Rehabilitation is Associated with Lower Mortality in Patients with Dengue Fever in Intensive Care Units: A Retrospective Study

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Original Article

Rehabilitation is Associated with Lower Mortality in Patients with Dengue Fever in Intensive Care Units: A Retrospective Study

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Objective: The study aimed to examine the effect of rehabilitation on mortality in patients with dengue in intensive care units (ICUs).

Design: This was a retrospective cohort study. In this study, 142 patients with dengue from ICUs were enrolled from August to December, 2015. They were divided into two groups: patients with or without rehabilitation. The relationship between rehabilitative therapy and the risk of dengue-related mortality was assessed using a multivariate Cox regression model after adjustment for related variables.

Results: Of the 142 patients, 70 (49.3%) were men, and the mean age was 69.97 ± 15.93 years. The average length of stay in the hospital was 14.79 ± 16.14 days. The results of the Cox regression indicated that rehabilitated patients had a lower risk of dengue-related mortality [adjusted hazard ratio (HR) = 0.196; 95% confidence interval (CI) = 0.059–0.656].

Conclusion: Rehabilitation was found to be associated with lower risk of mortality in patients with dengue fever in the ICUs. More randomized control trials are required to consolidate the effect. (Tw J Phys Med Rehabil 2020; 48(2): 105 - 111)

Key Words: rehabilitation, intensive care unit (ICU), mortality, dengue

INTRODUCTION

Dengue is one of the most prevalent mosquito-borne viral diseases, with symptoms such as general malaise, headache, fever, and hemorrhagic fever with shock. Patients with severe symptoms were transferred to the intensive care units (ICUs) for further observation and management. During the 2015 dengue outbreak in Taiwan, 43,784 people were infected, and more than 200 died. The epidemic placed an enormous burden on the health care system of Taiwan.

Therefore, studies were conducted to determine the factors that could predict the dengue-associated mortality rate. A retrospective study conducted in Brazil on dengue cases reported mostly worldwide identified the factors associated with dengue-associated mortality.[1] Additionally, another retrospective study conducted in Taiwan assessed clinical manifestations and outcomes in critically ill patients with dengue.[2]

Moreover, rehabilitation in the ICU, including positioning, joint mobilization, resistive breathing exercise, muscle strengthening, and ambulation training, was advised for application.[3, 4] Emerging evidence suggests that rehabilitation not only facilitates removal of the endotracheal tube and improves physical function (i.e., muscle power and functional exercise capacity) but also alleviates cognitive impairment and psychiatric morbidity.[5-9] However, few studies have demonstrated the effect of rehabilitation on mortality rate in ICU patients, much less for those with dengue.

Considering the increasing impact of dengue and the related severe complications, our study examined the effect of rehabilitation on mortality in patients with dengue in the ICU.

MATERIALS AND METHODS

Data source

ICU data sets were obtained from the Chi-Mei hospital database from August to December, 2015. Data were anonymized and de-identified prior to analysis. The study protocol was reviewed and approved by the Institutional Review Board of Chi-Mei Hospital, Tainan, Taiwan (IRB10503-005), and the requirement for informed consents was waived.

Study population

This was a retrospective cohort study. Patients in the ICU for more than 24 hours diagnosed as having dengue fever, confirmed positive through the dengue polymerase chain reaction assay, positive dengue immunoglobulin-M, or nonstructural protein 1 antigen test, from August to December, 2015, were selected. Patients under 18 years of age were excluded.

Rehabilitation in the ICU

Patients were then divided into two groups, those with or without rehabilitation, based on the medical records. Rehabilitation exercises were implemented by board-certified physical therapists and occupational therapists. Patients received rehabilitation by undergoing passive range of motion training, breathing muscle training, core muscle training, ankle pumping, sitting balance training, standing balance training, or ambulation training from the first day after ICU admission till discharge from the ICU. The rehabilitation sessions were conducted for 30 minutes per day from Monday to Friday during ICU hospitalization and were discontinued following discharge.

Considering the different characteristics of each patient, different rehabilitation methods were adopted. Patients who were drowsy received passive range of motion exercises of shoulder, elbow, wrist, hip, knee, and ankle joints. Those who were mechanically ventilated received breathing muscle training. Conscious patients who were unable to sit or stand received core muscle training and ankle pumping exercises. Finally, training for sitting balance, standing balance, and ambulation was performed for those unable to sit, stand, and ambulate independently, respectively. Vital signs such as blood pressure, body temperature, oxygen saturation, and breathing frequency were closely monitored during the rehabilitation sessions. Those who were not rehabilitated, received usual care.

Variables measured

Information including sex, age, and severity scores—the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Therapeutic Intervention Scoring System (TISS), and Glasgow Coma Scale (GCS) score were collected. APACHE II is a classification system that evaluates the severity of diseases in the ICU and comprises the patient's age and 12 physiological measurements.[10] TISS is a system that measures the workload and calculates the ICU costs.[11]

Underlying diseases and comorbidities including diabetes mellitus (DM), hypertension (H/T), coronary artery disease (CAD), cerebral vascular accident (CVA), and end-stage renal disease (ESRD) were recorded.

Additionally, we evaluated the (1) utilization of a mechanical ventilator (MV) and continuous veno-venous hemofiltration (CVVH), (2) laboratory data at or during admission, and (3) medical expenses. Blood urea nitrogen (BUN), creatinine, sodium (Na), potassium (K), serum lactate, procalcitonin (PCT), C-reactive protein (CRP), B-type natriuretic peptide (BNP), and activated partial thromboplastin time (APTT) were assessed at the time of ICU admission.

Statistical analysis

Categorical and continuous variables are represented as numbers (percentages) and means ± standard deviation, respectively. The differences between the rehabilitation and control groups were examined using univariate analysis (independent two-sample t test and χ^2 and Fisher's exact tests), and Kaplan-Meier curves was plotted.

Variables in the multivariate survival analysis using Cox's regression model were selected based on the significant variables found previously using univariate analysis. Furthermore, we registered the time spent on the hospitalization and followed up survival or not for 100 days since the patients were admitted. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were also obtained. Statistical significance was set at $p<0.05$. Data were analyzed using SPSS 19.0 (SPSS, Inc., Chicago, IL) for Windows.

Table 1. Demographic and clinical variables of dengue inpatient groups

Variables	All patients (n = 142)	Rehabilitation (n = 36)	Non-rehabilitation (n = 106)	p value
Gender (male)	70 (49.3%)	23 (63.9%)	47 (44.3%)	0.054 [a]
Age	69.97±15.93	75.97±10.13	67.93±17.03	0.008 [b]
APACHE II score	18.01±9.63	17.81±6.80	18.08±10.48	0.859 [b]
TISS	22.88±11.18	22.72±10.39	22.93±11.50	0.920 [b]
Glasgow Coma Scales	12.01±4.20	11.67±3.90	12.14±4.31	0.565 [b]
Use of MV	50 (35.2%)	16 (44.4%)	34 (32.1%)	0.226 [a]
Use of CVVH	20 (14.1%)	4 (11.1%)	16 (15.1%)	0.782 [c]
Mortality	32 (22.5%)	3 (8.3%)	29 (27.4%)	0.02 [c]
Diagnostic test				.
NS1	114 (80.3%)	29 (72.2%)	85 (80.2%)	1.000 [c]
IgM	39 (27.5%)	10 (27.8%)	29 (27.4%)	1.000 [c]
IgG	36 (25.4%)	9 (30.6%)	27 (25.5%)	1.000 [c]
PCR	37 (26.1%)	11 (31.8%)	26 (24.5%)	0.504 [c]
Bacteremia	35 (24.7%)	5 (13.9%)	20 (18.9%)	0.616 [c]
Comorbidity				
DM	70 (49.3%)	24 (66.7%)	46 (43.4%)	0.020 [c]
H/T	90 (63.4%)	29 (80.6%)	61 (57.5%)	0.016 [c]
CAD	27 (19.0%)	7 (19.4%)	20 (18.9%)	1.000 [c]
CVA	16 (11.3%)	10 (27.8%)	6 (5.7%)	0.001 [c]
ESRD	12 (8.5%)	3 (8.3%)	9 (8.5%)	1.000 [c]
BUN	35.84±29.90	36.94±22.41	35.44±32.23	0.800 [b]
Creatinine	2.31±2.45	2.46±2.22	2.26±2.54	0.670 [b]
Na	134.00±5.56	134.87±6.07	133.71±5.37	0.281 [b]
K	3.91±.96	3.96±.98	3.97±1.05	0.712 [b]
lactate	3.74±4.94	2.82±2.49	4.10±5.57	0.081 [b]
PCT	12.59±35.01	17.07±38.27	10.84±33.78	0.428 [b]
CRP	49.29±72.96	58.59±75.97	46.01±71.97	0.383 [b]
BNP	4788.46±7492.85	4596.82±6391.89	4876.51±8029.38	0.900 [b]
APTT	47.68±31.51	42.87±30.94	49.43±31.70	0.294 [b]
Hospital length	14.79±16.14	28.68±24.26	10.34±8.79	0.001 [b]
Medical expense (NT$1,000)	182.20±260.52	313.43±348.14	138.62±206.96	0.006 [b]

n = 142

[a] Statistics are based on the analysis of the χ^2 test.

[b] Statistics are based on the t test

[c] Statistics are based on the analysis of Fisher's exact test

APACHE = Acute Physiology and Chronic Health Evaluation, TISS = Therapeutic Intervention Scoring System; MV: mechanical ventilation; CVVH: continuous veno-venous hemofiltration; APTT: activated partial thromboplastin time.

Table 2. Cox regression analysis of rehabilitation therapy and risk of dengue-related

Variables	β	SE	p value	HR	HR 95.0% CI	
					Lower	Upper
Age	0.003	0.016	0.856	1.003	0.973	1.034
DM	0.395	0.396	0.318	1.484	0.683	3.224
H/T	0.768	0.495	0.121	2.155	0.817	5.684
CVA	0.250	0.412	0.545	1.284	0.572	2.879
Rehabilitation	-1.629	0.616	0.008	0.196	0.059	0.656

n = 142

SE: standard error; HR: hazards ratio; DM = diabetes mellitus, H/T = hypertension, CVA = cerebrovascular accident.
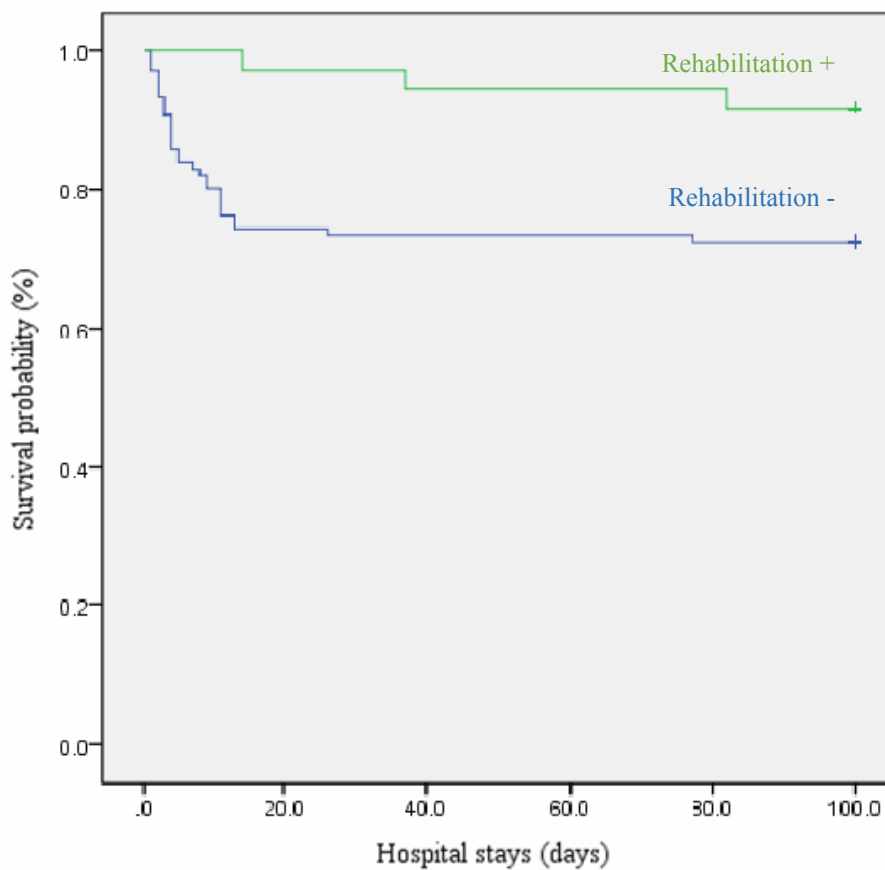Reference groups: patients without rehabilitation therapy for "rehabilitation."

Figure 1. Survival curves for the risk of dengue mortality according to the rehabilitation therapy during hospitalization.

RESULTS

From August to December, 2015, 165 patients were included in the database. After exclusion of 23 patients who were below 18 years old, 142 patients (69.97 ± 15.93 years) were enrolled in this study, including 36 patients (75.97 ± 10.13 years) receiving rehabilitation and 106 (67.93 ± 17.03 years) not receiving rehabilitation. Respiratory distress was managed with mechanical ventilation

(35.2%).

With respect to the demographics of the eligible patients, the prevalence of DM, H/T, and CVA were higher in patients who received rehabilitation than in those who did not (66.7%, 80.6%, and 27.8% each in the rehabilitation group; 43.4%, 57.5%, and 5.7% each in the non-rehabilitation group). No significant difference between the two groups in terms of the incidence of CAD and ESRD was obtained.

Overall, the patients in the rehabilitation group were predominantly older (p = 0.008), longer length of stay (LOS) in hospital (p = 0.001), and higher medical expense (p = 0.006). Furthermore, patients who received rehabilitation had lower risks of mortality than those who did not (8.3% versus 27.9%, p = 0.02; Table 1).

The results of Cox regression using variables which were found to be significant in Table 1 including age, DM, H/T, CVA revealed that patients who received rehabilitation had a lower risk of mortality due to dengue than those who did not receive rehabilitation (HR = 0.196; 95% CI = 0.059–0.656; Table 2). Survival curves were acquired for mortality risks associated with dengue according to rehabilitation therapy during hospitalization (Figure 1).

DISCUSSION

This study is the first to analyze the impact of rehabilitation on the mortality of patients with dengue admitted to the ICU in Taiwan.

First, we found that patients with dengue receiving rehabilitation in the ICU had lower mortality risks (HR = 0.196; 95% CI = 0.059–0.656), which was adverse to the recent results of a randomized controlled study by Schaller and colleagues'.[12] The study examined early and goal-directed mobilization of the patients in the surgical ICU of five university hospitals in different countries. The report stated that rehabilitation programs had a positive impact on mobilization, reduced the LOS, and improved functional mobility. Although in-hospital mortality was higher in the mobilization group, it was nonsignificant. In addition, in another systemic review by Claire and colleagues that included 1753 patients conducted for determining the effect of active mobilization and rehabilitation in ICU on mortality and function demonstrated that rehabilitation programs have no impact on short- and long-term mortalities, but may improve mobility status and muscle strength.[13]

Second, we found that the LOS in the hospital was significantly higher among patients who received rehabilitation (28.68 ± 24.26 days vs 10.34 ± 8.79 days, p = 0.001) than in patients who did not receive rehabilitation. A literature review by Alex et al. of 26 peer review articles revealed ICU LOS to be reduced in several studies examining early rehabilitation, though each study had different protocols for physical therapy.[14] By contrast, another randomized controlled trial conducted in Austria demonstrated that the difference in LOS between the early rehabilitation and control groups was nonsignificant.[15]

Third, we found that medical expenses were higher in the rehabilitation group than in the control group (313.43 ± 348.14 vs 138.62 ± 206.96 thousand NT dollars, p = 0.006). One study showed that rehabilitation in patients with and without mechanical ventilation could reduce the LOS and average daily cost in the ICU, resulting in an annual net cost savings of 1.5 million dollars.[16] Another study found that the implementation of the rehabilitation program not only reduced LOS from 6.5 to 5.8 days but also resulted in a reduction of 12.0 million dollars in medical expenses from February 2011 through the end of December 2013.[17]

Our study had some limitations. First, this was a retrospective cohort study, and hence, the lack of objective criteria for who received rehabilitation or who did not is a major concern. Second, the selection bias may be presented in our study. There might be arguments that only patients with stable hemodynamics were capable of receiving rehabilitation and would definitely have a better outcome. However, the severity scales such as APACHE II and TISS between two groups didn't show significant difference though. Still, we couldn't exclude the possibility of the presence of selection bias. Third, the numbers of the subject are relatively small, which could cause imprecision of the statistics. Thus, further studies with a prospective randomized control design are required to confirm and improve our results.

CONCLUSION

We found that rehabilitation is associated with lower the risk of mortality in patients with dengue in the ICUs. However, further randomized control trials are required to consolidate this effect.

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復健與加護病房內登革熱病人較低的死亡率相關－回溯性研究

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研究目的：研究復健對於因登革熱重症進入加護病房病人死亡率的影響。

研究設計：本研究爲回溯性世代追蹤研究。收案期間自 2015 年 8 月至 12 月，共有 142 位病人因登革熱重症進入加護病房。透過資料回溯復健的有無，將病人族群分成復健組與無復健組，並進行相關的資料分析。其中，使用 Cox 迴歸分析顯著影響死亡率的變數。

結果：142 位病人平均年齡爲 69.97 ± 15.93 歲，70 位病人(49.3%)爲男性，平均待在住院時間爲 14.79 ± 16.14 天。Cox 迴歸分析發現有復健的登革熱重症族群死亡的風險比(hazard ratio, HR)爲 0.196 (95%信賴區間爲 0.059 – 0.656)。

結論：復健與加護病房內登革熱病人較低的死亡率相關。未來需要更進一步的隨機對照試驗去確定此一研究的因果關係。（台灣復健醫誌 2020；48(2)：105 - 111）

關鍵詞：復健(rehabilitation)，重症加護病房(ICU)，死亡率(mortality)，登革熱(dengue)