

Auxiliary effect of clopidogrel on neurological rehabilitation in patients with post-stroke motor disorders

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Abstract: This study investigates the auxiliary effect of clopidogrel on neurorehabilitation in patients with post-stroke movement disorders to evaluate its efficacy in rehabilitation treatment. A randomized controlled study is conducted, dividing patients into a conventional treatment group and a clopidogrel treatment group. The Fugl-Meyer score, Barthel Index, and NIHSS score are employed to assess and compare the patients' motor function, daily activity ability, and neurological function before and after treatment. The scores for the Experimental Group exceed those of the Control Group for all measures, with p-values less than 0.05 or 0.01. These results indicate that the clopidogrel treatment group outperforms the conventional treatment group in stroke rehabilitation. This study examines clopidogrel's auxiliary effect through a long-term experiment on the rehabilitation of patients with post-stroke movement disorders, offering new treatment ideas and methods for clinical practice.

Keyword: Clopidogrel medication; rehabilitation therapy; post-stroke motor disorders; recovery of motor function; neurological function

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INTRODUCTION

Stroke remains a leading cause of death and long-term disability worldwide, primarily caused by the blockage or rupture of cerebral blood vessels. This condition significantly affects patients' quality of life and imposes economic burdens on both families and society (Tosto-Mancuso *et al.*, 2022; Wolf *et al.*, 2022). Common post-stroke motor disorders, such as paralysis, ataxia, and muscle weakness, further limit daily activities for affected individuals (Beghi *et al.*, 2021). Traditional rehabilitation methods-encompassing physical, occupational, psychological, and speech therapy (Zafarovna, 2022; Eschweiler *et al.*, 2021; Yoon *et al.*, 2021) - often achieve limited success due to individual variability in recovery. Emerging techniques, including transcranial stimulation, robot-assisted therapy, virtual reality, and functional electrical stimulation, show promise for improving motor function. However, challenges such as varying efficacy and high costs remain (HHuo *et al.*, 2021; Aloraini, 2022).

Rehabilitation therapy for post-stroke motor disorders remains a prominent research focus (Kelly *et al.*, 2021). As medicine and technology advance, rehabilitation methods for these disorders have seen continuous improvement (Kwakkel *et al.*, 2023). The high incidence and disability rates associated with stroke drive the exploration of more effective rehabilitation strategies. Traditional therapies include physical, occupational, and speech therapy, as well as psychotherapy. While these methods can partially improve motor function, their effects are often suboptimal. Recently, the antiplatelet drug clopidogrel has garnered attention in stroke research. Studies indicate that

clopidogrel effectively reduces thrombosis by inhibiting platelet aggregation, thereby decreasing the risk of stroke recurrence (Watanabe *et al.*, 2022). Additionally, clopidogrel offers a neuroprotective effect, as it mitigates ischemia-reperfusion injury in brain tissue, reduces inflammation, and promotes the survival and regeneration of nerve cells (Gimbel *et al.*, 2020). Long-term follow-up studies of stroke patients reveal that those taking clopidogrel demonstrate significantly better motor function recovery during rehabilitation compared to those who do not (Silvain *et al.*, 2020).

Further exploration of clopidogrel's combined use with other rehabilitation methods, such as repetitive transcranial magnetic stimulation (rTMS), has shown promising results. Timm *et al.* (2021) found that combining clopidogrel with rTMS significantly enhanced motor function recovery. rTMS generates electrical currents in the cerebral cortex, regulates neural activity, and promotes neural recovery, thus complementing clopidogrel's pharmacological benefits.

In developed countries, rehabilitation research for post-stroke motor disorders has made significant advancements. Multiple clinical trials in the United States and Europe demonstrate that clopidogrel (Hiatt *et al.*, 2020) is highly effective in preventing cardiovascular and cerebrovascular diseases and also exhibits a degree of neuroprotective effect. A relevant research team verifies through a double-blind randomized controlled experiment that clopidogrel (Verma *et al.*, 2020) is effective in improving motor function in stroke rehabilitation.

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Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are two widely used neuromodulatory technologies in stroke rehabilitation (Rahayu *et al.*, 2020), both of which have yielded positive results in enhancing patients' motor function. Robotic-assisted therapy and virtual-reality therapy are also prominent topics in stroke rehabilitation research. Robotic-assisted therapy employs advanced mechanical apparatus to facilitate extensive physical training, thereby restoring motor abilities. Virtual-reality therapy enhances patients' enthusiasm for training by creating an immersive environment, thus boosting the effectiveness of rehabilitation.

Functional electrical stimulation therapy is an emerging option in stroke rehabilitation. Studies indicate that it can effectively enhance motor abilities (Mawase *et al.*, 2020). Researchers have explored combining clopidogrel with new rehabilitation techniques (Zandvliet *et al.*, 2020) to identify comprehensive treatment strategies. Findings suggest that the combination of clopidogrel and robotic-assisted therapy significantly improves motor function in post-stroke patients. As an antiplatelet drug, clopidogrel is increasingly recognized for its supportive role in neurological rehabilitation. Integrating clopidogrel with other rehabilitation methods is expected to further enhance recovery outcomes and the quality of life for post-stroke patients.

Clopidogrel is an antiplatelet drug widely used to prevent cardiovascular disease, and, as reported by Lee *et al.* (2022), it can also prevent stroke recurrence by inhibiting platelet aggregation while providing certain neuroprotective effects. According to Wang *et al.* (2021), clopidogrel supports the regeneration and repair of nerve cells. To explore clopidogrel's role in neurorehabilitation, a controlled trial is conducted (Lun *et al.*, 2022; Kang *et al.*, 2023). The experiment involves various rehabilitation treatments, divided into several experimental and control groups. Patients in control groups 1 through 5 receive functional electrical stimulation therapy, virtual-reality therapy, robot-assisted therapy, neuromodulation technology therapy and conventional rehabilitation therapy, respectively (Levin & Demers, 2021). Meanwhile, patients in experimental groups 1 through 5 receive the same treatments as the control groups, with the addition of clopidogrel (Valeria *et al.*, 2021).

The study assesses clopidogrel's supplemental function in different stroke rehabilitation regimens by comparing the therapeutic outcomes of patients across the groups. Evaluation indicators include motor function, daily living ability, and neurological function (You *et al.*, 2020). Systematic evaluation and analysis verify whether clopidogrel has an auxiliary role in the neurorehabilitation of stroke patients (Meschia *et al.*, 2020).

MATERIALS AND METHODS

Patient selection and grouping

The patient selection criteria are as follows: age between 50 and 75 years, at least 6 months post-first stroke, mild to moderate motor disorders, absence of serious comorbidities or other diseases affecting rehabilitation outcomes, and the ability to understand and sign an informed consent form. The exclusion criteria are: severe dysfunction of the heart, liver, or kidneys; allergy to clopidogrel; current use of drugs affecting platelet function; severe mental or cognitive impairment. The treatment is administered three to five times per week for 6 months. The treatment method is depicted in fig. 1.

According to the selection criteria, patients can be randomly divided into control and experimental groups, with each category containing five groups of 20 individuals.

Control group 1 receives routine rehabilitation – physical, occupational, psychological, and speech therapy – 3 to 5 times weekly for 6 months; Control group 2 follows the same regimen plus neuromodulation; Control group 3 adds robot-assisted therapy; Control group 4 adds virtual-reality therapy; Control group 5 adds functional electrical stimulation. Experimental group 1 receives conventional rehabilitation plus clopidogrel 75 mg daily; Experimental group 2 combines rehabilitation, neuromodulation, and clopidogrel 75 mg daily; Experimental group 3 combines rehabilitation, robot-assisted therapy, and clopidogrel 75 mg daily; Experimental group 4 combines rehabilitation, virtual-reality therapy, and clopidogrel 75 mg daily; Experimental group 5 combines rehabilitation, functional electrical stimulation, and clopidogrel 75 mg daily. All interventions last 6 months.

The gender distribution and stroke type proportions of the enrolled patients are summarized in fig. 2.

Treatment time and follow-up

During the treatment period, monthly follow-ups are conducted to separately record patients' motor functions. These follow-ups use the Fugl-Meyer Scale, the Barthel Index, and the NIHSS Scale (Everard *et al.*, 2021; Saes *et al.*, 2022) to quantify motor function and daily living abilities. Detailed physical examinations are performed for each patient to objectively assess recovery of motor function. The study documents patient performance during rehabilitation training (Terry & Kayes, 2020), observing changes in balance ability and muscle condition.

After treatment, patients are followed for 12 months, with comprehensive evaluations conducted every 3 months to assess the durability of the treatment effect. Follow-up involves continuous monitoring of patients' motor function and daily living abilities. Regular laboratory tests are conducted to ensure patients remain in good physical condition. Questionnaires and face-to-face interviews are

employed to understand changes in patients' lives and evaluate their self-care capabilities.

The t-test is employed to analyze gender and disease types across various control and experimental groups. All P-values are greater than 0.05, indicating no statistical significance. Consequently, gender and disease type do not influence the comparison results between the control and experimental groups.

RESULTS

Evaluation and experimental effects

This study compares the therapeutic effects between control groups and experimental groups by evaluating the following indicators:

Motor function

The changes in Fugl-Meyer score can be used to evaluate the recovery of motor function, and the scoring criteria are shown in table 2.

Daily living ability

The change in the Barthel Index can be used to evaluate daily living ability, and the scoring criteria are shown in table 3.

Recovery of neurological deficits can be evaluated by assessing changes in the NIHSS score. The scoring criteria are detailed in table 4.

During the experiment, patient data is collected and processed using the SPSS 18.0 statistical software package. Basic statistics, including mean, standard deviation, and median for each variable, are calculated. Additionally, histograms, box plots, and other graphs are generated to visually display the data distribution.

In the t-test, the p-value indicates significance. A p-value greater than 0.05 suggests the results are not significant. Conversely, a p-value less than 0.05 implies significance, indicating a real difference not attributable to random factors. When the p-value is less than 0.01, the result is considered very significant, meaning the difference is extremely unlikely to be due to random chance.

Experimental evaluation

Assessing motor function enables a more precise understanding of stroke patients' recovery status and helps identify weak points in their upper and lower limb rehabilitation. This understanding can improve the evaluation of stroke patients and guide adjustments in training focus. Additionally, assessing improvements in daily life offers a practical and detailed perspective on the effectiveness of rehabilitation, highlighting key challenges in patients' real-life rehabilitation. The specific results are presented in table 5. fig. 3 illustrates the overall trend of these evaluation indicators for both the control and experimental groups throughout the study.

Table 5 indicates that the scores of control groups 1 to 5 closely resemble those of experimental groups 1 to 5. This similarity suggests that most patients in both the control and experimental groups have comparable conditions at the onset of treatment. Consequently, this reduces experimental error and enhances the accuracy of the experimental results.

The final Fugl-Meyer scores for Control Group 1 and Experimental Group 1 are 55.0 ± 4.8 and 60.0 ± 4.8 , respectively, resulting in a difference of 5 points. Similarly, the final Barthel Index scores are 65.8 ± 4.9 for Control Group 1 and 75.8 ± 4.9 for Experimental Group 1, indicating a 10-point difference. The final NIHSS scores for Control Group 1 and Experimental Group 1 are 7.0 ± 1.0 and 5.5 ± 1.0 , respectively, showing a difference of 1.5 points.

The final Fugl-Meyer scores for Control Group 2 and Experimental Group 2 are 56.8 ± 4.7 and 62.5 ± 4.7 , respectively, indicating a difference of 5.7 points. The final Barthel Index scores for these groups are 68.4 ± 5.1 and 78.0 ± 5.1 , showing a difference of 9.6 points. Additionally, the final NIHSS scores are 6.5 ± 0.9 for Control Group 2 and 5.2 ± 0.9 for Experimental Group 2, with a difference of 1.3 points.

The final Fugl-Meyer scores for Control Group 3 and Experimental Group 3 are 58.7 ± 4.9 and 65.0 ± 4.9 , respectively, indicating a difference of 6.3 points. The final Barthel Index scores are 70.0 ± 5.0 for the Control Group and 80.0 ± 5.0 for the Experimental Group, representing a difference of 10 points. Similarly, the final NIHSS scores are 6.2 ± 1.0 for the Control Group and 5.0 ± 1.0 for the Experimental Group, with a difference of 1.2 points.

The final average Fugl-Meyer scores for Control Group 4 and Experimental Group 4 are 57.4 ± 5.0 and 61.8 ± 5.0 , respectively, resulting in a difference of 4.4 points. For the Barthel Index, the final averages are 69.1 ± 5.2 for the Control Group 4 and 77.5 ± 5.2 for the Experimental Group 4, indicating a difference of 8.4 points. Regarding the NIHSS scores, the Control Group 4 averages 6.6 ± 1.0 , while the Experimental Group 4 averages 5.3 ± 1.0 . The Experimental Group's score is 1.3 points lower than that of the Control Group.

The final average Fugl-Meyer scores are 59.0 ± 5.1 for the Control Group 5 and 66.0 ± 5.1 for the Experimental Group 5. Notably, Experimental Group 5 scores 7 points higher than the Control Group. In terms of the Barthel Index, Control Group 5 has a final average of 71.2 ± 5.3 , while Experimental Group 5 scores 81.0 ± 5.3 , showing a 9.8-point advantage for the Experimental Group. The final average NIHSS scores are 6.0 ± 0.9 for Control Group 5 and 4.8 ± 0.9 for Experimental Group 5, indicating that the Experimental Group has a score 1.2 points lower than the Control Group.

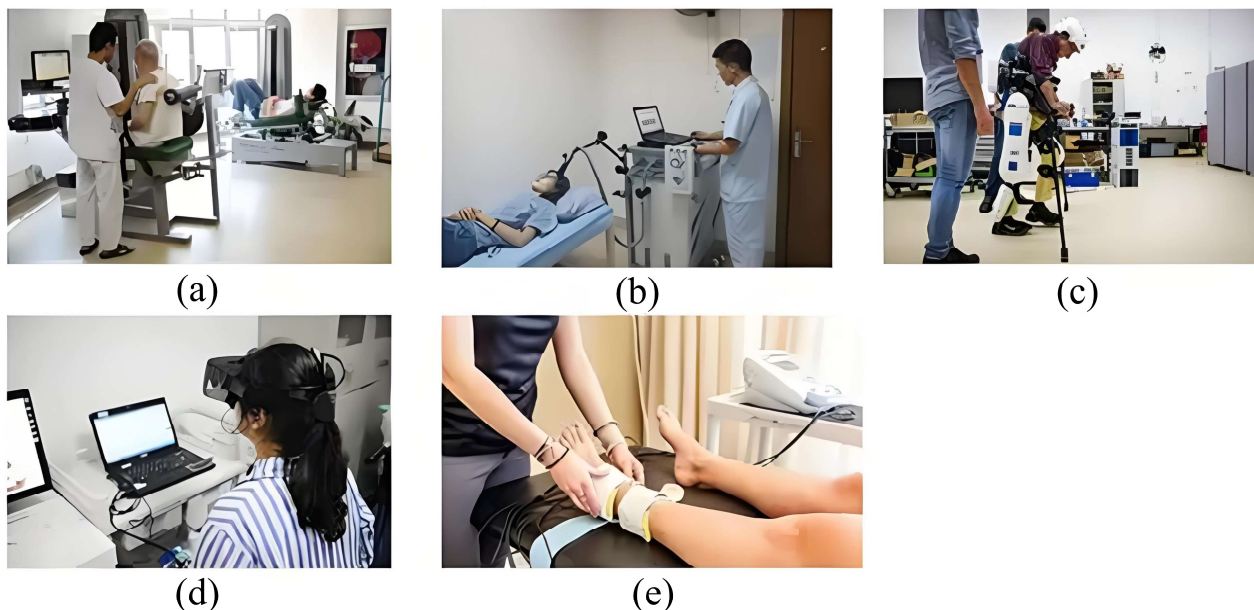


Fig. 1: Treatment methods. (a) Conventional rehabilitation treatment. (b) Neuromodulation therapy. (c) Robot-assisted therapy. (d) Virtual reality therapy. (e) Functional electrical stimulation therapy.

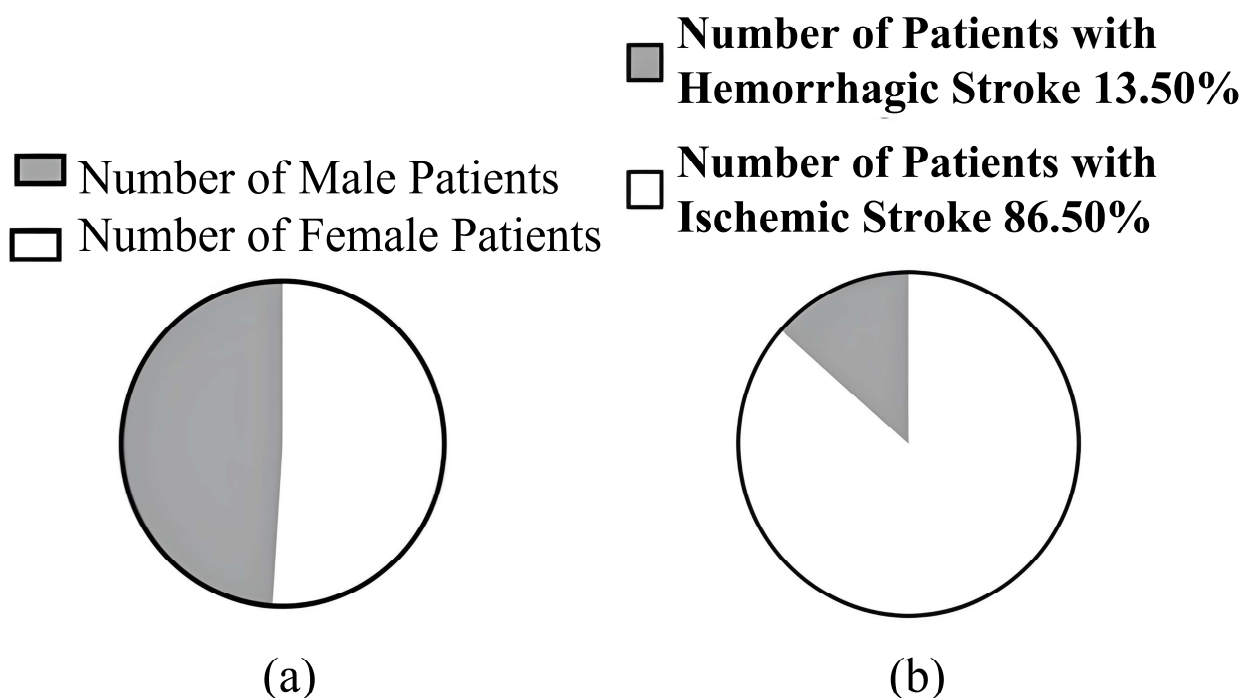


Fig. 2: Basic information scale. (a) Gender ratio in patients. (b) Proportion of disease types among patients

Table 1: Basic Information

Category	Control Group					Experiment Group				
	1	2	3	4	5	1	2	3	4	5
Number of Male Patients	11	10	9	11	11	10	10	11	9	10
Number of Female Patients	9	10	11	9	9	10	10	9	11	10
Number of Patients with Ischemic Stroke	17	18	17	17	16	18	17	18	17	18
Number of Patients with Hemorrhagic Stroke	3	2	3	3	4	2	3	2	3	2

Table 2: Fugl-Meyer scoring criteria.

Area	Full Marks	Excellent	Well	Normal	Worse
Upper Limb Motor Function	66	> 60	45 - 60	30 - 44	<30
Lower Limb Motor Function	34	> 30	24 - 30	17 - 23	< 17
Balance	14	> 12	10 - 12	7 - 9	<7
Sensory Function	24	> 20	15 - 20	10 - 14	<10
Joint Function And Pain	88	> 80	70 - 80	60 - 69	<60
Total Score	226	>200	150 - 200	100 - 149	<100

Table 3: Barthel Index Standards.

Scoring Criteria	Scope	Situation Description
Excellent	91 - 100	Independence
Well	61 - 90	Mildly Dependent
Normal	41 - 60	Moderate Dependence
Worse	21 - 40	Heavy Dependence
	0 - 20	Complete Dependence

Table 4: NIHSS Scoring Standards.

Scoring Criteria	Scope	Situation Description
Excellent	0-1	Asymptomatic
Well	2-4	Mild Disability
Normal	5-15	Moderate Disability
Worse	16-20	Moderate to Severe Disability
	21	Severe Disability

Table 5: Statistics of evaluation indicators.

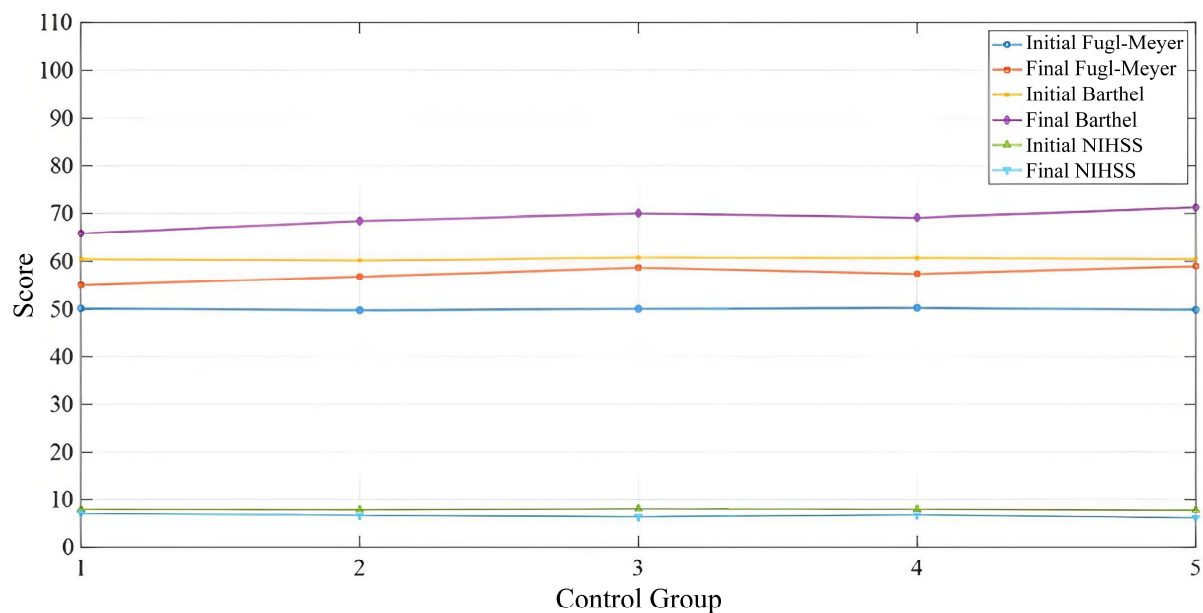
Category	Initial Fugl-Meyer Score (M ± SD)	Final Fugl-Meyer Score (M ± SD)	Initial Barthel Index (M ± SD)	Final Barthel Index (M ± SD)	Initial NIHSS Score (M ± SD)	Final NIHSS Score (M ± SD)
Control Group 1	50.2 ± 5.0	55.0 ± 4.8	60.5 ± 5.2	65.8 ± 4.9	8.0 ± 1.1	7.0 ± 1.0
Control Group 2	49.8 ± 4.9	56.8 ± 4.7	60.2 ± 5.0	68.4 ± 5.1	7.9 ± 1.0	6.5 ± 0.9
Control Group 3	50.1 ± 5.1	58.7 ± 4.9	60.8 ± 5.3	70.0 ± 5.0	8.1 ± 1.2	6.2 ± 1.0
Control Group 4	50.3 ± 5.2	57.4 ± 5.0	60.7 ± 5.4	69.1 ± 5.2	8.0 ± 1.1	6.6 ± 1.0
Control Group 5	49.9 ± 4.8	59.0 ± 5.1	60.5 ± 5.1	71.2 ± 5.3	7.8 ± 1.0	6.0 ± 0.9
Experiment Group 1	50.0 ± 5.0	60.0 ± 4.8	60.6 ± 5.2	75.8 ± 4.9	8.0 ± 1.1	5.5 ± 1.0
Experiment Group 2	49.7 ± 4.9	62.5 ± 4.7	60.3 ± 5.0	78.0 ± 5.1	7.9 ± 1.0	5.2 ± 0.9
Experiment Group 3	50.0 ± 5.1	65.0 ± 4.9	60.7 ± 5.3	80.0 ± 5.0	8.1 ± 1.2	5.0 ± 1.0
Experiment Group 4	50.2 ± 5.2	61.8 ± 5.0	60.6 ± 5.4	77.5 ± 5.2	8.0 ± 1.1	5.3 ± 1.0
Experiment Group 5	49.8 ± 4.8	66.0 ± 5.1	60.4 ± 5.1	81.0 ± 5.3	7.8 ± 1.0	4.8 ± 0.9

Table 6: Statistical analysis results of Control Group 2 and Experimental Group 2.

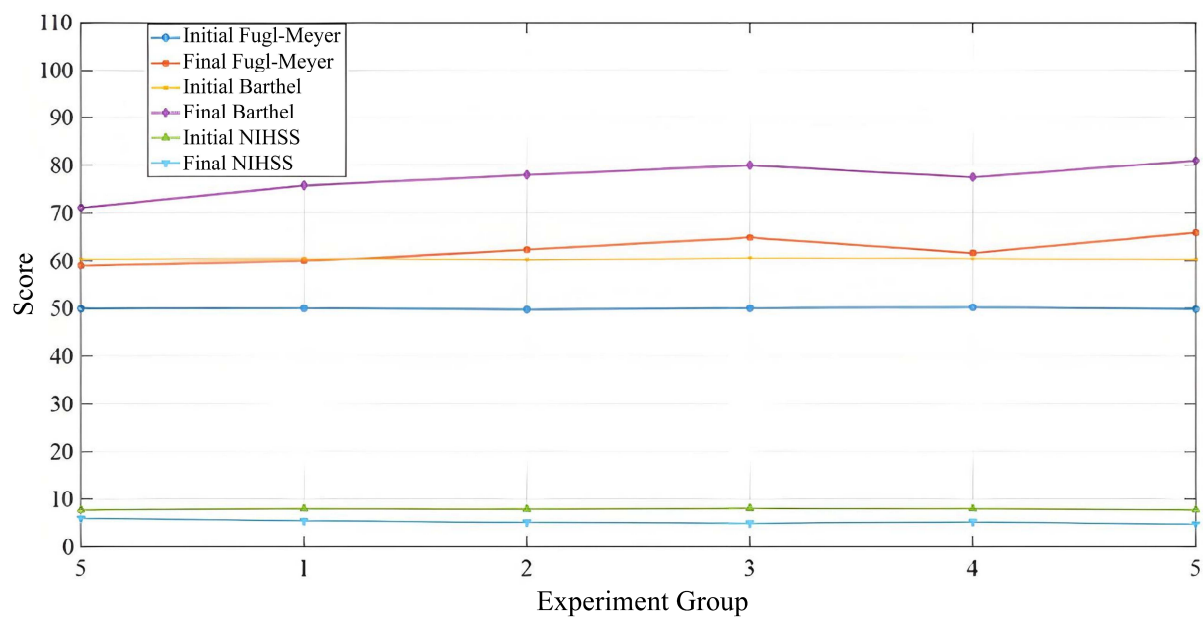
Category	Number of Cases	Fugl-Meyer Score		Barthel Index		NIHSS Score	
		Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Control Group 2	20	49.8 ± 4.9	56.8 ± 4.7	60.2 ± 5.0	68.4 ± 5.1	7.9 ± 1.0	6.5 ± 0.9
Experiment Group 2	20	49.7 ± 4.9	62.5 ± 4.7	60.3 ± 5.0	78.0 ± 5.1	7.9 ± 1.0	5.2 ± 0.9
p		>0.05	<0.01	>0.05	<0.01	>0.05	<0.01

Table 7: Statistical analysis results of Control Group 3 and Experimental Group 3.

Category	Number of Cases	Fugl-Meyer Score		Barthel Index		NIHSS Score	
		Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Control Group 3	20	50.1 ± 5.1	58.7 ± 4.9	60.8 ± 5.3	70.0 ± 5.0	8.1 ± 1.2	6.2 ± 1.0
Experiment Group 3	20	50.0 ± 5.1	65.0 ± 4.9	60.7 ± 5.3	80.0 ± 5.0	8.1 ± 1.2	5.0 ± 1.0
p		>0.05	<0.01	>0.05	<0.01	>0.05	<0.01



(a)



(b)

Fig. 3: Overall trend. (a) Overall trend of the control group. (b) Overall trend of the Experimental Group.

Table 8: Statistical analysis results of control group 4 and experimental group 4

Category	Number of Cases	Fugl-Meyer Score		Barthel Index		NIHSS Score	
		Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Control Group 4	20	50.3 ± 5.2	57.4 ± 5.0	60.7 ± 5.4	69.1 ± 5.2	8.0 ± 1.1	6.6 ± 1.0
Experiment Group 4	20	50.2 ± 5.2	61.8 ± 5.0	60.6 ± 5.4	77.5 ± 5.2	8.0 ± 1.1	5.3 ± 1.0
p		>0.05	<0.01	>0.05	<0.01	>0.05	<0.01

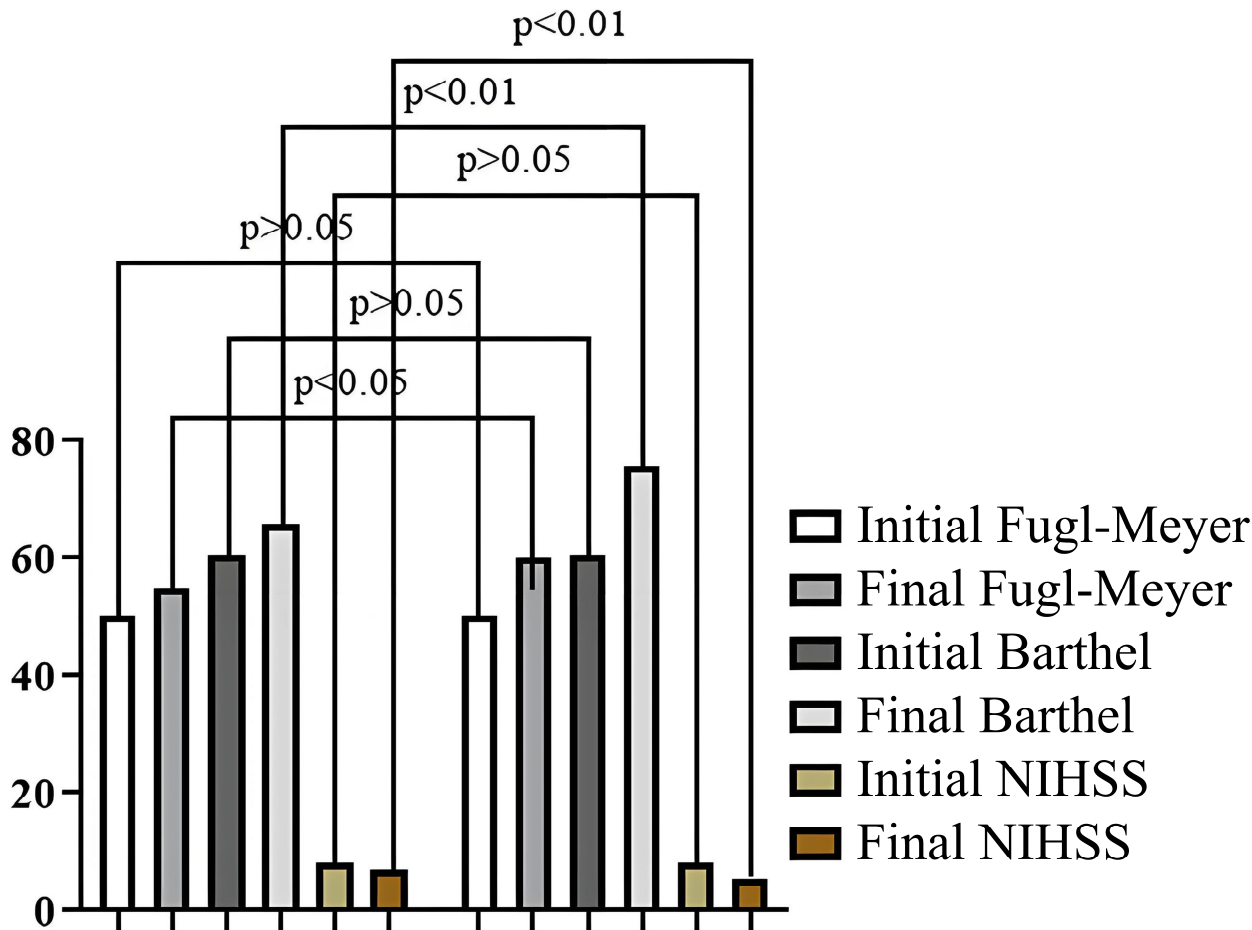


Fig. 4: Statistical analysis of control group 1 and experimental group 1.

Table 9: Statistical analysis results of control group 5 and experimental group 5

Category	Number of Cases	Fugl-Meyer Score		Barthel Index		NIHSS Score	
		Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Control Group 5	20	49.9 ± 4.8	59.0 ± 5.1	60.5 ± 5.1	71.2 ± 5.3	7.8 ± 1.0	6.0 ± 0.9
Experiment Group 5	20	49.8 ± 4.8	66.0 ± 5.1	60.4 ± 5.1	81.0 ± 5.3	7.8 ± 1.0	4.8 ± 0.9
p		>0.05	<0.01	>0.05	<0.01	>0.05	<0.01

Experimental analysis

Effect of clopidogrel on conventional rehabilitation therapy

A statistical analysis is conducted to compare Control Group 1 and Experimental Group 1. The results are presented in fig. 4.

Fig. 4 presents Control Group 1 on the left and Experimental Group 1 on the right. The data from fig. 4 demonstrates that the Fugl-Meyer score and Barthel Index for the 20 patients receiving oral clopidogrel alongside conventional rehabilitation treatment are significantly higher than those for patients receiving only conventional rehabilitation. Post-treatment scores for Experimental Group 1 are 60.0 ± 4.8 , 75.8 ± 4.9 , and 5.5 ± 1.0 ,

demonstrating increases of 9.1% and 15.2%, and a decrease of 21.4%, respectively, compared to Control Group 1. The p-values for these measurements post-treatment are less than 0.05, less than 0.01, and less than 0.01, respectively, indicating significant differences in the Fugl-Meyer score, Barthel Index, and NIHSS score. These results suggest that clopidogrel enhances the neurological rehabilitation of stroke patients undergoing routine rehabilitation, improving their daily living abilities and neurological function status.

Evaluation of the effect of clopidogrel

Statistical analysis comparing Control Group 2 and Experimental Group 2 is presented in table 6. According to the data presented in table 6, patients in Experimental

Group 2 exhibit higher Fugl-Meyer scores and Barthel Index values following treatment compared to those in Control Group 2. Specifically, these scores are 62.5 ± 4.7 and 78.0 ± 5.1 , respectively, representing increases of 10.0% and 14.0%. Conversely, the score of 5.2 ± 0.9 is 20% lower than that of Control Group 2. All p-values after treatment are less than 0.01, indicating a very significant difference. These results suggest that clopidogrel enhances neuroregulatory therapy in stroke patients by improving motor function and self-care ability while significantly reducing neurological dysfunction.

Statistical analysis is conducted to compare Control Group 3 with Experimental Group 3, and the results are presented in table 7.

According to the data presented in table 7, the post-treatment scores are 65.0 ± 4.9 , 80.0 ± 5.0 , and 5.0 ± 1.0 , respectively. These scores represent a 10.7% and 14.3% increase, and a 19.4% decrease, respectively, compared to those in the Control Group 3. The p-values following treatment are all less than 0.01, indicating significant differences in the Fugl-Meyer score, Barthel Index, and NIHSS score. These results suggest that clopidogrel significantly enhances the effectiveness of robot-assisted therapy in stroke patients, improving motor function and quality of life while reducing neurological deficits.

A statistical analysis is conducted comparing Control Group 4 and Experimental Group 4, and the results are presented in table 8.

According to the data in Table 8, after treatment, the Experimental Group 4 achieves Fugl-Meyer scores of 61.8 ± 5.0 , Barthel Index scores of 77.5 ± 5.2 , and NIHSS scores of 5.3 ± 1.0 . These values indicate increases of 7.7% and 12.2% for the Fugl-Meyer and Barthel Index scores, respectively, and a decrease of 19.7% for the NIHSS score, when compared to those of Control Group 4. All p-values post-treatment are less than 0.01, signifying significant differences in the Fugl-Meyer score, Barthel Index, and NIHSS score between the groups. This suggests that clopidogrel has a beneficial auxiliary effect when combined with virtual-reality therapy in stroke patients.

Statistical analysis is conducted between Control Group 5 and Experimental Group 5, with the results presented in table 9.

Based on the data presented in Table 9, the Barthel Index and NIHSS score for Experimental Group 5 post-treatment are 66.0 ± 5.1 , 81.0 ± 5.3 , and 4.8 ± 0.9 , respectively. These scores are 11.9% and 13.8% higher, and 20% lower, respectively, compared to the Control Group 5. The p-values for all measures after treatment are less than 0.01, demonstrating significant differences in the Fugl-Meyer score, Barthel Index, and NIHSS score. These results suggest that clopidogrel effectively enhances functional electrical stimulation therapy in stroke patients. Among all

experimental groups, Experimental Group 5 exhibits the most substantial treatment effect.

DISCUSSION

This study employs a randomized controlled trial to investigate the auxiliary role of clopidogrel in the neurological rehabilitation of patients with post-stroke movement disorders. The research results indicate that the use of clopidogrel significantly improves patients' motor functions and daily living activities. These improvements are observed in conventional rehabilitation therapy as well as in programs that incorporate neuromodulation technology, robot-assisted therapy, virtual-reality therapy, and functional electrical stimulation therapy (Tosto-Mancuso *et al.*, 2022; Kwakkel *et al.*, 2023; Huo *et al.*, 2021).

After receiving clopidogrel treatment, patients in the Experimental Group exhibit significantly better Fugl-Meyer scores, Barthel Index scores, and NIHSS scores compared to the Control Group patients who do not receive clopidogrel. This finding confirms clopidogrel's positive role in stroke rehabilitation and introduces new therapeutic strategies for clinical practice.

Clopidogrel, an antiplatelet drug, primarily prevents stroke recurrence by inhibiting platelet aggregation and exhibits some neuroprotective effects (Si *et al.*, 2022; Li & Gu, 2023). In this study, clopidogrel not only reduces thrombosis and the risk of stroke recurrence but also enhances neurological rehabilitation by promoting nerve cell regeneration and repair (Kim *et al.*, 2023; Paul *et al.*, 2023).

In addition, this study finds that clopidogrel, when combined with various rehabilitation methods, exhibits synergistic effects. Whether used alongside neuromodulation technology, robot-assisted therapy, virtual-reality therapy, or functional electrical stimulation therapy, clopidogrel significantly enhances patient recovery outcomes. These findings suggest that future clinical practice can benefit from personalized rehabilitation plans that integrate clopidogrel with diverse rehabilitation strategies tailored to individual patient needs, optimizing rehabilitation outcomes.

This study does have certain limitations. First, the limited sample size may impact the generalizability and reliability of the results. Second, the short study period does not allow for long-term follow-up to observe patient recovery comprehensively. Future studies can address these issues by expanding the sample size and extending the study duration to more thoroughly evaluate the long-term effects of clopidogrel in stroke rehabilitation.

CONCLUSION

This study investigates the auxiliary impact of clopidogrel on neurological rehabilitation in patients experiencing

post-stroke motor disorders. Participants are divided into a Control Group and an Experimental Group, with the former receiving standard rehabilitation and the latter undergoing comprehensive treatment combined with clopidogrel. To assess patient recovery under these different treatment modalities, the Fugl-Meyer score, Barthel Index, and NIHSS score are analyzed.

Findings reveal that clopidogrel significantly enhances various rehabilitation therapies, including conventional rehabilitation therapy, neuromodulation technology, robot-assisted therapy, virtual-reality therapy, and functional electrical stimulation therapy. Statistical analyses demonstrate p-values below 0.05 or 0.01, confirming clopidogrel's significant auxiliary effect across these treatment methods. The most pronounced effect is observed in functional electrical stimulation therapy, while the impact on virtual-reality therapy is less substantial. This study serves as a valuable reference for the rehabilitation treatment of stroke patients and supports the broader clinical application of clopidogrel.

Ethical approval

This study was approved by Shaoxing People's Hospital (2022 No. 095 -Y- 01).

Conflicts of interest

The authors declare that they have no financial conflicts of interest.

REFERENCES

- Aloraini SM (2022). Effects of constraint-induced movement therapy for the lower extremity among individuals post-stroke: A randomized controlled clinical trial. *NeuroRehabilitation*, **51**(3): 421-431.
- Beghi E, Binder H, Birlle C, Bornstein N, Diserens K, Groppe S, Homberg V, Lisnic V, Pugliatti M and Randall G. (2021). European Academy of Neurology and European Federation of Neurorehabilitation Societies guideline on pharmacological support in early motor rehabilitation after acute ischaemic stroke. *Eur J Neurol.*, **28**(9): 2831-2845.
- Eschweiler M, Bohr L, Kessler J, Fink GR, Kalbe E and Onur OA (2021). Combined cognitive and motor training improves the outcome in the early phase after stroke and prevents a decline of executive functions: A pilot study. *NeuroRehabilitation*, **48**(1): 97-108.
- Everard G, Luc A, Doumas I, Ajana K, Stoquart G, Edwards MG and Lejeune T (2021). Self-rehabilitation for post-stroke motor function and activity-a systematic review and meta-analysis. *NNR*, **35**(12): 1043-1058.
- Gimbel M, Qaderdan K, Willemsen L, Hermanides R, Bergmeijer T, de Vrey E, Heestermans T, Gin MTJ, Waalewijn R and Hofma S (2020). Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): The randomised, open-label, non-inferiority trial. *The Lancet*, **395**(10233): 1374-1381.
- HHuo CC, Zheng Y, Lu WW, Zhang TY, Wang DF, Xu DS and Li ZY (2021). Prospects for intelligent rehabilitation techniques to treat motor dysfunction. *Neural Regen. Res.*, **16**(2): 264-269.
- Hiatt WR, Bonaca MP, Patel MR, Nehler MR, Debus ES, Anand SS, Capell WH, Brackin T, Jaeger N and Hess CN (2020). Rivaroxaban and aspirin in peripheral artery disease lower extremity revascularization: Impact of concomitant clopidogrel on efficacy and safety. *Circulation*, **142**(23): 2219-2230.
- Kang J, Park KW, Lee H, Hwang D, Yang HM, Rha SW, Bae JW, Lee NH, Hur SH and Han JK (2023). Aspirin versus clopidogrel for long-term maintenance monotherapy after percutaneous coronary intervention: The HOST-EXAM extended study. *Circulation*, **147**(2): 108-117.
- Kelly C, Meyer J, Hanks V and Barefield C (2021). Neurorehabilitation for an individual with bilateral thalamic stroke and preexisting visual impairment presenting with impaired use of sensory cues: A case report. *Physiother Theory Pract.*, **37**(10): 1139-1145.
- Kim Y, Weissler EH, Pack N and Latz CA (2023). A systematic review of clopidogrel resistance in vascular surgery: Current perspectives and future directions. *Ann. Vasc. Surg.*, **91**: 257-265.
- Kwakkel G, Stinear C, Essers B, Munoz-Novoa M, Branscheidt M, Cabanas-Valdés R, Lakičević S, Lampropoulou S, Luft AR and Marque P (2023). Motor rehabilitation after stroke: European Stroke Organisation (ESO) consensus-based definition and guiding framework. *ESJ.*, **8**(4): 880-894.
- Lee CR, Luzum JA, Sangkuhl K, Gammal RS, Sabatine MS, Stein CM, Kisor DF, Limdi NA, Lee YM and Scott SA (2022). Clinical pharmacogenetics implementation consortium guideline for CYP2C19 genotype and clopidogrel therapy: 2022 update. *Clin Pharmacol Ther.*, **112**(5): 959-967.
- Levin MF and Demers M (2021). Motor learning in neurological rehabilitation. *Disabil. Rehabil.*, **43**(24): 3445-3453.
- Li Q and Gu X (2023). Research progress of genes related to clopidogrel resistance. *Adv Clin Exp Med.*, **13**: 3828.
- Lun R, Dhaliwal S, Zitkyte G, Roy DC, Hutton B and Dowlatsahi D (2022). Comparison of ticagrelor vs clopidogrel in addition to aspirin in patients with minor ischemic stroke and transient ischemic attack: A network meta-analysis. *JAMA Neurol.*, **79**(2): 141-148.
- Mawase F, Cherry-Allen K, Xu J, Anaya M, Uehara S and Celnik P (2020). Pushing the rehabilitation boundaries: Hand motor impairment can be reduced in chronic stroke. *Neurorehabil. Neural repair*, **34**(8): 733-745.
- Meschia JF, Walton RL, Farrugia LP, Ross OA, Elm JJ, Farrant M, Meurer WJ, Lindblad AS, Barsan W and Ching M (2020). Efficacy of clopidogrel for prevention of stroke based on CYP2C19 allele status in the POINT

- trial. *Stroke*, **51**(7): 2058-2065.
- Paul M, Paul JW, Hinwood M, Hood RJ, Martin K, Abdolhoseini M, Johnson SJ, Pollack M, Nilsson M and Walker FR (2023). Clopidogrel administration impairs post-stroke learning and memory recovery in mice. *Int. J. Mol. Sci.*, **24**(14): 11706.
- Rahayu UB, Wibowo S, Setyopranoto I and Hibatullah Romli M (2020). Effectiveness of physiotherapy interventions in brain plasticity, balance and functional ability in stroke survivors: A randomized controlled trial. *NeuroRehabilitation*, **47**(4): 463-470.
- Saes M, Mohamed Refai M, van Beijnum BJF, Bussmann J, Jansma EP, Veltink PH, Buurke JH, van Wegen EE, Meskers CG and Krakauer J (2022). Quantifying quality of reaching movements longitudinally post-stroke: A systematic review. *NNR*, **36**(3): 183-207.
- Si J, Feng X and Liu M (2022). Analysis of the responsiveness and safety of elderly patients taking different doses of clopidogrel and ticagrelor. *J. Clin. Cardiol.*, **38**(6): 460-466.
- Silvain J, Lattuca B, Beygui F, Rangé G, Motovska Z, Dillinger JG, Boueri Z, Brunel P, Lhermusier T and Pouillot C (2020). Ticagrelor versus clopidogrel in elective percutaneous coronary intervention (ALPHEUS): A randomised, open-label, phase 3b trial. *The Lancet*, **396**(10264): 1737-1744.
- Terry G and Kayes N (2020). Person centered care in neurorehabilitation: A secondary analysis. *Disabil. Rehabil.*, **42**(16): 2334-2343.
- Timm A, Knecht S, Florian M, Pickenbrock H, Studer B and Schmidt-Wilcke T (2021). Frequency and nature of pain in patients undergoing neurorehabilitation. *Clin. Rehabil.*, **35**(1): 145-153.
- Tosto-Mancuso J, Tabacof L, Herrera JE, Breymann E, Dewil S, Cortes M, Correa-Esnard L, Kellner CP, Dangayach N and Putrino D (2022). Gamified neurorehabilitation strategies for post-stroke motor recovery: challenges and advantages. *Curr. Neurol. Neurosci. Rep.*, **22**(3): 183-195.
- Valeria C, Carmine S, Valentina M, Teresa I, Maria C, Martina T, Giancarlo A, Giovanna N, Graziamaria C and Amelia F (2021). The need of a multicomponent guiding approach to personalize clopidogrel treatment. *Pharmacogenomics J.*, **21**(2): 116-127.
- Verma SS, Bergmeijer TO, Gong L, Reny JL, Lewis JP, Mitchell BD, Alexopoulos D, Aradi D, Altman RB and Bliden K (2020). Genomewide association study of platelet reactivity and cardiovascular response in patients treated with clopidogrel: A study by the international clopidogrel pharmacogenomics consortium. *Clin Pharmacol Ther.*, **108**(5): 1067-1077.
- Wang Y, Meng X, Wang A, Xie X, Pan Y, Johnston SC, Li H, Bath PM, Dong Q and Xu A (2021). Ticagrelor versus clopidogrel in CYP2C19 loss-of-function carriers with stroke or TIA. *New Engl J Med.*, **385**(27): 2520-2530.
- Watanabe H, Morimoto T, Natsuaki M, Yamamoto K, Obayashi Y, Ogita M, Suwa S, Isawa T, Domei T and Yamaji K (2022). Comparison of clopidogrel monotherapy after 1 to 2 months of dual antiplatelet therapy with 12 months of dual antiplatelet therapy in patients with acute coronary syndrome: The STOPDAPT-2 ACS randomized clinical trial. *JAMA Cardiology*, **7**(4): 407-417.
- Wolf S, Holm S, Ingwersen T, Bartling C, Bender G, Birke G., Meyer A, Nolte A, Ottens K and Pade O (2022). Pre-stroke socioeconomic status predicts upper limb motor recovery after inpatient neurorehabilitation. *Ann. Med.*, **54**(1): 1265-1276.
- Yoon H, Park C, Park I, Kim K and Cha Y (2021). A precision neurorehabilitation using SSEP for early detection of sensory deficit and restoration of the motor recovery in balance, gait and activities of daily living in acute stroke. *Technol. Health Care*, **29**(S1): 377-383.
- You SC, Rho Y, Bickdeli B, Kim J, Siapos A, Weaver J, Londhe A, Cho J, Park J and Schuemie M (2020). Association of ticagrelor vs clopidogrel with net adverse clinical events in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *JAMA*, **324**(16): 1640-1650.
- Zafarovna OM (2022). Rehabilitation of Stroke Patients. *CAJMNS.*, **3**(2): 319-323.
- Zandvliet SB, Kwakkel G, Nijland RH, van Wegen EE and Meskers CG (2020). Is recovery of somatosensory impairment conditional for upper-limb motor recovery early after stroke?. *NNR.*, **34**(5): 403-416.