity and mortality of ICH patients remain to be high despite the more aggressive stroke care and the use of NLR to predict outcome of ICH patients is promising. The results of this study support the potential use of NLR as a measure of inflammation after ICH which can be used as a marker to predict in-hospital mortality and functional outcome.

Many studies support the findings of this study regarding the significant association of admission NLR with short term (30-day and 90-day) mortality and outcome.[3,4,6,7] One study was able to demonstrate that elevated NLR at admission is associated with poor long-term morbidity and mortality in patients with ICH.[8] In contrast with our study, Sun et al. demonstrated that elevated NLR is associated with larger hematoma volumes and did not show any significant association with 3-month all-cause mortality or disability.[2]

The low level correlation of NLR with ICH volume in our study can be possibly explained by several factors. Kothari method was used for the quantification of ICH volume, and this method can have a slight degree of estimation error particularly in irregularly shaped ICH. More accurate methods like computer-assisted volumetric analysis can be utilized to better estimate ICH volume.[9] In addition, our study only measured ICH volume within 24 hours from the onset of symptoms and did not analyze those patients who have had an expansion of ICH bleed along the course of admission. These factors may confound the true association of NLR with ICH volume.

Secondary brain injury after ICH is thought to result from the development of inflammatory response which is initiated by inflammatory signaling via the activation of microglia, and subsequently stimulating the release of pro-inflammatory cytokines and chemokines around the hematoma.[10] In addition, a systemic inflammatory response develops which is reflected by the elevated number of inflammatory cells like neutrophils, monocytes, and lymphocytes. The activation of inflammatory cells results to the disruption of blood-brain barrier, tissue damage, and neuronal cell death which may further worsen peri-hematomal edema growth. NLR is an inflammatory marker that can be utilized to measure the degree of inflammation (neutrophil) and immune status (lymphocyte) of a patient. Lymphocytes play an important role in host defense against pathogens by inducing cellular and humoral immune responses. Reduced lymphocyte counts in lymphoid organs and peripheral blood renders ICH patients more prone to infections, which may have critical implications on the prognosis of ICH. The association of NLR with the mortality of ICH can be attributed to the increase of peri-hematoma or systemic inflammatory response and ICH-induced immunosuppression.[3]

Our study has several limitations. First, this was a retrospective study performed in a single tertiary hospital therefore a causal relationship could not be established. We cannot totally rule out the possibility that other unmeasured or inadequately measured factors could confound the true association because of a relatively small sample size and the retrospective nature of the study. Secondly, our study did not exclude patients who underwent neurosurgical procedure which may have implications on the outcome of ICH and could affect the NLR association with in-hospital mortality and functional outcome. Lastly, our study did not measure out-of-hospital mortality and this could limit our power to detect significant association between NLR and all-cause death since the period of follow up was relatively short. More prospective studies with longer follow up period are warranted to strengthen the association of NLR with all-cause death of ICH patients. The strengths of the study mainly include the enrollment of patients despite the ICH location, use of widely accessible laboratory variables, and the cost-effectiveness of NLR.

Measurement of peripheral biomarkers of inflammation in ICH represents a reliable measure of the inflammatory burden following ICH. NLR is an inflammatory marker which can be used to predict outcome of ICH patients and shows convincing results as proven by several studies. Its use in the future as a marker for mortality and morbidity in ICH patients can be supported by doing more prospective studies and molecular analysis which can potentiate the role of inflammation in the prognosis of ICH.

CONCLUSION

As a conclusion, our study demonstrated that ICH patients with NLR >7 and NLR >6.4 showed significant association with increased in-hospital mortality and poor functional outcome, respectively, but, showed low level correlation with ICH volume. Secondary brain injury brought about by different inflammatory mechanisms in ICH has significant implications for the outcome of stroke patients. NLR is a widely accessible inflammatory marker that can be used to measure inflammatory burden following ICH, and can therefore be utilized to predict outcomes.

Acknowledgment

The authors are very grateful for the guidance and assistance of Dr. Elmer Llanes in making this study possible.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

There is no potential conflict of interest relevant to this study.

Funding Source

This study did not receive any form of funding support from any sponsor.

REFERENCES

1. Navarro JC, Baroque AC 2nd, Lokin JK, Venketasubramanian N. The real stroke burden in the Philippines. Int J Stroke. 2014 Jul;9(5):640-1. doi: 10.1111/ijs.12287.
2. Sun Y, You S, Zhong C, Huang Z, Hu L, Zhang X, et al. Neutrophil to lymphocyte ratio and the hematoma volume and stroke severity in acute intracerebral hemorrhage patients. Am J Emerg Med. 2017 Mar;35(3):429-33. doi: 10.1016/j.ajem.2016.11.037.
3. Ye Z, Ai X, Fang F, Hu X, Faramand A, You C. The use of neutrophil to lymphocyte ratio as a predictor for clinical outcomes in spontaneous intracerebral hemorrhage. OncoTarget. 2017 Aug;8(52);90380-9. doi: 10.18632/oncotarget.20120
4. Tao C, Hu X, Wang J, Ma J, Li H, You C. Admission neutrophil count and neutrophil-to-lymphocyte ratio predict 90-day outcome in intracerebral hemorrhage. Biomark Med. 2017 Jan;11(1);33-42. doi: 10.2217/bmm-2016-0187.
5. Banks JL, Marotta CA. Outcomes validity and reliability of the Modified Rankin Scale: Implications for stroke clinical trials: A literature review and synthesis. Stroke. 2007 Mar;38(3);1091-6. doi: 10.1161/01.STR.0000258355.23810.c6.
6. Lattanzi S, Cagnetti C, Provinciali L, Silvestrini M. Neutrophil-to-lymphocyte ratio predicts the outcome of acute intracerebral hemorrhage. Stroke. 2016 Jun;47(6);1654-7. doi: 10.1161/STROKEAHA.116.013627.
7. Wang F, Hu S, Ding Y, Ju X, Wang L, Lu Q, et al. Neutrophil-to-lymphocyte ratio and 30-day mortality in patients with acute intracerebral hemorrhage. J Stroke Cerebrovasc Dis. 2016 Jan;25(1);182-7. doi: 10.1016/j.jstrokecerebrovasdis.2015.09.013.
8. Zhang F, Ren Y, Fu W, Yang Z, Wen D, Hu X, et al. Predictive accuracy of neutrophil-to-lymphocyte ratio on long-term outcome in patients with spontaneous intracerebral hemorrhage. World Neurosurg. 2019 May;125:e651-e657. doi: 10.1016/j.wneu.2019.01.143.
9. Wang C, Juan C, Liu Y, Hsu H, Liu H, Chen C, et al. Volume-dependent overestimation of spontaneous intracerebral hematoma volume by the ABC/2 formula. Acta Radiol. 2009 Apr;50:3,306-11. doi: 10.1080/02841850802647039.
10. Gusdon AM, Gialdini G, Kone G, Baradaran H, Merkler AE, Mangat HS, et al. Neutrophil-lymphocyte ratio and perihematomal edema growth in intracerebral hemorrhage. Stroke. 2017 Sep;48(9):2589-92. doi: 10.1161/STROKEAHA.117.018120.

APPENDIX

Modified Rankin Scale (MRS) in classifying outcome of ICH patients[5]

Modified Rankin Scale (MRS)	Scale	Description
Good Functional Outcome	0	No symptoms at all
	1	No significant disability despite symptoms; able to carry out all usual duties and activities
	2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
Poor Functional Outcome	3	Moderate disability; requiring some help, but able to walk without assistance
	4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
	5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
Dead	6	Dead