RESEARCH ARTICLE

Intraparenchymal Umbilical Cord Mesenchymal Stem Cell Transplantation in Patients with Subacute Ischemic Stroke: A Preliminary Study of Safety and Early Clinical Outcomes

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Abstract

BACKGROUND: Intravenous thrombolysis and mechanical thrombectomy are current standard treatments for ischemic stroke, however their narrow therapeutic window limits eligibility for many patients. Umbilical cord-derived mesenchymal stem cells (UC-MSCs) have emerged as a promising regenerative therapy, but their safety and efficacy need to be further elucidated. Interleukin-6 (IL-6) and brain-derived neurotrophic factor (BDNF) may provide biological insights into the inflammatory and neuroregenerative responses following UC-MSC transplantation. This study was conducted to evaluate the safety and preliminary efficacy, including IL-6 and BDNF level, after stereotactic intraparenchymal UC-MSC transplantation.

METHODS: Subjects with subacute ischemic stroke received stereotactic intraparenchymal transplantation of 2×10^7 allogeneic UC-MSCs into the perolesional ischemic area, 13 to 20 days after stroke onset. Safety was assessed by monitoring the adverse events. Early efficacy was evaluated using the National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), Magnetic Resonance Imaging (MRI), and serum biomarkers, including IL-6 and BDNF. Serum IL-6 levels were measured using electrochemiluminescence immunoassay (ECLIA), while BDNF levels were measured using enzyme-linked immunosorbent assay (ELISA).

RESULTS: No serious adverse events related to UC-MSCs administration were observed during the three-month follow-up. No serious adverse events related to UC-MSC administration were observed during the three-month follow-up. From baseline to the third month, improved mRS and NIHSS scores were observed (mean Δ: −0.75 and +4.00, respectively), along with reduced IL-6 (mean Δ: −2.76 pg/mL) and increased BDNF (mean Δ: +3.16 ng/mL).

CONCLUSION: UC-MSC transplantation was well tolerated, with improvements in NIHSS and mRS and favorable changes in IL-6 and BDNF levels. These findings suggest that direct intraparenchymal UC-MSCs transplantation may be safe, as no severe adverse events were observed in this preliminary study.

KEYWORDS: ischemic stroke, umbilical cord-derived mesenchymal stem cells (UC-MSCs), interleukin-6, brain-derived neurotrophic factor

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Introduction

Stroke is the world's second leading cause of death, affecting about 13.8 million people and causing 5.5 million deaths each year. According to The Global Burden of Disease (GBD) Stroke Collaboration, 87% of cases are ischemic, with rising mortality, morbidity, disability-adjusted life years (DALYs), and economic burden throughout the year.(1,2) Ischemic stroke is characterized by a sudden onset of brain function impairment lasting more than 24 hours or leading to death.(3,4) Unfortunately, spontaneous recovery from ischemic stroke remains limited.(5) The current standard treatments for acute ischemic stroke include intravenous thrombolysis and mechanical thrombectomy to restore cerebral blood flow and minimize irreversible brain injury. However, their clinical application is limited by strict eligibility criteria and narrow therapeutic time windows. Intravenous thrombolysis is generally administered within 4.5 hours of symptom onset, while mechanical thrombectomy is primarily indicated for selected patients with large-vessel occlusion within 6 hours and, in selected cases, up to 24 hours based on advanced imaging. Consequently, many patients are not eligible for these reperfusion therapies and remain at risk of persistent neurological disability.(6,7)

After ischemic events, a cascade of cytokine- and mediator-driven processes occurs, involving neural progenitor cells (NPCs) within the sub-granular zone (SGZ) and subventricular zone (SVZ). NPCs within these niches undergo proliferation, migrate toward the ischemic area, differentiate, and form synaptic connections.(8) Nevertheless, only 10–20% of newly generated neurons survive and function effectively due to the inadequate microenvironment within the penumbra, which lacks sufficient neurotrophic factors, exhibits increased toxicity, and shows heightened inflammation compared to the neurogenic niche.(9) Mesenchymal stem cells (MSCs) exert paracrine effects by producing abundant neurotropic factors, cytokines and signaling mediator that can reduce neuroinflammation and enhance angiogenesis-neurogenesis after stroke.(10-15) Some preclinical studies demonstrated that MSCs offer promising potential to promote neurogenesis and facilitate neurological recovery by enhancing the endogenous neurogenesis.(6,7) Therefore, translating these preclinical findings into clinical practice may effectively reduce stroke-related morbidity and its broader societal burden.

National Institutes of Health Stroke Scale (NIHSS), a standardized scale for quantifying neurological impairment, and the modified Rankin Scale (mRS), which evaluates the degree of disability and functional independence in daily activities, are largely used to assess treatment outcomes.(16) In addition to clinical outcomes, biological markers may provide insight into the mechanisms underlying recovery after ischemic stroke. Interleukin-6 (IL-6) is an important mediator of post-stroke inflammation and may contribute to secondary neuronal injury when persistently elevated, whereas brain-derived neurotrophic factor (BDNF) plays an important role in neuronal survival, synaptic plasticity, and neuroregeneration. It is important to assess IL-6 and BDNF levels following UC-MSC transplantation to evaluate the changes in inflammatory and neurotrophic responses.(15) Together, these clinical and biological parameters provide complementary information on neurological recovery, functional outcomes, and potential biological responses following UC-MSC transplantation in patients with ischemic stroke. However, to date, the translation of these encouraging preclinical outcomes into clinical practice remains limited. Therefore, this study was conducted to evaluate the safety and preliminary efficacy of stereotactic intraparenchymal transplantation of UC-MSCs in patients with subacute ischemic stroke using clinical and biological outcome measures.

Methods

Study Subjects

Five patients with subacute ischemic stroke, 2–4 weeks after stroke onset, were consecutively recruited and included in this preliminary clinical study. All subjects presented with acute-onset neurological deficits consistent with ischemic stroke and were confirmed by neuroimaging findings using computed tomography (CT) and magnetic resonance imaging (MRI) to assess the ischemic lesion (Figure 1).

Preparation and Transplantation of UC-MSCs

The UC-MSCs (MeSCPro®; PT Prodia StemCell Indonesia, Jakarta, Indonesia) used in this study were manufactured according to established Good Manufacturing Practice (GMP) procedures. UC-MSCs were isolated using the explant method and cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with human platelet lysate. Cells were maintained at 37°C in a humidified atmosphere containing 5% CO_2, with medium changes every 3–4 days until approximately 80% confluence was reached. The cells were harvested and prepared as a cell suspension in sterile 0.9% sodium chloride (NaCl) solution for transplantation.

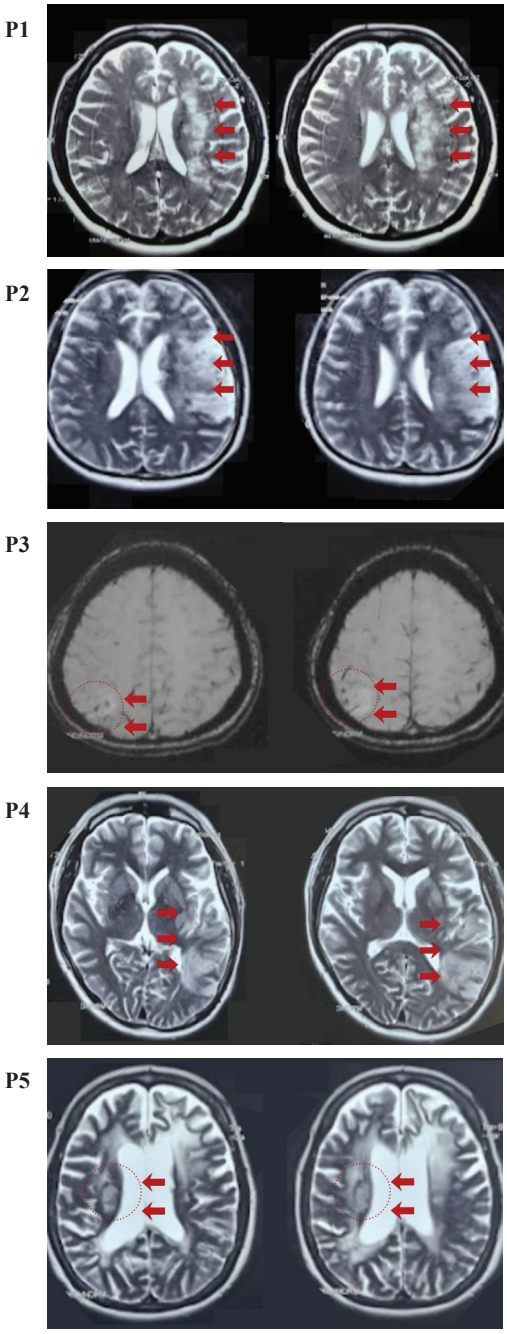


Figure 1. Baseline MRI images of Patient-1 (P1) to -5 (P5) before UC-MSC transplantation. The results show supratentorial ischemic lesions (red arrows) with varying locations, infarct volumes, and arterial territories. Brain atrophy was also observed in P5.

Before administration, the final UC-MSC preparation was assessed for cell viability and compliance with predefined release criteria. The cells fulfilled the International Society for Cellular Therapy (ISCT) minimal criteria, including plastic adherence, spindle-shaped morphology, positive expression of class of differentiation (CD)73, CD90, and CD105 (Figure 2), and negative expression of CD34, CD45, CD14, CD19, and human leukocyte antigen–DR isotype (HLA-DR).

The intraparenchymal UC-MSCs (2×10^7 cells) transplantation was performed using a stereotactic technique guided by an imaging-based navigation system (Inomed™ Planning Software; Inomed Medizintechnik, Emmendingen, Germany) to precisely target the ischemic penumbra while minimizing damage to the surrounding healthy brain tissue. Before surgery, the target points adjacent to the infarct and the planned trajectory were mapped based on MRI. Under general anesthesia, a specialized tube was inserted through a burr hole into the predetermined target using the Inomed™ Stereotactic System (Inomed Medizintechnik). A total of 2×10^7 cells in 1 mL of NaCl was injected across three points along a single trajectory over 10-15 minutes, ensuring homogeneous cell distribution within the ischemic area. Subjects were monitored post-procedurally for adverse events.

Safety and Feasibility Assessment

Safety was evaluated by monitoring for UC-MSCs-related complications including toxic reactions, allergic responses, graft rejection, and infection as well as surgical complications such as hemorrhage, fever, seizure, headache, and neurological deterioration.

Assessment of Clinical Efficacy (NIHSS and mRS)

To further evaluate the early therapeutic response following UC-MSCs transplantation, both clinical and biological efficacy outcomes were assessed. Clinical efficacy was assessed using the NIHSS and mRS scores. The NIHSS is a standardized 15-item assessment used to quantify stroke severity, with higher scores ranging from 0 to 42 and higher scores indicating greater neurological impairment. Functional outcome was evaluated using the mRS, a 7-point scale ranging from 0 (no symptoms) to 6 (death), with higher scores indicating greater disability and dependence in daily activities. Assessments were performed at baseline (prior to transplantation), one month, and three months after treatment.

Analysis of IL-6 and BDNF Levels

Serum IL-6 levels were measured using Elecsys IL-6 reagent (Roche Diagnostics, Mannheim, Germany) on a Cobas e601 analyzer (Roche Diagnostics). The measuring range of this assay is 1.5–5,000 pg/mL, with analytical sensitivity of 1.5 pg/mL. Meanwhile, BDNF levels were measured with enzyme-linked immunosorbent assay.(ELISA) using the Quantikine™ ELISA Total BDNF Immunoassay (Catalog

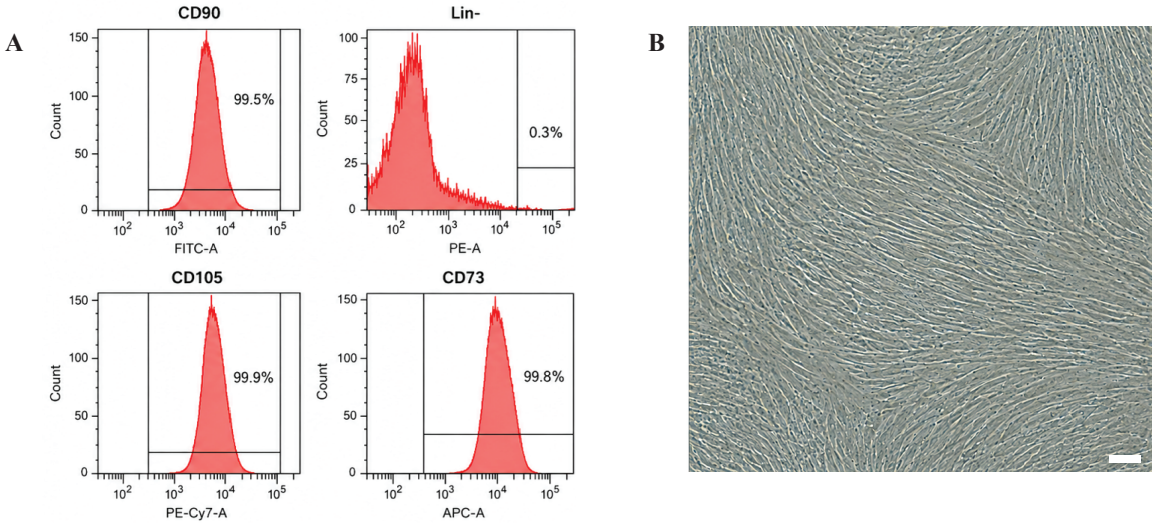


Figure 2. Immunophenotypic and morphology characterization of UC-MCSs. A: Positive expressions of CD90, CD105, and CD73. B: spindle-shaped morphology. White bar: 100 μm.

No. DBNT00; R&D Systems, Minneapolis, MN, USA), which is a solid-phase quantitative sandwich ELISA using a horseradish peroxidase (HRP)-based colorimetric detection system. The detection range was 15.6–1,000 pg/mL, with sensitivity of 1.35 pg/mL. This kit detected total BDNF. with absorbance measured at 450 nm.

Results

Subjects Characteristics

Five subjects with subacute ischemic stroke were enrolled. Their ages were ranging from 26 to 59 years old. Comorbidities were common, including hypertension in three subjects and diabetes mellitus in one subjects who also had hypertension (Table 1). All subjects received standard acute stroke management but were ineligible for thrombectomy because of delayed presentation beyond the therapeutic window.

Safety and Feasibility

No severe adverse events were observed throughout the three-month follow-up period. Complications including toxic reactions, allergic responses, graft rejection, and infection were also not observed. Two subjects (Patient-1 and -5) experienced mild postoperative headaches that were resolved within a few days with standard analgesic treatment, with no evidence of stroke progression. These findings indicate that intraparenchymal UC-MSCs transplantation was well tolerated, with a satisfactory overall safety profile.

UC-MSCs Improved Clinical Outcomes

To observe the early efficacy, changes in neurological status following UC-MSCs transplantation were assessed using the NIHSS, where higher scores indicate greater neurological impairment. Baseline NIHSS scores ranged from 7 to 20. Consistent improvement in NIHSS scores was observed in Patient-2, -3, and -4, whereas Patient-1 and -5 showed no change throughout the follow-up period. Improvement in NIHSS score was observed from baseline to the third month with mean Δ +4.00 (n=4) (Table 2).

Meanwhile, the functional independence and overall disability were evaluated using the mRS, with higher scores reflecting increased dependence on others for daily activities. The UC-MSCs transplantation was able to reduce mRS score with mean Δ: −0.75 from baseline to the third months (n=4). The mRS score showed similar pattern with NIHSS score, where Patient-1, -3, and -5 remained unchanged, while Patient-2 and -4 showed improvements (Table 2). Calculation of mean Δ NIHSS and mRS scores only included Patient-1 to -4 since numerical data for Patient-5 was incomplete.

UC-MSCs Reduced IL-6 and Increased BDNF Levels

Serum IL-6 and BDNF levels were assessed at baseline, one month, and three months after UC-MSC transplantation. The individual IL-6 and BDNF values for each subject were presented in Table 3. The mean serum IL-6 level showed a decreasing trend during the follow-up period, whereas the mean BDNF level showed an increasing trend. The decrease in IL-6 and increase in BDNF levels represent favorable changes in inflammatory and neurotrophic responses,

Table 1. Baseline characteristics and neurological profiles of subjects receiving UC-MSCs transplantation.

Characteristics	Patient				
	P1	P2	P3	P4	P5
Sex	Female	Male	Female	Male	Female
Age	59 y.o.	26 y.o.	54 y.o.	33 y.o.	58 y.o.
Time of transplantation[a]	14 days	20 days	16 days	13 days	16 days
Cormobidities	Hypertension	None	Hypertension	None	Hypertension, DM
Vascular territority	MCA, deep perfoating branch	MCA	MCA branch	MCA/PCA border zone	MCA branch
Speech dysfunction	Aphasia	None	Dysarthria/aphasia	Moderate aphasia	Dysarthria
Ataxia	Right led and trunk	None	None	None	Right leg and trunk
Cranial nerve dysfunction	Left CN VII paresis	Right CN VII paresis	Left CN VII paresis	None	Left CN VII, CN XII paresis
Independence in daily living	Dependent	Dependent	Dependent	Dependent	Dependent
Extremity weakness	Right hemiplegia	Right hemiparesis	Left hemiparesis	Left hemiparesis	Left hemiparesis
Walking ability	Imbalanced	Imbalanced	Imbalanced	Independent with assistance	Imbalanced

[a]Time from stroke to transplantation. MCA: Middle cerebral artery; PCA: Posterior cerebral artery; CN: Cranial nerve; MRI: Magnetic resonance imaging; DM: diabetes mellitus; y.o.: years old.

respectively, following UC-MSC transplantation. (mean Δ: −2.76 pg/mL) and increased BDNF (mean Δ: +3.16 ng/mL) (n=4). Calculation of mean Δ IL-6 and BDNF levels only included Patient-1 to -4 since numerical data for Patient-5 was incomplete.

Discussion

The present study demonstrated that stereotactic intraparenchymal UC-MSC transplantation was associated with favorable biological and clinical responses in subjects with subacute ischemic stroke. Most subjects showed reduced serum IL-6 levels with maintained or increased BDNF concentrations, accompanied by improvements in neurological and functional outcomes. Serum IL-6 has been investigated as a biomarker of post-stroke neuroinflammation. Its biological effects are context-dependent, with classical signaling contributing to anti-inflammatory and regenerative responses, whereas trans-signaling promotes neuroinflammation. IL-6 is produced by both immune and non-immune cells, including microglia, macrophages, astrocytes, endothelial cells, and neurons. Following ischemic injury, astrocyte-derived IL-6 contributes to debris clearance, neurogenesis, angiogenesis, neuronal differentiation, and immunomodulation through Th1-to-Th2 polarization.(17) However, persistent IL-6 elevation promotes excessive neuroinflammation, blood-brain barrier disruption, and secondary neuronal injury. In contrast, BDNF facilitates synaptic plasticity, axonal remodeling, and long-term neurological recovery. In this context, reduced IL-6 together with maintained or increased BDNF may reflect attenuation of inflammation and enhanced neuroregenerative activity.(18) However, variability in biomarker responses was also observed. Although IL-6 generally declined and BDNF was maintained or increased during follow-up, these changes did not always occur linearly or directly parallel clinical improvement. Such variability may reflect differences in individual biological responses, infarct characteristics, and comorbid conditions, emphasizing the complexity of post-stroke recovery.

UC-MSCs transplantation is expected to counteract the limitation of NPC survival through paracrine mechanisms that suppress neuroinflammation and promote endogenous neurogenesis.(13,14,19) In this study, all subjects underwent transplantation during the subacute phase (2–4 weeks after stroke). Previous studies have suggested that this period is associated with increased endogenous NPCs begin to proliferate and reach their peak activity, potentially enhancing the regenerative effects of UC-MSC therapy.(9,20,21) Compared with intravenous and intra-arterial administration, this approach provides more precise targeting, minimizes off-target cell distribution, and requires a lower cell dose.(21,22) No severe adverse events, neurological deterioration, infection, graft rejection, or surgical complications were observed during the three-month follow-up, supporting the safety and feasibility of stereotactic intraparenchymal UC-MSC transplantation.

Neurological improvement, reflected by reductions in NIHSS scores. These findings are consistent with previous experimental and clinical studies demonstrating improved neurogenesis and neurological recovery following MSC transplantation.(11,23–27) Nevertheless, the magnitude and timing of recovery varied among patients, likely reflecting

Table 2. Clinical outcomes (mRS and NHSS scores) of subjects from baseline until the third month.

Patient	mRS Score				NIHSS Score			
	Baseline	Month-I	Month-III	Δ	Baseline	Month-I	Month-III	Δ
P1	4	4	3	-1	17	17	15	2
P2	4	3	3	-1	18	18	10	8
P3	4	4	4	0	12	11	10	2
P4	2	2	1	-1	6	4	2	4
P5	4	4	4	N/A	9	9	N/A	N/A
			Mean Δ	-0.75			Mean Δ	+4.00
			Median Δ	-1.00			Median Δ	+3.00

Δ = Score Baseline − Score Month-III. Calculation of mean and median Δ were only for Patient-1 to -4, since there are incomplete data for Patient-5.

differences in infarct size, infarct location, age, and comorbidities such as hypertension and diabetes mellitus. The observed clinical improvements may be related to the established paracrine activity of UC-MSCs through the secretion of anti-inflammatory cytokines, growth factors, and neurotrophic mediators that promote angiogenesis, neurogenesis, and neuronal repair.

Patient-1 demonstrated delayed neurological improvement, becoming evident only three months after transplantation. The large infarct volume and coexisting hypertension may have created a more hostile inflammatory microenvironment requiring greater neuroregenerative capacity.(28) These findings suggest that infarct volume may influence the optimal UC-MSC dose required to achieve therapeutic benefit. In contrast, Patient-5 showed no neurological improvement throughout follow-up. This patient presented with diabetes mellitus, hypertension, and severe cerebral atrophy. These conditions have been associated with persistent neuroinflammation, impaired angiogenesis, and reduced NPC populations, thereby limiting endogenous neurogenesis and tissue repair.(29–36)

There are some limitations to generalize the findings of this current study since the sample size are small and there are absence of a control group that prevents direct attribution of the observed clinical and biological improvements to UC-MSC therapy. We also acknowledged the incomplete data collection for Parient-5 that might reduce the statistical power of this study. The short follow-up period captured also only early therapeutic responses and may not reflect long-term clinical and biological outcomes. Future studies involving larger samples, appropriate control groups, complete data collection, and longer follow-up periods are suggested to improve statistical power, generalizability, and assessment of long-term outcomes.

Conclusion

Improvements in NIHSS and mRS scores were observed in most subjects and were accompanied by favorable changes in serum IL-6 and BDNF levels following UC-MSC transplantation. This preliminary study suggests that

Table 3. Biomarker outcomes (IL-6 and BDNF levels) of subjects from baseline until the third month.

Patient	IL-6				BDNF			
	Baseline	Month-I	Month-III	Δ	Baseline	Month-I	Month-III	Δ
P1	13.00	9.45	7.55	-5.45	18.93	21.14	20.38	+1.45
P2	3.41	3.28	2.60	-0.81	37.18	32.07	40.60	+3.42
P3	7.78	14.80	4.48	-3.30	25.95	39.43	32.09	+6.14
P4	5.88	1.93	4.42	-1.46	26.66	33.02	28.29	+1.63
P5	2.62	2.73	3.61	+0.99	N/A	N/A	N/A	N/A
			Mean Δ	-2.76			Mean Δ	+3.16
			Median Δ	-2.38			Median Δ	+2.53

Δ = Level Baseline − Level Month-III. Calculation of mean and median Δ were only for Patient-1 to -4, since there are incomplete data for Patient-5.

stereotactic intraparenchymal UC-MSC transplantation may be feasible and acceptably safe for the treatment of patients with subacute ischemic stroke. These findings should be interpreted with caution given the exploratory design, very small sample size, absence of a control group, and short follow-up period.

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Authors Contribution

MAA, KL, and CRS were involved in conceptualization of the study and the methodology. RH and NZ performed formal analysis. MAA, AF, CRS, RH, and NZ performed the investigation. MAA, NZ, ET, and RF wrote the original draft. MAA, CRS, RH, and NZ revised, review, and edited the manuscript. KL, CRS, and AW were involved in the supervision of the study. RH and NZ were involved in the project administration. AW and CRS were involved in the funding acquisition. All authors agreed to submit the manuscript, read and approved the final draft, and take full responsibility of its content, including the accuracy of the data and the fidelity of the trial to the registered protocol, validation, visualization, resource.

Ethical Statement

This study was conducted at Gatot Soebroto Army Central Hospital, Jakarta, Indonesia, and approved by the Ethics Committee of RSPAD Gatot Soebroto (Approval No. 34/V/KEPK/2023). All procedures were performed in accordance with the ethical standards of the institutional and national research committees. The trial is registered at ClinicalTrials.gov under registration number NCT05008588.

Conflict of Interest

The authors declare no conflict of interest.

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