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ORIGINAL COMMUNICATION

Impact of virtual reality-based rehabilitation on functional outcomes in patients with acute stroke: a retrospective case-matched study

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Abstract

Background and objectives To date, the efficacy of the virtual reality (VR) application for acute stroke compared with conventional therapy (CT) remains unclear. This retrospective study aims to assess the impact of adjuvant VR technology on multidimensional therapy for patients with acute-stage stroke.

Methods 100 acute ischemic stroke patients with onset within 7 days who underwent combined adjuvant VR-based rehabilitation program and CT (intervention group–VR + CT) were compared to an equal number of cross-matched patients who received CT alone. While the intervention group received 40-min CT plus 20-min VR program (seven times for 1 week), the comparison group received time-matched CT alone. The National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), medical cost-effectiveness, and shortening of hospital stay were used as outcome measures.

Results Posttreatment, the VR + CT group revealed significantly improved NIHSS and mRS ($P < 0.001$), whereas only the mRS improvement was remarkable in the CT group. In between-group comparisons, the intervention group had better improvements of symptom severity (NIHSS percentage improvement from the baseline; 20.18% vs. 4.59%, $P < 0.005$), functional outcomes (mRS improvement from the baseline; −0.58 vs. −0.23, $P < 0.001$), and reduced medical cost (Taiwan dollar; 49474 vs. 66306, $P < 0.005$). Furthermore, the VR + CT group reached markedly higher proportion of functional independence in activities of daily living (mRS, 0–2) at discharge compared with the CT group (68% vs. 60%, $P < 0.001$).

Conclusions This study suggests that the combination of VR-based rehabilitation and traditional therapy could be more effective for neurorehabilitation than CT alone in the early improvement of symptom severity, functional outcomes, and lower medical expenditure in acute stroke patients.

Keywords Virtual reality · Neurorehabilitation · Acute stroke · National Institutes of Health Stroke Scale · Modified Rankin Scale · Activities of daily living · Lower medical expenditure

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Introduction

Stroke is an essential global health-care issue, being the second leading cause of death and the third leading cause of disability worldwide. Stroke poses a substantial economic and social burden, affecting millions of people globally. A stroke can result from ischemic (85%) or hemorrhagic (15%) brain injury. The primary poststroke sequelae vary depending on the location and severity of brain lesions attributed to sensory, motor, and cognitive impairment, which could result in sensorimotor functional impairment; this could cause changes in balance, affecting motor control in the execution of daily activities, increase the risk of falls, and might lead to severe injuries [1–5]. Approximately, 55–80% of stroke survivors experience persistent functional limitations associated with the declined quality of life [5–9], thereby necessitating poststroke functional recovery in these individuals.

Neurorehabilitation is critical in the treatment of patients with stroke, as it can enhance the neurological recovery and elicit neuroplastic adaptations [6]. Most neuroplastic changes occur during the early stages of stroke, thereby maximizing the possibility of recovery [10]. A recent neurophysiological study [6] reported superior functional recovery after 6 months in patients who received rehabilitation earlier within 1-week poststroke than in those who started within 1 month. If interventions were initiated promptly, functional recovery could be improved, and disability could be minimized because of the remarkable potential of brain remodeling during this period [9–13].

During recovery, patients have to relearn voluntary control over the affected muscles. In conventional therapy (CT), relearning through physical and occupational therapies is based on one-to-one therapist–patient interactions, which focus on high-intensity, repetitive, and task-specific practice. These therapeutic modalities are vital for effective therapy in all stages after stroke [7]. Furthermore, active performance and motivation correlate with superior rehabilitation outcomes [6, 14].

Virtual reality (VR) is an innovative technology that is extensively applied in clinical trials in the stroke rehabilitation field [11]. VR comprises using interactive simulations created with computer–human interfaces to present users with opportunities to engage in three-dimensional environments that appear and feel similar to the real world. Patients with stroke can perform real-time tasks and interact with virtual objects. Moreover, it offers augmented performance-derived kinematic feedback during training and simultaneously boosts repetitive task-oriented practice, thereby facilitating sensorimotor recovery [3, 7, 9, 12].

Reportedly, VR produced positive results in subacute-to-chronic stroke patients with significant improvement, mainly in the function of extremities [7, 11, 12, 15, 16]. However, limited data and small sample sizes in studies [10, 11, 15, 17] comparing VR training to CT for stroke therapy limit conclusive results on VR effectiveness. The prognosis of poststroke neurological functional recovery comprises various domains beyond the improvement of muscle strength of paretic extremities. There is a lack of global examination of clinical benefits and usability of VR training at the initial stages of acute stroke. Hence, this study aims to assess the efficacy of early intervention in adjuvant VR technology at the initial stage (especially, onset time within 7 days) of acute stroke patients with larger sample size and investigate how VR therapies affect different clinical outcomes using more versatile measures.

Methods

Study patients

Patients with dysfunction due to acute ischemic stroke considered for the study were screened from admissions to the Stroke Center of Department of Neurology, Tri-Service General Hospital, National Defense Medical Center (Taipei, Taiwan) during June 1, 2016–June 1, 2017. Based on the previous evidence of efficacy of the adjuvant VR [7, 11, 12, 15, 16], the rehabilitation program in our hospital offered adjuvant therapy with VR for all poststroke patients to select voluntarily. In accordance with this optional additional therapy, patients with acute ischemic stroke who underwent combined CT and VR programs (VR + CT group) were compared with an equal number of cross-matched patients who received CT alone (CT group). The inclusion criteria were as follows: (1) diagnosis of acute ischemic stroke with the onset time < 7 days; (2) minor to moderate stroke severity as defined by the National Institutes of Health Stroke Scale (NIHSS) score ≦ 16; (3) limited effort against gravity in limbs' motor performance as defined by NIHSS subitem score of motor arm/leg ≦ 2, thus able to maintain posture unaided while sitting in a wheelchair or at the edge of the bed; and (4) clear consciousness with the ability to understand CT/or VR instructions. The exclusion criteria were as follows: (1) severe stroke (NIHSS score ≧ 17); (2) diagnosis of global aphasia or transient ischemic attack; (3) visual or auditory impairment with the inability to clearly see or hear the feedback from the VR and CT; (4) evidence from neurological examination or report in the patient's clinical history of apraxia and neglect syndrome that could affect the compliance with the rehabilitation programs; and (5) other medical comorbidities that could affect movement.

Those criteria were decided by study design meetings for the feasible screening, within a defined population of post-acute stroke patients without severe neuropsychological impairments, most likely capable of managing the interaction with a rehabilitation setting, independently of their outcomes at baseline.

This study was approved by the Institutional Review Board on Human Subjects Research and Ethics Committees of Tri-service General Hospital, National Defense Medical Center, Taiwan.

Study protocol

Case matching and allocation were performed with respect to age-, sex-, comorbidity-, stroke subtype-, and stroke severity-matched two treatment groups. While the intervention group received a 40-min CT plus 20-min VR program (seven times for 1 week), the comparison group received time-matched CT alone. Both groups resumed standard training regimens 1 week later and kept maintenance exercises after discharge.

CT comprised range of motion (ROM) exercises, fine motor training, strengthening limb exercises, and cognition rehabilitation contributed by these aforementioned programs. The ROM exercises and coordination training comprised an overhead pulley, the range of motion arc, and inserting rings to a horizontal bar. Fine motor training comprised turning coins, finger taps, and inserting an object into small holes in a pegboard. Strengthening exercises comprised upper body exercises and weight pulley exercises. Balance training comprised standing and weight shifting. Each exercise took approximately 5 min.

The VR device comprised the Kinect sensor (Microsoft Corporation, Redmond, WA) incorporating infrared light, a video camera, a television monitor, and a number of VR programs. Patients in the intervention group were treated in a 20-m^2 room equipped with the apparatus mentioned above; this provided a spacious environment free from external noise to perform activities without hindrance. The wireless device could capture full-body images and project it to the monitor in real time, allowing patients to become immersed in the VR scene and interact with virtual environments and objects. Patients could see their body movements, allowing them to move freely in the real world while manipulating virtual objects in the 3-D virtual world. We selected four software programs for training, designed to incorporate an appropriate level of challenge to match the ability and fitness of people with stroke. The first program was Reaching task (aimed at ROM and coordination training); patients were instructed to reach toward a stationary target at a given location of different heights, depths, and directions. The second program was Tracing task (aimed at strengthening exercises and upper-extremity ROM training); patients were instructed to track a moving airplane by lengthening the arm and immersing the hand as it flew in 3D space. The third program was Kung Fu-Soccer (aimed at strengthening lower-extremity exercises, balance training, and trunk stabilization); patients were instructed to raise the leg and kick upcoming soccer from varying heights and directions. The final task was cognition training; patients were instructed to perform basic mathematical calculations, serial number arrangement according to value, color discrimination, and vocabulary comprehension. These four programs could be performed either standing or seated. Each program was performed for approximately 5 min, with instructions given by a physical therapist, followed by a break of 1 min between programs. During the training, the challenge level was progressively increased by adjusting the amplitude, frequency, speed, complexity, and number of hints.

Outcome measures

In this study, we used the NIHSS score, modified Rankin Scale (mRS) score, derived subitems from the NIHSS and mRS including progress in the NIHSS or mRS (ΔNIHSS or ΔmRS, which was indexed by subtracting values of the score at admission from that at discharge), NIHSS percentage improvement from the baseline (ΔNIHSS%), medical cost-effectiveness, and shortening of the hospital stay as outcome measures. The NIHSS score, a stroke scale established by the National Institutes of Health in the 1980s, is an objective assessment scale to quantify the impairment caused by stroke, covering the following 11 major items: consciousness, eye movement, visual field, facial paralysis, upper and lower limb muscle strength, limb ataxia, sensation, language, dysarthria, and inattention; each item is scored between 0 and 4, where 0 typically indicates normal function for that ability, while higher scores indicate a level of impairment. The total score ranged from 0 to 42 points; the higher the score, the higher was the stroke severity. Although this is not a complete neurological examination, it covers vital neurological assessments and is quantifiable. Neurologists and non-neurologists, nurses, and technical staff with proper training can assess while maintaining credibility [18, 19].

The mRS, a grading scale to measure the global disability or dependence in daily activities of patients with a stroke or other causes of neurological disability, is used to evaluate functional outcomes in this study. The scale runs from 0 to 6, where 0 indicates perfect health without symptoms; 1, no significant disability (able to execute all usual duties and activities); 2, slight disability (unable to execute all previous activities, but able to look after own affairs without assistance); 3, moderate disability (requiring some help, but able to walk unassisted); 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); and 6, death [20]. Of note, it is the most widely applied scale for assessing stroke recovery [18, 21, 22]. All

NIHSS and mRS assessments were performed by clinical staff between admittance and discharge. Medical costs (Taiwan dollar, TWD) billed by the hospital to the Bureau of National Health Insurance on behalf of each patient across the entire hospitalization period were collected.

Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences, version 22.0 (SPSS Inc., Chicago, IL). We defined the statistical significance as $P < 0.05$. Descriptive statistics were generated for all variables, and distributions of variables are expressed as the mean ± standard deviation. Differences in demographic and clinical characteristics between the two treatment groups at baseline were analyzed using Chi-square test, whereas the mean age difference was analyzed with a *t* test. Furthermore, paired *t* test was used to compare the differences between the preintervention and postintervention.

Results

We initially examined 263 patients with acute stroke between June 2016 and June 2017. Of these, 63 patients were not enrolled to be analyzed, primarily because clinical conditions did not fulfill the inclusion criteria owing to medical comorbidities or poor willingness to attend routine rehabilitation programs. One hundred patients with acute ischemic stroke fulfilled the inclusion criteria who underwent combined CT plus adjuvant VR-based rehabilitation program were compared retrospectively with 100 cross-matched patients who received time-matched CT alone. The demographic and baseline clinical features of the study patients did not differ markedly between the two treatment groups on

Table 1 The demographic and clinical characteristics of 200 registered patients

	VR + CT group (*n* = 100)		CT group (*n* = 100)		*P* value
	n	%	*n*	%	
Demographic					
Mean age (mean ± SD, years)	67.97 ± 11.38		67.68 ± 11.13		0.855
Male sex	64	64.00	61	61.00	0.661
mRS on admission					0.790
0	0	0	1	1.00	
1	27	27.00	27	27.00	
2	29	29.00	27	27.00	
3	15	15.00	19	19.00	
4	29	29.00	26	26.00	
5	0	0	0	0	
NIHSS on admission					0.521
0–7	89	89.00	86	86.00	
8–16	11	11.00	14	14.00	
≧ 17	0	0	0	0	
Risk factors					
Hypertension	68	68.00	62	62.00	0.374
Diabetes	42	42.00	34	34.00	0.244
Hyperlipidemia	54	54.00	54	54.00	0.999
Smoking	39	39.00	28	28.00	0.099
Atrial fibrillation	15	15.00	12	12.00	0.535
History of stroke	27	27.00	29	29.00	0.753
History of coronary events	22	22.00	11	11.00	0.036*
Stroke subtype					0.015*
Large artery atherosclerosis	51	51.00	36	36.00	
Small vessel occlusion	31	31.00	47	47.00	
Cardioembolism	10	10.00	15	15.00	
Others	8	8.00	2	2.00	

VR virtual reality, *CT* conventional therapy, *SD* standard deviation, *NIHSS* National Institutes of Health Stroke Scale, *mRS* modified Rankin Scale

*$P < 0.05$ with the Chi-square test or *t* test

admission (Table 1 presents information about 200 enrolled patients; intervention group: 100 patients of whom 64% were males, mean age: 67.97 ± 11.38 years; comparison group: 100 patients of whom 61% were males, mean age: 67.68 ± 11.13 years). Posttreatment, none of the patients in either group expressed fatigue or other significant adverse events associated with the overall treatment protocol.

We used the NIHSS and mRS for within-group comparisons. The derived subitems including ΔmRS, ΔNIHSS, and ΔNIHSS%, associated with medical cost and hospital stay, were used for between-group comparisons. Table 2 presents the improvement between pre- and posttreatment by early rehabilitation (either VR + CT or CT) in within-group comparisons. The intervention group exhibited statistically significant improvement in both mRS and NIHSS scores ($P < 0.001$). Compared with the intervention group, the comparison group exhibited significant improvement only in the mRS, but not in the NIHSS ($P > 0.05$). Table 3 shows the posttreatment intergroup analysis. The intervention group demonstrated better results in the percentage change of stroke severity improvement (ΔNIHSS%; 20.18% vs. 4.59%, $P < 0.005$), functional outcome progress (ΔmRS; − 0.58 vs. − 0.23, $P < 0.001$), and medical cost-effectiveness (TWD; 49,474 vs. 66,306, $P < 0.005$) compared with those of the comparison group. We observed no significant difference in the remaining parameters (ΔNIHSS and shortening the hospital stay) between the two groups. Regarding the population of functional independence in activities of daily living (ADL; representation for mRS ≦ 2), the VR + CT group attained significantly higher proportion of better mRS outcome (68%) at discharge compared with the CT group (60%, $P < 0.05$). Figure 1 presents this distribution.

Discussion

This study identified the potential efficacy and feasibility of early intervention with add-on VR technology at an early stage for patients with acute stroke. We evaluated 200 patients immediately after the intervention and reassessed at discharge to verify the therapeutic effects. In addition, patients enrolled in the study were allocated into two groups by a retrospective cross-matching method to minimize study bias. As patients' demographic and baseline characteristics did not differ significantly, each group was set in a similar clinical background.

In this study, within-group comparisons revealed the improved functional recovery (ΔmRS) postintervention of early rehabilitation for either training. The descriptive results of the intergroup analysis revealed an increase in the clinical benefit immediately after add-on VR therapy beyond CT for reducing the stroke severity (ΔNIHSS%) and functional ability in daily activities (ΔmRS). Furthermore, we observed a markedly higher proportion of independence capacity in ADL (mRS score, 0–2) in the intervention group at the time of discharge. As the intervention group exhibited better results, we anticipated a marked impact on shortening hospital stays; however, this was not the case. Although the

Table 2 Improvement of mRS and NIHSS after intervention—within-group comparison

	VR + CT group (*n* = 100)			CT group (*n* = 100)		
	Preintervention	Postintervention	*P* value	Preintervention	Postintervention	*P* value
mRS	2.46 ± 1.18	1.88 ± 1.23	< 0.001***	2.42 ± 3.04	2.19 ± 1.27	< 0.001***
NIHSS	3.36 ± 2.90	2.72 ± 2.63	< 0.001***	3.91 ± 3.04	3.62 ± 3.31	0.151

***$P < 0.001$ with the paired *t* test. Values are presented as mean ± standard deviation

VR virtual reality, *CT* conventional therapy, *NIHSS* National Institutes of Health Stroke Scale, *mRS* modified Rankin Scale

Table 3 The outcome analysis postintervention—intergroup comparison

	VR + CT group (*n* = 100)	CT group (*n* = 100)	*P* value
ΔmRS	− 0.58 ± 0.68	− 0.23 ± 0.62	< 0.001***
ΔNIHSS	− 0.64 ± 1.90	− 0.29 ± 2.00	0.206
ΔNIHSS%	− 20.18 ± 53.43	− 4.59 ± 58.08	0.005**
Hospital stay (days)	9.92 ± 6.44	10.46 ± 11.83	0.689
Medical cost (TWD)	49,473.66 ± 37,653.51	66,305.77 ± 123,167.06	0.042*

Values are presented as mean ± standard deviation. ΔmRS or ΔNIHSS was indexed by subtracting values of the score at admission from that at discharge

VR virtual reality, *CT* conventional therapy, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale, *ΔmRS* mRS change from the baseline, *ΔNIHSS* NIHSS change from the baseline, *ΔNIHSS%* NIHSS percentage improvement from the baseline, *TWD* Taiwan dollar

*$P < 0.05$ with the *t* test. **$P < 0.01$ with the *t* test. ***$P < 0.001$ with the *t* test

a

Distribution of mRS	0	1	2	3	4	5
VR+CT group (n=100)	12	33	23	19	13	0
CT group (n=100)	6	31	23	19	20	1

b

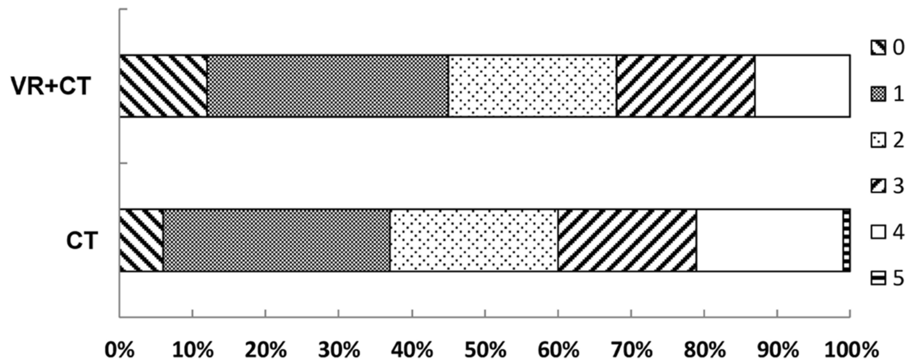

Fig. 1 **a** The distribution of the mRS at discharge: an intergroup comparison. **b** The stacked bar histogram demonstrates that the VR + CT group achieved a significantly higher proportion of functional independence in ADL (mRS, 0–2; 68%) at discharge than the CT group (60%, $P < 0.05$). *mRS* modified Rankin Scale, *VR* virtual reality, *CT* conventional therapy, *ADL* activities of daily living

intervention group tended to present with shortened hospital stays, we observed no significant difference between the groups; this could be possibly attributed to the high level of patients' satisfaction in the intervention group at the end of this optional additional training. Indeed, 15 patients of the VR + CT group requested for a longer stay to continue using VR facilities. Notably, the intervention group exhibited marked medical cost-effectiveness compared with that of CT alone, highlighting the clinical benefit of the combination treatment.

Recent studies have investigated the reliability of VR therapy for subacute-to-chronic stroke patients. Most studies [3, 5, 8, 12, 16, 17, 23–26] have explored motor recovery of the upper limb and exhibited robust effects independent of stroke etiology in favor of combined VR therapy over CT. A systematic review [1, 13, 16, 27] suggested that VR was not a substitute for conventional rehabilitation and proposed that combination therapy could reach the best synergistic effect for individuals with stroke; this supports Kim et al. demonstrating that cognitive function improved remarkably in patients with stroke who received a combination VR training compared with those who only received VR training [4].

Research regarding the application of VR at acute-to-subacute phase poststroke is limited. Most studies [6, 10, 11, 15] comprised sample sizes that were too small (all < 30 patients; 2–4 studies used descriptive statistics analysis) to draw definitive conclusions. Nonetheless, most investigations focused on the motor recovery of upper limbs measured with the muscle strength grading and Fugl-Meyer assessment scales; these investigations suggested that the utilization of VR in acute-to-subacute stroke individuals exhibited a positive impact on restoring the upper extremity impairment, consistent with previous studies demonstrating the usability of VR in patients with chronic stroke. Tim et al. used VR to train the upper limb function in the early rehabilitation phase of patients with stroke as an assistant device to CT with favorable results, validating the higher compliance, participation rate, and remarkable improvements in hand dexterity [6]. Similarly, Laver et al. reported that patients with low-to-moderate upper limb impairment might have the greatest benefit when the VR intervention was delivered in the acute, rather than chronic, phase of stroke [9, 23].

However, the overall poststroke neurological functional recovery is more than the performance of the muscle strength of affected extremities; it includes various domains such as speech, cognition, executive function, and ADL. To date, the examination of the clinical relevance of VR training remains inadequate. Furthermore, no study has yet explored its application at a very early stage for patients with stroke, especially those whose onset time was within 7 days.

Compared with other studies, this study was based on a larger sample (200 patients were enrolled and registered) associated with the assessment of treatment validity using multidimensional measurements; this enabled higher statistical power for the inferential analysis. We observed that the intervention group exhibited expedited functional recovery. An improvement in the stroke severity postintervention could be attributed to multidimensional tools and approach used to evaluate outcomes other than extremity muscle power. This study is the first to evaluate the usability of VR as adjunctive therapy in acute stroke phase for patients whose onset time was within 7 days, using the NIHSS and mRS scales besides using medical cost-effectiveness and length of hospital stay as measurement tools for the global functional assessment.

The NIHSS comprises 11 major subitems and covers crucial neurological assessment; its advantage is that it objectively assesses all aspects of stroke severity. Similarly, the mRS represents the poststroke dependence of people in their daily activities. Several studies [18, 19, 21, 22] have reported that the NIHSS and mRS values correlate with the global functional outcome poststroke, and they have become the most widely applied scales for evaluating stroke recovery. In this context, although there was an improvement in the mRS postintervention in either training group, the improvement was inadequate to attain independence in ADL. In addition, we surveyed the population with mRS $\leqq$ 2 at the time of discharge as a representation of independence in ADL. The intervention group contained a markedly higher proportion of individuals capable of performing ADL without assistance. These data suggest that patients who received CT alone could be improved further by applying adjuvant therapy with VR training. Hence, a complementary approach with VR was superior to a standard rehabilitation regimen in the improvement of severity (represented as the NIHSS) and enhancement of the ADL performance, facilitating participation in social and daily activities, subsequently affecting their quality of life.

The reasons for the practical nature of VR in this study are multifold. First, a commercial game is designed primarily for leisure and might be unsuitable for stroke rehabilitation, as the target movements for training are not necessarily the ideal adaptive response. In contrast, the VR equipment in this study was designed explicitly for neurorehabilitation in the poststroke phase rather than marketed for entertainment gaming. The software programs in this study aimed at training the muscle strength and executive function of the paretic limbs, stabilization of the trunk, as well as impaired cognition and memory. In addition, using interprofessional cooperation and knowledge exchange between engineers of computer-based devices and supervising therapists as experts of human movements and patient-centered needs, this approach could facilitate therapists in instructing patients to adapt to specific rehabilitative purposes. We attribute these descriptive results to the types of VR programs selected during the treatment. Furthermore, personal progress could be recorded in the integrated software, and a feedback option was provided. Finally, the wireless Kinect sensor used in this study was user-friendly, eliminating the need to attach additional markers to the hands, making the modality more beneficial than other VR apparatus such as virtual gloves or exoskeletons [6].

Several possible mechanisms exist for the beneficial effects obtained by VR as an accessory tool in the sensorimotor training of individuals poststroke. The kinematic feedback of visual, vestibular, and somatosensory feedback from VR could modulate a neural network in the motor, premotor, and parietal cortex, generate an immediate self-correction, activate mirror neuron firing, and augment cortical reorganization [3, 7, 9, 11, 12, 15, 24, 25]. Considering the concepts from taxonomy-based multitask learning models, VR therapy could provide a higher number of repetitions for task-oriented training by dynamic stepwise adjustment of difficulty levels; this would reinforce the ability to use the paretic limbs voluntarily and spontaneously in a natural environment for meaningful activities and decrease patients' frustration, thereby activating neuroplasticity in the fields of motor and cognition simultaneously [1–3, 7, 9, 12, 23]. Compared with conventional methods, VR training provides a more motivational, interactive, and pleasurable environment, making it less stressful for patients to engage in the program during the score performance [1, 2, 14, 16]. Furthermore, the variation of sensory environments in VR could provide patients more safety than CT for performing activities that require greater control of postural stability [1], such as the Kung Fu-Soccer program in this study.

This study has several limitations. First, because of the lack of additional brain imaging, there is incomplete evidence supporting specific benefits of VR at the level of cortical neuroplasticity [1, 10, 12, 14, 15]. This pragmatic study was aimed at comparing the effect of the VR therapy with standard treatment in a real clinical setting, thus a non-randomized technique was used for patients' allocation. This approach makes the detection of possible confounding factors difficult, biasing our findings. Although the cross-matching paired patients were assigned to each group, it is possible that patients using the new VR technology were more motivated than patients receiving CT. Second, the optimal duration of the VR treatment (2–22 h) is variable and unclear [1]. In addition, we cannot exclude the potential for spontaneous recovery given that the stroke was in the acute phase; thus, the restoration may not have reached a plateau [15]. Owing to the short experimental period and the lack of postintervention follow-up, we were unable to determine whether VR had a sustained impact. Furthermore, for ethical reasons, routine rehabilitation therapy was not withheld. As all patients received maintenance exercises after the end point, no information could be identified on the mixed effects. Hence, an adequate longitudinal follow-up is warranted to systematically examine whether VR merely speeds up recovery or it could markedly enhance recovery. Based on the supporting evidence of the better effectiveness in VR-based rehabilitation for acute stroke individual in our study, future directions for research applying a similar designed therapy in prospective randomized controlled multicenter trials were encouraged.

Conclusions

This study emphasizes that in the aftermath of an acute stroke, the combination of VR-based rehabilitation and traditional restorative approaches could be more effective than conventional rehabilitation alone in the early improvement of symptom severity, functional outcomes, and lower medical cost. Thus, the VR program could be a valuable supplemental option for early neurorehabilitation in an acute inpatient setting. However, for VR-based training to enter the routine practice of the acute stroke rehabilitation and be a substitute for CT, further high-quality randomized controlled clinical trials with long-term, follow-up periods are warranted to establish the optimal dosage, duration, and frequency for the individualization of VR protocols for different patients.

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Author contributions J-TL and F-CY designed the study and prepared the ethics application documents. T-HH compiled the majority of the manuscript. R-CL, S-LC, C-HC, C-KT, C-LT, and Y-KL participated in study design meetings. W-CC and C-HC carried out the data analysis; All authors read and approve the final manuscript.

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Compliance with ethical standards

Ethical approval The study was approved by the Institutional Review Board on Human Subjects Research and Ethics Committees of Tri-Service General Hospital, National Defense Medical Center, Taiwan. (TSGHIRB No. 1-106-05-041).

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