

## Predictors of functional outcome of patients in neurological intensive care unit

Yerim Kim MD, Seok-Beom Kwon MD PhD, Hyun-Ju Park MD, Min-Ji Kim MD, \*Seong-Sook Hong MD PhD, Suk Yun Kang MD PhD, San Jung MD, Sung-Hee Hwang MD PhD

Department of Neurology, Hallym University College of Medicine, South Korea; \*Department of Radiology, Soonchunhyang University College of Medicine, South Korea

### Abstract

**Background:** Little is known regarding the functional outcome and quality of life of neuro-ICU survivors. In Korea, the neuro-ICU concept was introduced relatively late and data about long term outcome and predictors concerning functional outcome is scarce. The main objective of this study was to analyze functional outcome and mortality, and to determine prognostic predictors for the outcome in patients admitted to Korean neuro-ICUs. **Methods:** Consecutive adult ( $\geq 15$ -years-of-age) patients admitted to a neuro-ICU due to various causes including ischemic or hemorrhagic stroke, and other neurological or neurosurgical problems such as traumatic brain injury, seizure, or drug intoxication during an 18-month period from July 2008 through December 2009 were included. Demographic and clinical variables were compared between groups stratified based on 6-month modified Rankin scale score. **Results:** Of 555 patients, there were significant differences in age ( $P=0.013$ ), sex ( $P=0.02$ ), hospital stay ( $P<0.01$ ), neuro-ICU stay ( $P<0.01$ ), admission diagnosis ( $P=0.001$ ), intubation ( $P<0.01$ ), mechanical ventilation ( $P<0.01$ ), tracheostomy ( $P<0.01$ ), comorbid conditions such as atrial fibrillation ( $P<0.01$ ), cardiac complication ( $P<0.01$ ) and pulmonary complication ( $P<0.01$ ), a high Therapeutic Intervention Scoring System (TISS-28) score ( $P<0.01$ ), and a high Acute Physiology and chronic health evaluation (APACHE) II score ( $P<0.01$ ) between favorable and unfavorable outcome groups. The overall mortality rate was 15.0% ( $n=83$ ). In multivariable logistic regression analysis, age, sex, high TISS-28, high APACHE II score, intubation, and cardiac complication were independent predictors of unfavorable outcome.

**Conclusion:** The identified predictors for functional outcomes in Korean neuro-ICU patients will be an important aid in diagnosing and treating neuro-ICU patients.

### INTRODUCTION

Intensive care units (ICUs) were initially developed to intensively manage patients at risk due to acute, life threatening disease.<sup>1</sup> The demand for intensive care services has been growing because of new technologies and the increasing age of the general population, resulting in more interventions in high-risk patients.<sup>2</sup> The specialization of ICUs toward particular patients who have neurologic problems spurred the creation of neurological ICUs (neuro-ICUs).<sup>1,3-5</sup>

Although globally and in Korea many patients have been admitted and treated in neuro-ICUs, neuro-ICUs have been introduced in Korea only relatively recently and still might account for only a small portion of the total ICU facilities.<sup>6-7</sup> There were only limited data on the long term outcome and determined predictors for functional outcome globally and few studies in Korea.<sup>6-13</sup>

Despite recent advances in acute treatment, neurologic deficits including stroke, traumatic brain injury, and seizure are still leading causes of mortality and severe morbidity.<sup>14</sup> Reliable outcome prediction at the acute stage in the neuro-ICUs is thus important. Neurologists can play an active role in controlling the predictable factors associated with poor outcomes. The aim of this study was to analyze long term outcomes of patients in the neuro-ICUs and to evaluate the neurologic and non-neurologic predictors of functional outcome.

### METHODS

Consecutive patients admitted to the neuro-ICU due to various causes including major neurological and neurosurgical disorders during the 18-month period from July 2008 through December 2009 were analyzed. The design of this retrospective

study was approved by our Institutional Review Board. This study was performed at the 15 bed neuro-ICU of Kangnam Sacred Heart Hospital of Hallym University Medical Center, Seoul, Korea. The neuro-ICU team was composed of neurointensivists (S.B. Kwon, S.Y. Kang, S. Jung and S.H. Hwang) and specialized nurses for neurologic intensive care.

We evaluated demographic data (age, sex, and smoking), admission diagnoses, mortality, length of ICU stay, complications (cardiac, pulmonary, or others), mechanical ventilation, modified Rankin Scale (mRS), Therapeutic Intervention Scoring System (TISS-28), Acute Physiology and chronic health evaluation (APACHE) II score, and comorbid conditions such as hypertension, diabetes mellitus, pulmonary disease, atrial fibrillation, chronic renal failure, cancer, previous stroke, congestive heart failure, smoking, and liver cirrhosis.

The admission diagnoses were determined by the main cause of admission of the patients with neurological problems to the neuro-ICU.

Cardiac complications were defined as presence of acute myocardial infarctions or cardiac arrests. Pulmonary complications included acute respiratory distress syndrome (ARDS), pneumothorax, and pneumonia with or without intubation. Complications included not only cardiac or pulmonary events but also renal failure, bed sore, varix bleeding, and deep vein thrombosis. Because we did not distinguish the modes of mechanical ventilation, the term mechanical ventilation meant patients who received intubation tubes and who were required mechanical ventilation support. Functional outcome was evaluated by the mRS at 6 months. The mRS is a clinician reported measure of global disability that has been widely applied for evaluating recovery from stroke.<sup>15</sup> The scale runs from 0 – 6, running from perfect health without symptoms to death: 0, No symptoms; 1, No significant disability. Able to carry out all usual activities, despite some symptoms; 2, Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities; 3, Moderate disability. Requires some help, but able to walk unassisted; 4, Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted; 5, Severe disability. Requires constant nursing care and attention, bedridden, incontinent; 6, Death. The mRS was dichotomized into values for unfavorable outcome (mRS 3 – 6, indicating moderate to severe disability or death; n=216)

and favorable outcome (mRS 0 – 2, indicating no disability to moderated disability; n=339). Patients who had died in the neuro-ICU (n=83) were also included in the initial analysis.

Statistical analysis was performed with SPSS 12.0.1 for Windows. Patient characteristics from the two groups were compared using Pearson chi square test for the categorical variables and independent t-test for the continuous variables. Multivariate logistic regression analyses were performed to find predictors of functional outcome. A *P* value of <0.05 was considered statistically significant.

## RESULTS

*Patient characteristics:* During the 18 month period, we identified 555 patients admitted to the NICU (207 females, 37.3%). The mean age of the group was 59.2±17.1 years.

*Admission diagnosis:* The eight main diagnoses that were used in the data analyses were cerebral infarction (24.9%, n=138), intracerebral hemorrhage (24.1%, n=134), subarachnoid hemorrhage (12.1%, n=67), traumatic brain injury (26.3%, n=146), seizure (1.3%, n=7), drug intoxication (3.8%, n=21), encephalitis (1.3%, n=7), and others (5.4%, n=30) (Table 1). Other diagnoses included brain tumor, Guillain-Barré syndrome (GBS), posterior reversible encephalopathy syndrome (PRES), sepsis, severe pneumonia, and hepatic encephalopathy.

*Length of neuro-ICU stay:* The mean length of neuro-ICU stay was 11.3± 14.4 days (range, 1 – 94 days) and the mean total hospital day was 22.7±22.2 days (range 1 – 211 days).

*Mortality:* Of all the patients enrolled in the study, 83 subjects (15.0%) died during neuro-ICU stay. (Table 2) The common causes of death were brainstem failure (51.8%, n=43), herniation (25.3%, n=21), acute respiratory distress syndrome (9.6%, n=8), sepsis (7.2%, n=6), and acute renal failure (3.6%, n=3). Tension pneumothorax (1.2%, n=1) and aspiration pneumonia (1.2%, n=1) were the causes of death in 2 cases.

*Intubation, mechanical ventilation, tracheostomy:* Most of the endotracheal intubations were done because of altered consciousness, respiratory failure, or elective intubation for surgery. The mechanical ventilations were electively applied to most of the post-operative patients

**Table 1. Demographic information in 555 neuro-ICU patients.**

Variable	N=555	favorable outcome group (mRS 0-2) N=339	unfavorable outcome group (mRS 3-6) N=216	P
Age (y)	59.21 ± 17.11 (15 – 105)	55.65±17.11	64.79±15.77	0.013 <sup>§</sup>
Sex (M/F)	348/207	226/113	122/94	0.020*
Hospital day (D)	22.65 ± 22.18 (1 – 211)	21.09±15.18	25.08±29.94	<0.01 <sup>§</sup>
NICU stay (D)	11.33 ± 14.39 (1 – 94)	8.00±10.20	16.56±18.02	<0.01 <sup>§</sup>
<b>Final diagnosis</b>				0.001*
<b>Cerebral infarction</b>	138 (24.9)	67 (19.8)	71 (32.9)	
<b>ICH</b>	134 (24.1)	63 (18.6)	71 (32.9)	
<b>SAH</b>	67 (12.1)	44 (13.0)	23 (10.6)	
<b>Traumatic brain injury</b>	146 (26.3)	110 (32.3)	36 (16.7)	
<b>Seizure</b>	7 (1.3)	5 (1.5)	2 (0.9)	
<b>Drug intoxication</b>	21 (3.8)	19 (5.6)	2 (0.9)	
<b>encephalitis</b>	7 (1.3)	6 (1.8)	1 (0.45)	
<b>Brain tumor</b>	5 (0.9)	4 (1.2)	1 (0.45)	
<b>others</b>	30 (5.4)	21 (6.2)	9 (4.2)	

mRS, modified Rankin Scale; NICU, Neuro Intensive Care Unit; ICH, Intracerebral hemorrhage; SAH, Subarachnoid hemorrhage; y, years old; D, days; \*, Pearson chi square test; §, independent t-test;

who had received burr hole or craniotomy for intracranial hemorrhage. Of the 555 patients admitted to the neuro-ICU during the 18 month period, 165 (29.7%) patients required intubation for airway protection and 31 (5.6%) patients had a tracheostomy. Among these 165 endotracheally intubated patients, 114 patients required mechanical ventilation because of loss of respiratory drive and lack of vital capacity. While the remaining 51 patients maintained endotracheal tubes due to respiratory failure and then removed after a while.

**TISS-28 and APACHE II scores:** The modified TISS-28 score and the APACHE II score were recorded at admission (mean±SD, 12.84±7.60 and 9.62±8.26, respectively). The mean TISS-28 and APACHE II score in favorable outcome group was 9.41±3.42 and 7.53±5.63, respectively. The respective score in the unfavorable group was 18.25±9.09 and 12.85±10.37. There were

significant differences in the TISS-28 and the APACHE II score between the two groups (both  $P<0.01$ ).

**Outcome analyses:** Unfavorable outcome (mRS 3 – 6) accounted for 38.9% and favorable outcome (mRS 0-2) for 61.1% (Fig. 1). In univariable analysis, age ( $P=0.013$ ), sex ( $P=0.020$ ), hospital stay ( $P\leq 0.01$ ), NICU stay ( $P<0.01$ ), diagnoses on admission ( $P=0.001$ ), death ( $P<0.01$ ), intubation ( $P<0.01$ ), mechanical ventilation ( $P<0.01$ ), tracheostomy ( $P<0.01$ ), atrial fibrillation ( $P<0.01$ ), complications (cardiac and pulmonary) ( $P<0.01$ ), high score in TISS-28 ( $P<0.01$ ), and high APACHE II score ( $P<0.01$ ) were significantly different between the two groups.

Those patients with unfavorable outcome (mRS 3 – 6) were older, female dominant, and had longer duration of hospital stay and NICU stay. Also, they had higher TISS-28 and APACHE II scores. Intubation, mechanical ventilation,

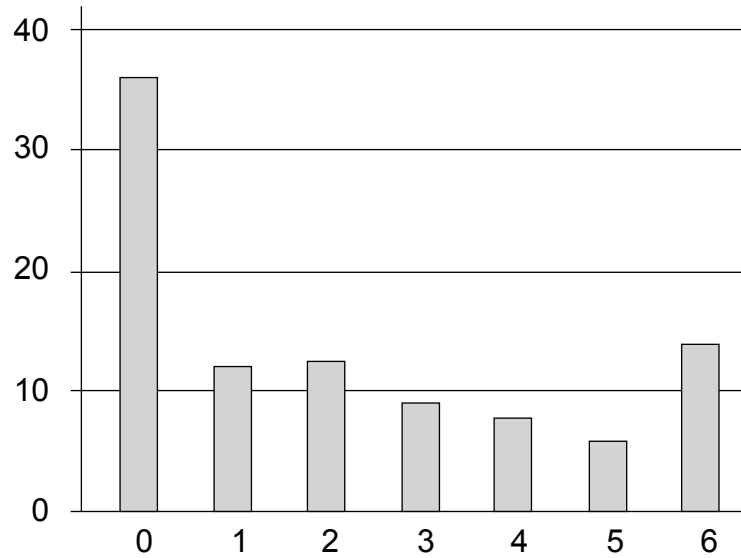
**Table 2. Clinical findings in 555 neuro-ICU patients.**

Variable	N=555	favorable outcome group (mRS 0-2) N=339	unfavorable outcome group (mRS 3-6) N=216	P
<b>Intubation</b>	165 (29.7)	20 (5.9)	145 (67.1)	<0.01*
<b>Mechanical ventilation</b>	114 (20.5)	9 (2.7)	105 (48.6)	<0.01*
<b>Tracheostomy</b>	31 (5.6)	2 (0.6)	29 (13.4)	<0.01*
<b>Comorbid condition</b>				
<b>HTN</b>	257 (46.3)	148 (43.7)	109 (50.5)	0.139*
<b>DM</b>	100 (18.0)	54 (15.9)	46 (21.3)	0.136*
<b>Pulmonary disease</b>	14 (2.5)	7 (2.1)	7 (3.2)	0.559*
<b>AF</b>	39 (7.0)	13 (3.8)	26 (12.0)	<0.01*
<b>CRF</b>	8 (1.4)	4 (1.2)	4 (1.9)	0.778*
<b>Cancer</b>	10 (1.8)	5 (1.5)	5 (2.3)	0.691*
<b>Previous stroke</b>	97 (17.5)	51 (15.0)	46 (21.3)	0.076*
<b>CHF</b>	33 (5.9)	16 (4.7)	17 (7.9)	0.178*
<b>Smoking</b>	52 (9.4)	31 (9.1)	11 (9.7)	0.938*
<b>LC</b>	4 (0.7)	1 (0.3)	3 (1.4)	0.332*
<b>Complications</b>				
<b>Cardiac complication</b>	53 (9.5)	11 (3.2)	42 (19.4)	<0.01*
<b>Pulmonary complication</b>	95 (17.1)	24 (7.1)	71 (32.9)	<0.01*
<b>Ventilation apply (days)</b>	6.94 ± 9.68	2.50±1.195	7.30±9.98	0.999§
<b>TISS-28</b>	12.84 ± 7.60	9.41±3.42	18.25±9.09	<0.01§
<b>APACHE II</b>	9.62 ± 8.26	7.53±5.63	12.85±10.37	<0.01§
<b>Death (Mortality)</b>	83 (15.0)	0 (0)	83 (38.4)	<0.01*

mRS, Modified Rankin Scale; HTN, Hypertension; DM, Diabetes; AF, Atrial fibrillation; CRF, Chronic Renal Failure; CHF, Congestive Heart Failure; LC, Liver Cirrhosis; TISS-28, Therapeutic Intervention Scoring System; APACHE, Acute Physiologic And Chronic Health Evaluation; y, years old; D, days; \*, Pearson chi square test; §, independent t-test

tracheostomy, atrial fibrillation, and cardiac and pulmonary complications were more prevalent in patients with unfavorable outcome (mRS 3 – 6) (Tables 1 and 2). In multivariable logistic regression analysis, sex appeared to be the most important risk factor for unfavorable outcome using mRS, with a 2.33-fold difference between females and males (OR 2.33, 95% CI 1.31 – 4.15,  $P=0.004$ ). Age was correlated linearly with an increase risk of unfavorable outcome of 1.03 for every year of age (OR 1.03, 95% CI 1.01

– 1.05,  $P=0.002$ ). Other factors associated with unfavorable outcome (mRS 3 – 6) in the neuro-ICU patients were high TISS-28 score (OR 1.15, 95% CI 1.08 – 1.22,  $P=0.0001$ ), APACHE II (OR 1.05, 95% CI 1.02 – 1.09,  $P=0.005$ ), intubation (OR 0.35, 95% CI 0.15 – 0.81,  $P=0.014$ ), and cardiac complication (OR 0.29, 95% CI 0.12 – 0.73,  $P=0.008$ ). Other factors such as length of stay in the ICU, mechanical ventilation, tracheotomy, and pulmonary complication were not statistically correlated with poor outcome (Table 3).



	Favorable outcome % (mRS score)	Unfavorable outcome % (mRS score)
mRS, 6 months	61.1 (0~2)	38.9 (3~6)

mRS, Modified Rankin Scale

Figure 1 Distribution of favorable and unfavourable outcome by mRS.

**Table 3. Multivariable analysis of the risk factors for unfavorable outcome (assessed by mRS 3 – 6) in neuro-ICU patients using multiple logistic regression analysis.**

	Odd Ratio	95% C.I		P – value
<b>Age</b>	1.03	1.01	1.05	0.002
<b>Sex</b>	2.33	1.31	4.15	0.004
<b>Final diagnosis</b>	0.89	0.79	1.01	0.066
<b>TISS-28</b>	1.15	1.08	1.22	0.0001
<b>APACHE II</b>	1.05	1.02	1.09	0.005
<b>Intubation</b>	0.35	0.15	0.81	0.014
<b>Mechanical ventilation</b>	0.44	0.17	1.11	0.08
<b>Tracheostomy</b>	1.07	0.37	3.16	0.901
<b>Atrial fibrillation</b>	0.43	0.17	1.06	0.067
<b>Cardiac complication</b>	0.29	0.12	0.73	0.008
<b>Pulmonary complication</b>	0.52	0.26	1.06	0.073

TISS-28, Therapeutic Intervention Scoring System; APACHE, Acute Physiologic And Chronic Health Evaluation

## DISCUSSION

During the past decade, several studies published in Korean medical journals have reported correlations between prognosis and ICU care. One 2002 study reported on factors concerned with death of ICU patients by the APACHE III.<sup>6</sup> Another study reviewed the clinical outcomes of patients readmitted to the ICU.<sup>7</sup> The latter study, similar to the present study, included the patient demographics, diagnosis on ICU admission, comorbid diseases, APACHE II score on ICU admission, length of ICU stay, and the outcomes on ICU discharge. Yet, there have been few reports about ICU outcomes and mortalities, and specific neurologic patients in neuro-ICUs.<sup>1,8,12,16,17</sup> Despite the paucity of data, parallels can be drawn among the available data. Factors such as age, sex, TISS-28 score, APACHE II score, cardiac and pulmonary complication, and endotracheal intubation have similar results, whereas other factors such as tracheostomy and mechanical ventilation show different consequences. Previously, age, sex, length of hospital day, length of neuro-ICU stay, TISS-28 score, and diagnosis on admission were reported as independent predictors of unfavorable outcomes.<sup>1,9,10,12,16,18</sup> Kiphuth IC et al. reported that the diagnoses of hemorrhagic stroke and cerebral neoplasm predispose for poor functional outcome, whereas GBS or myasthenia gravis were related to good functional outcome one year after discharge.<sup>12</sup> Considering that the prevalence of neurologic problems such as stroke increases with age, age alone is an important prognostic factor in the elderly patients admitted to neuro-ICUs.<sup>16,19</sup>

In one study, sex was associated with clinical outcome (decreased risk for female patients)<sup>1</sup>; on the contrary, female patients showed increased risks for unfavorable outcomes in our study. The association between sex and outcome is contentious. Previous studies reported that sex did not significantly differ between survivors and non-survivors in ischemic stroke patients.<sup>8,20</sup> However, despite the lack of significance, female patients were older (mean age  $\pm$  SD; male,  $57.4 \pm 17.2$ , female,  $62.2 \pm 16.5$ ) and had more prolonged hospital or neuro-ICU stay. Furthermore, female patients had more cerebral infarction and intracerebral hemorrhage, and less traumatic brain injury. All of these differences between males and females may lead to the different functional outcomes.

The impact of pulmonary complications related to the functional outcomes has also been contentious. In one study, the odds of ICU death were statistically significant for cardiovascular,

respiratory, and renal failures.<sup>21</sup> However, another study reported that pulmonary complications did not determine the functional outcomes.<sup>20</sup> In our study, although there was significant differences between patients with favorable and unfavorable outcomes, there was no statistical significance on pulmonary complication for the predictors of functional outcome.

The TISS-28 assesses the intensity required to perform 28 therapeutic activities in the ICU.<sup>1</sup> The TISS score and the APACHE II score have the potential to be useful tools for internal quality control of ICU. We also found a significant correlation that the TISS-28 and the APACHE II score were associated with worse outcome (mRS, 3–6;  $P=0.0001$  and  $P=0.005$ , respectively) (Table 3). These findings are similar to the previous results.<sup>1,22</sup>

It is generally accepted that endotracheal intubation and mechanical ventilation is associated with high mortality. In one study, the 1-year mortality of patients with an acute ischemic stroke requiring mechanical ventilation was 72.4%.<sup>23</sup> In our study, although there was a significant correlation between intubation and poor outcomes, no correlations were evident with mechanical ventilation and tracheostomy. One of the reasons is that some Koreans still have a Confucius belief, and are reluctant to have foreign material introduced into their bodies. Tracheotomies can be delayed as long as possible. As well, we usually applied ventilators electively to those patients with neurosurgical problems that required neurosurgery. Whether a respiratory failure might exist or not after neurosurgical treatment, most of the patients were sedated with anesthetic drugs and also needed a mechanical ventilator at least for a couple of hours. In one study, the use or timing of use of endotracheal intubation or tracheostomy did not significantly detract from the outcomes.<sup>20</sup>

The overall mortality rate in our study (15.0%) was lower than those of Western studies (18.0 – 26.6%).<sup>1,21</sup> A Korean study also reported that the mortality of ICU patients was 31.0%, but this study was not focused only on the ICU patients with neurological problems.<sup>6</sup> Specialized treatment in a neuro-ICUs may be beneficial to the critically ill patients with neurologic problems.<sup>15,16</sup> Neurological patients who are cared for in specialized neuro-ICUs can undergo more invasive hemodynamic monitoring, more neurologic capturing by specialists, and tracheostomy than those patients in general ICUs.<sup>5</sup>

This study has some important limitations. First, this study was a single center study, with

all the possible corresponding biases. Thus, the results have low power to be generalized to all other neuro-ICUs. Second, this study does not provide very long-term follow-up data (6 month functional outcome). These two limitations ask for long-term, multicenter studies. Third, we designed the study including both ischemic and hemorrhagic stroke patients. But, the pathophysiology of the two conditions and predictors for mortality are occasionally different between the two groups.<sup>24</sup>

Despite the limitations, this study is the first report about the predictors of functional outcome in neuro-ICU patients with neurological and neurosurgical problems in Korea. Previously, there were only a few reports about outcome predictors in neurologic patients.<sup>1,9</sup> However, considering the differences of outcomes, it is important to detect predictable risk factors for poor outcomes and manage aggressively.

In conclusion, the data presented here suggest that age, sex, high TISS-28, high APACHE II score, intubation, and cardiac complication are important independent predictors for outcome in neurocritical care patients. We expect that this study may have clinical implications for treating neuro-ICU patients. In addition, further studies to evaluate long term outcomes and to gain data of other centers will be needed for the generalization of our results.

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