UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

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Zakład Pielęgniarstwa Internistycznego, Katedra Pielęgniarstwa i Położnictwa,
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Katedra i Klinika Pediatrii i Chorób Infekcyjnych, Wydział Lekarski,
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Wpływ treningu usprawniającego pacjentów po udarze niedokrwiennym mózgu na poziom wybranych czynników wzrostu i plastyczności neuronalnej, mięśniowej i naczyniowej

Effect of rehabilitation training of patients after ischemic stroke on the level of selected growth factors and neuronal, muscular and vascular plasticity

Rozprawa na stopień naukowy doktora nauk medycznych

Promotor

Prof. dr hab. Joanna Rosińczuk

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Wrocław 2023

Składam serdeczne podziękowania Pani Promotor
– Prof. dr hab. Joannie Rosińczuk –
za wskazówki metodyczne i wsparcie merytoryczne
podczas realizacji projektu badawczego
oraz pisania publikacji wchodzących w skład
cyklu będącego przedmiotem niniejszej
rozprawy doktorskiej.

Pragnę podziękować również Pani
– Prof. dr hab. Eugenii Murawskiej-Ciałowicz –
z Zakładu Fizjologii i Biochemii Akademii
Wychowania Fizycznego we Wrocławiu
za dotychczasową współpracę
naukowo-badawczą.

Spis treści

1. Słowa kluczowe

Badania laboratoryjne (ang. *laboratory blood tests*)

Biomarkery (ang. *biomarkers*)

C-reaktywna proteina (ang. *C-reactive protein,* CRP)

Ocena funkcjonalna (ang. *functional assessment*)

Okres regeneracyjno-kompensacyjny (ang. *recovery-compensation stage*)

Proprioceptywne nerwowo-mięśniowe torowanie (ang. *proprioceptive neuromuscular facilitation*, PNF)

Regeneracja po udarze (ang. *post-stroke recovery*)

Rehabilitacja neurologiczna (ang. *neurological rehabilitation*)

Rekonwalescencja (ang. *reconvalescence*)

Skala Udarów Narodowego Instytutu Zdrowia (ang. *National Institutes of Health Stroke Scale*, NIHSS)

Terapia lustrzana (ang. *mirror therapy,* MT)

Terapia zajęciowa (ang. *occupational therapy*, OT)

Udar niedokrwienny mózg (ang. *ischaemic stroke*)

Witamina D (ang. *vitamin D*)

Wskaźnik Barthel (ang. *Barthel Index*, BI)

Wyniki funkcjonalne (ang. *functional outcomes*)

Zdrowie (ang. *health*)

Zmodyfikowana Skala Rankina (ang. *modified Rankin Scale*, mRS)

2. Wykaz skrótów

ADLs czynności życia codziennego (ang. *activities of daily living*)

AHA Amerykańskie Towarzystwo Kardiologiczne (ang. *American Heart Association*)

ARIC projekt *Atherosclerosis Risk in Communities*

ASA Amerykańskie Towarzystwo Udarowe (ang. *American Stroke Association*)

BI Wskaźnik Barthel (ang. *Barthel Index*)

CMIA test immunologiczny z mikrocząsteczkami (ang. *chemiluminescent microparticle immunoassay)*)

CRP C-reaktywna proteina (ang. *C-reactive protein*)

EBM Medycyna Oparta na Dowodach Naukowych (ang. *Evidence-Based Medicine*).

EROS projekt *European Registers Of Stroke*

FIM Pomiar Niezależności Funkcjonalnej (ang. *Functional Independence Measure*)

FRI Wskaźnik Funkcjonalny Repty (ang. *Repty Functional Index*)

HRQOL jakość życia uwarunkowana stanem zdrowia (ang. *health-related quality of life*)

IGF-1 insulinopodobny czynnik wzrostu 1 (ang. *insulin-like growth factor 1*)

ISRCTN platforma *International Standard Randomised Controlled Trial Number*

mRS zmodyfikowana Skala Rankina (ang. *modified Rankin Scale*)

MT terapia lustrzana (ang. *mirror therapy*)

OT terapia zajęciowa (ang. *occupational therapy*)

OUN ośrodkowy układ nerwowy

PNF proprioceptywne nerwowo-mięśniowe torowanie (ang. *proprioceptive neuromuscular facilitation*)

SMART reguła neurorehabilitacji określająca cele jako Specyficzne, Mierzalne, Adekwatne, Realistyczne i Terminalne (ang. *Specific, Measurable*, *Attainable*, *Realistic* and *Time-related*)

WHO Światowa Organizacja Zdrowia (ang. *World Health Organization*)

3. Lista publikacji wchodzących w skład pracy doktorskiej

1) **Borowicz Wojciech**, Ptaszkowski Kuba, Murawska-Ciałowicz Eugenia, Rosińczuk Joanna: Proprioceptive neuromuscular facilitation and mirror therapy methods are comparable methods of rehabilitation after a first-ever ischemic stroke: a randomized study, Sustainability, vol. 14, nr 22, 2022, art.15246 [11 s.], DOI:10.3390/su142215246
Praca oryginalna / MEiN = 140,00 / IF = 4,964

2) **Borowicz Wojciech**, Ptaszkowski Kuba, Ptaszkowska Lucyna, Murawska-Ciałowicz Eugenia, Rosińczuk Joanna: Assessment of changes in serum C-reactive protein levels in patients after ischemic stroke undergoing rehabilitation - a retrospective observational study, Journal of Clinical Medicine, vol. 12, nr 3, 2023, art.1029 [11 s.], DOI:10.3390/jcm12031029
Praca oryginalna / MEiN = 100,00 / IF = 3,889

3) **Borowicz Wojciech**, Ptaszkowski Kuba, Ptaszkowska Lucyna, Rosińczuk Joanna, Murawska-Ciałowicz Eugenia: The Association Between Serum Vitamin D Levels and Physical Outcomes of Patients who Underwent Rehabilitation Following Ischemic Stroke. Medical Science Monitor, In Press, DOI: 10.12659/MSM.940115 [9 s.], DOI:10.12659/MSM.940115
Praca oryginalna / MEiN = 140,00 / IF = 3,386

4) **Borowicz Wojciech**, Szczepańska Marta, Rosińczuk Joanna: C-Reactive protein as a biomarker affecting neurorehabilitation outcomes in post-stroke patients: state of knowledge and global trends in research, Journal of Education, Health and Sport, Uniwersytet Mikołaja Kopernika w Toruniu, vol. 13, nr 4, 2023, s. 92-107, DOI:10.12775/jehs.2023.13.04.010
Praca przeglądowa / MEiN = 40,00 / IF = 0,000

Punktacja prac z cyklu:

Punktacja Impact Factor:	12,239
Punktacja Ministerstwa Edukacji i Nauki:	420,00

4. Działalność naukowa, dydaktyczna, zawodowa i organizacyjna

I. Dane naukometryczne:

Publikacje w czasopismach naukowych: 18

- Publikacje w czasopiśmie z IF: 9
- Publikacje w czasopiśmie bez IF: 9

Cytowania wg WoS CC: 26

Indeks Hirscha wg WoS CC: 4

Sumaryczna punktacja IF: 38,338

Sumaryczna punktacja MEiN: 1639,00

II. Udział w projektach naukowych:

1) Międzyośrodkowy projekt naukowo-badawczy: *Wpływ treningu usprawniającego pacjentów po udarze niedokrwiennym mózgu na poziom wybranych czynników wzrostu i plastyczności neuronalnej, mięśniowej i naczyniowej*. Kierownik projektu: Prof. dr hab. Eugenia Murawska-Ciałowicz (AWF Wrocław). Finansowanie projektu: grant wewnętrzny Akademii Wychowania Fizycznego we Wrocławiu. Numer projektu: PN/BK/2020/5. Rola w projekcie: członek zespołu badawczego (2019 – 2021).
2) Międzynarodowy projekt naukowo-dydaktyczny: *The 2nd edition of the international didactic-scientific project Comparative Global Ag(e)ing.* Instystucja koordynująca projekt: University of Nebraska Omaha, USA. Rola w projekcie: członek zespołu badawczego (2020).

III. Współpraca naukowo-badawcza:

1) Prof. dr hab. Eugenii Murawskiej-Ciałowicz, Zakład Fizjologii i Biochemii, Wydział Wychowania Fizycznego i Sportu, Akademia Wychowania Fizycznego we Wrocławiu.
2) Dr. Sílvia Rocha-Rodrigues, Research Centre in Physical Activity and Health, Faculty of Sport, University of Porto, Portugal.

IV. Działalność dydaktyczna:

1) Zajęcia ze studentami na kierunku pielęgniarstwo I i II stopnia, Wydział Nauk o Zdrowiu, Uniwersytet Medyczny we Wrocławiu: Patologia, Neurologia i pielęgniarstwo neurologiczne, Wybrane zagadnienia opieki pielęgniarskiej w neurologii dziecięcej (2018 – 2021).

2) Zajęcia ze studentami na kierunku lekarskim i kierunku lekarskim *English Division*, Uniwersytet Medyczny we Wrocławiu: Choroby zakaźne (2021 – obecnie).

V. Działalność zawodowa:

1) Lekarz stażysta – staż podyplomowy w Dolnośląskim Centrum Onkologicznym we Wrocławiu (2018 – 2019).
2) Lekarz młodszy asystent (rezydent) – specjalizacja z pediatrii w Katedrze i Klinice Pediatrii i Chorób Infekcyjnych, Uniwersytet Medyczny we Wrocławiu; Kierownik: Prof. dr hab. Leszek Szenborn (2019 – obecnie).
3) Studia doktoranckie w Zakładzie Pielęgniarstwa Internistycznego, Katedra Pielęgniarstwa i Położnictwa, Wydział Nauk o Zdrowiu, Uniwersytet Medyczny we Wrocławiu; Promotor: Prof. dr hab. Joanna Rosińczuk (2018 – obecnie).

VI. Działalność organizacyjna:

1) Członek Zespołu Hospitującego Zajęcia na Wydziale Lekarskim Uniwersytetu Medycznego we Wrocławiu (2018 – 2019).
2) Członek Rady Dyscypliny Nauki Medyczne Uniwersytetu Medycznego we Wrocławiu (2019 – 2020).
3) Członek Rady Dyscypliny Nauki o Zdrowiu Uniwersytetu Medycznego we Wrocławiu (2020 – obecnie).

VII. Udział w konferencjach naukowych:

1) IV of Young International Students Coference Medical Researches 04-05th April 2014: Patients' preferences of doctors during the treatment a tan outpatients' clinc. Autorzy: **Borowicz Wojciech**, Kalota Aleksandra, Martyna Pawlak, Hanna Wiciak.
2) 7th Internacional Interdisciplinary and Educatinally-Instrctional Conference Young Physiotherapy Spring Time 23-24 May 2014 in Wrocław Poland: Preferencje pacjentów w wyborze lekarza podczas leczenia ambulatoryjnego na wolnym rynku usług medycznych. Autorzy: Wiciak Hanna, **Borowicz Wojciech**, Kalota Aleksandra, Pawlak Martyna.
3) V of Young International Students 'Coference Medical Researches Wrocław 09-11.04.2015: Sesja Zdrowia Publicznego i Medycyny Społecznej: The assessnment of professional burnout of medical Staff with the use of the LBQ questionnare-

preliminary. Autorzy: Hanna Wiciak, Aleksander Słupski, **Wojciech Borowicz** – praca wyróżniona.

4) VIII Studenckie Sympozjum Naukowe Wrocławskie Dni Zdrowia Publicznego 19-20 maja 2015: Czy praca na uczelni może stać się profilaktyką wypalenia zawodowego? Autorzy: **Wojciech Borowicz**, Martyna Pawlak, Aleksander Słupski, Hanna Wiciak.
5) Międzynarodowa Interdyscyplinarna Konferencja Naukowo-Szkoleniowa 8 Majówka Młodej Fizjoterapii 22-23 maj 2015 Wrocław: Wypalenie zawodowe wśród lekarzy i fizjoterapeutów. Autorzy: Wiciak Hanna, **Borowicz Wojciech** – sesja plakatowa praca wyróżniona I miejsce.
6) IX Dni Fizjoterapii AWF Wrocław 12-13 czerwca 2015: Postępy w rehabilitacji –od badań naukowych do praktyki klinicznej. Autorzy: Jadwiga Kuciel-Lewandowska, Łukasz Lewandowski, **Wojciech Borowicz**, Małgorzata Paprocka-Borowicz.
7) XXII Międzynarodowe Dni Inwalidy „ Życie bez bólu" - 18-20 marca 2016 Zgorzelec: Częstość oraz przyczyny występowania dyskopatii u dzieci na podstawie trzyletnich obserwacji pacjentów hospitalizowanych w Oddziałach Rehabilitacji Dziecięcej. Autorzy: Agata Trafalska, Anna Maria Choińska, Ewa Gieysztor, **Wojciech Borowicz**.
8) VI of Young International Students 'Coference Medical Researches Wrocław 31.03-02.04.2016: Sesja Nauk o Zdrowiu: Extra meals in hospital – a bad habit or a necessity? Preliminary results. Autorzy: Julian Maciaszek, Dorota Łuc, Hanna Wiciak, **Wojciech Borowicz**.
9) Interdyscyplinarna Konferencja Naukowo-Szkoleniowa – 9 Majówka Młodej Fizjoterapii Wrocław 21.05.2016: Analiza czynników wpływających na jakość życia osób z Zespołem Post-Polio. Autorzy: **Borowicz Wojciech**, Wiciak Hanna, Łuc Dorota, Maciaszek Julian – praca wyróżniona III miejsce.
10) The 16th International Congress of Young Medical Scientists 19-21st May 2016, Poznań, Poland: Evaluation of hospital nutrition in selected hospitals in Wrocław. Autorzy: Maciaszek Julian, Łuc Dorota, Wiciak Hanna, **Borowicz Wojciech**.
11) II Międzynarodowym Kongresie Polskiego Towarzystwa Zdrowia Publicznego Wrocław 24-25.11.2017 – „Zdrowie Publiczne – efektywnie wykorzystać zasoby ochrony zdrowia": Ocena wypalenia zawodowego pracowników kadry medycznej Uniwersyteckiego Szpitala Klinicznego we Wrocławiu. Autor: **Wojciech Borowicz.**
12) Międzynarodowym Dniu Inwalidy XXIII-edycja "Życie bez bólu. Zdrowe dzieci - zdrowa Europa" Zgorzelec 23-25.03.2017: Interdyscyplinarna rehabilitacja podczas odzwyczajana od żywienia przez gastrostomię u dziecka z zespołem CHARGE-opis przypadku. Autorzy: Agata Trafalska, Zofia Nowicka, Anna Maria Choińska, Ewa Gieysztor, **Wojciech Borowicz**.

13) Międzynarodowym Dniu Inwalidy XXIII-edycja "Życie bez bólu. Zdrowe dzieci - zdrowa Europa" Zgorzelec 23-25.03.2017: Rozwój lecznictwa w uzdrowisku Morszczyn Zdrój. Autorzy: Jadwiga Kuciel-Lewandowska, Andrzej Kierzek, Bożena Bogut, Łukasz B. Lewandowski, **Wojciech Borowicz**, Patryk Pozowski, Małgorzata Paprocka-Borowicz.
14) VII International Students' Conference of Young Medical Researchers – Wroclaw 6-8.04.2017: Who's afarid of the HIV? Knowledge about the HIV infection among Wroclaw high school students. Autorzy: Anna Pers, **Wojciech Borowicz.**
15) Interdyscyplinarna Konferencja Naukowo-Szkoleniowa – 10 Majówka Młodej Fizjoterapii Wrocław 26-27.05 2017: Neuralgia popółpaśćowa (PHN) - wyzwanie dla lekarzy i fizjoterapeutów. Autor: **Wojciech Borowicz** – praca nagrodzona II miejsce w kategorii sesji plakatowych.
16) 17th International Congres of Young Medical Scientists, Poznan, June 1st-3rd: The older, the better? – knowledge about the HIV infection among Wrocław high school and university students. Autorzy: Anna Pers, Kamil Cebulski, **Wojciech Borowicz** – praca wygrała sesje Public Care.
17) IX Zjazd PTN AIDS. Wrocław, 22-24 czerwca 2017: Kto się boi wirusa HIV? - ocena stanu wiedzy na temat zakażenia wirusem hiv wśród licealistów. Autorzy: Małgorzata Inglot, Anna Pers, **Wojciech Borowicz**, Kamil Cebulski.
18) XXIV Międzynarodowe Dni Inwalidy „ Życie bez bólu i Zdrowe dzieci-zdrowa Europa" – 15-17 marca 2018 Zgorzelec: Postepowanie rehabilitacyjne u dzieci z porażeniem nerwu twarzowego hospitalizowanych w Oddziale Rehabilitacji Dziennej. Autorzy: Agata Trafalska, Mateusz Trafalski, **Wojciech Borowicz**, Anna Maria Choińska, Ewa Gieysztor.
19) XXIV Międzynarodowe Dni Inwalidy „ Życie bez bólu i Zdrowe dzieci-zdrowa Europa" – 15-17 marca 2018 Zgorzelec: Wpływ czynników socjodemograficznych na jakość życia pacjentów z Zespołem Post-Polio. Autorzy: **Wojciech Borowicz.**
20) IX Sympozjum Współczesna myśl techniczna w naukach medycznych i biologicznych 22-23 czerwca 2018: Zastosowanie fototerapii u pacjentów rehabilitowanych z powodu dysfunkcji narządu ruchu z objawami depresji. Autorzy: Agata Trafalska, Małgorzata Paprocka-Borowicz, Anna Krzesińska-Nowacka, **Wojciech Borowicz.**
21) XXV Międzynarodowe Dni Inwalidy „ Życie bez bólu" – 28-30 marca 2019 Zgorzelec : Zastosowanie funkcji asymetrii w ocenie chodu osób po jednostronnej amputacji powyżej stawu kolanowego. Autorzy: Mateusz Kowal, Sławomir Winiarski, Ewa Gieysztor, Anna Kołcz, **Wojciech Borowicz**, Małgorzata Paprocka-Borowicz.
22) XXV Międzynarodowe Dni Inwalidy „ Życie bez bólu" – 28-30 marca 2019 Zgorzelec: Problem aktywności seksualnej u osób po uszkodzeniu rdzenia kręgowego. Autorzy:

Wojciech Borowicz, Paulina Kołodziejczyk, Anna Krzesińska-Nowacka, Joanna Rosińczuk.

23) XXV Międzynarodowe Dni Inwalidy „ Życie bez bólu" – 28-30 marca 2019 Zgorzelec: Zespół Guillan-Barre zaburzenia mowy i połykania. Autorzy: Anna Krzesińska-Nowacka, **Wojciech Borowicz**, Paweł Czerwiński, Agata Trafalska, Małgorzata Paprocka-Borowicz.
24) XXV Międzynarodowe Dni Inwalidy „ Życie bez bólu" – 28-30 marca 2019 Zgorzelec: Zniekształcenia ułożeniowe głowy kompleksowe postepowanie terapeutyczne. Autorzy: Agata Trafalska, Anna Krzesińska-Nowacka, Mateusz Trafalski, Magdalena Kazimierska-Zając, **Wojciech Borowicz.**
25) XXV Międzynarodowe Dni Inwalidy „ Życie bez bólu" – 28-30 marca 2019 Zgorzelec: Użycie lasera biostymulacyjnego w leczeniu porażenia nerwu bródkowego o podłożu zapalnym - opis przypadku. Autorzy: Mateusz Trafalski, Agnieszka Kukawczyńska-Chwałek, Agata Trafalska, **Wojciech Borowicz.**
26) X Ogólnopolska Konferencja Naukowa Człowiek w wieku podeszłym we współczesnym społeczeństwie Poznań 7 czerwca 2019 Organizacja systemu wsparcia i pomocy w procesie starzenia na przykładzie miasta Wrocławia. Autorzy: **Wojciech Borowicz**, Aneta Wnętrzak, Eugenia Murawska-Ciałowicz, Joanna Rosińczuk.
27) XII Interdyscyplinarna Konferencja Naukowo-Szkoleniowa Majówka Młodej Fizjoterapii Wrocław 14 czerwca 2019 Dostępność informacji na temat rehabilitacji seksualnej u osób po urazie rdzenia kręgowego. Autor: **Wojciech Borowicz.**
28) 26th Congress of the European Society of Biomechanics. Milan, Italy July 11-14, 2021: Symmetry function in patients after unilateral TFA using a mechanical or microprocessor prosthetic knee. Autorzy: Sławomir Winiarski, Mateusz Kowal, Ewa Gieysztor, Anna Kołcz, Karolina Walewicz, **Wojciech Borowicz**, Alicja Rutkowska-Kucharska, Małgorzata Paprocka-Borowicz.
29) 47 Zjazd Psychiatrów Polskich "Gdy nauka spotyka się z praktyką". Łódź, 8-11 czerwca 2021: Postawy społeczne wobec szczepień w kontekście zdrowia psychicznego. Autorzy: Julian Maciaszek, Marta Lenart-Bugla, Dorota Szcześniak, Paweł Gawłowski, **Wojciech Borowicz**, Błażej Misiak, Joanna Rymaszewska.

5. Wstęp

Incydenty mózgowo-naczyniowe (*cerebrovascular accidents*, CVA) związane z udarem mózgu dotyczą milionów ludzi na całym świecie, a roczna zapadalność na nie stale rośnie. W starzejącym się społeczeństwie, w którym występują liczne czynniki ryzyka, udary mózgu i późniejsze deficyty neurologiczne w wyniku uszkodzenia struktur ośrodkowego układu nerwowego (OUN) będą stanowiły coraz większe wyzwanie dla całego systemu opieki zdrowotnej [1,2]. Skuteczne postępowanie diagnostyczne i terapeutyczne, ale także prognostyczne w zakresie rokowania co do powrotu sprawności ruchowej po udarze mózgu pozostają ważnym interdyscyplinarnym problemem medycznym [3].

Udar mózgu charakteryzuje się deficytem neurologicznym związanym z ostrym ogniskowym uszkodzeniem OUN [4]. Według Amerykańskiego Towarzystwa Kardiologicznego (*American Heart Association*, AHA) i Amerykańskiego Towarzystwa Udarowego (*American Stroke Association*, ASA) definicja udaru mózgu wymaga spójnej specyfikacji dla wielowymiarowych potrzeb praktyki klinicznej, badań naukowych i zdrowia publicznego. Terminologia powinna opierać się na postępach w naukach podstawowych, neuropatologii i neuroobrazowaniu, które umożliwiają szczegółową obserwację i zrozumienie złożonych mechanizmów udaru w niedokrwieniu i krwotoku mózgowym [5].

Według Światowej Organizacji Zdrowia (*World Health Organization*, WHO) udar mózgu jest drugim najbardziej śmiertelnym zespołem chorobowym dotykającym osoby w wieku 60 lat i starsze [6]. Rocznie na udar mózgu zapada około 15-17 milionów osób na całym świecie, przy czym aż 5 milionów przypadków kończy się śmiercią, a kolejne 5 milionów wiąże się z trwałym kalectwem, co pośrednio dotyczy zarówno rodzin osób dotkniętych chorobą, jak i całego społeczeństwa [7,8].

Dane z badania populacyjnego ponad miliona pacjentów w ramach międzynarodowego projektu *European Registers Of Stroke* (EROS) [9] ukazują, że nieznacznie częściej udar mózgu występuje wśród kobiet (51,4%). Ponadto, stwierdzono, że średni wiek dla szczytu zachorowań wynosi 73 lata, a przedział wiekowy 75-84 lata charakteryzuje się najwyższą zachorowalnością, dotyczącą prawie 33% osób. Wykazano, że średnia roczna zapadalność na udar mózgu w populacji europejskiej wynosi 101,2 na 100 000, przy czym najwyższa zapadalność występuje na Litwie – 239,3 na 100 000, a najniższa we Włoszech – 101,2 na 100 000; natomiast w Polsce – 147,2 na 100 000 [9].

W badaniu kohortowym przeprowadzonym w ramach projektu *Atherosclerosis Risk in Communities* (ARIC) z udziałem blisko 500 pacjentów po udarze mózgu opisano specyficzne objawy incydentów CVA według częstości występowania, do których zaliczono niedowład

połowiczy, porażenie mięśni mimicznych, porażenie mięśni kończyn, jednostronne i kontrlateralne zaburzenia czucia, zaburzenia mowy, niespecyficzne bóle głowy, zaburzenia chodu i równowagi, utratę połowy pola widzenia, zawroty głowy i napady padaczkowe [10]. W udarze mózgu dochodzi do ograniczenia świadomych, skoordynowanych zdolności ruchowych, zarówno precyzyjnych jak i globalnych, zaburzeń kontroli motorycznej i zdolności proprioceptywno-posturalnych [11,12]. W konsekwencji dochodzi do znacznego pogorszenia ogólnego poziomu czynności życia codziennego (*activities of daily living*, ADLs) i uczestnictwa w życiu społecznym, co skutkuje negatywnym wpływem na jakość życia pacjentów związaną ze zdrowiem (*health-related quality of life*, HRQOL) [13,14].

Głównym celem współczesnej rehabilitacji medycznej pacjentów po udarze mózgu jest dążenie do odzyskania utraconych funkcji poprzez aktywowanie mechanizmów reorganizacji neuronalnej. Odpowiednie oddziaływania, między innymi w programie rehabilitacji, wywołują przemodelowanie OUN, szczególnie w zakresie kory ruchowej [15–17]. Trening usprawniający i fizjoterapia w postępowaniu z pacjentami po udarze mózgu jest uwarunkowana rodzajem i nasileniem deficytów ruchowych i poznawczych, a także stadium choroby [18]. Poszczególne cele terapeutyczne w oparciu o regułę SMART (Specyficzne-*Specific*, Mierzalne-*Measurable*, Adekwatne-*Attainable*, Realistyczne-*Realistic* i Terminalne-*Time-related*) [19,20] przebiegają od możliwie pełnego przywrócenia pacjentom ich sprawności i odzyskania zdolności do wypełniania ról społecznych i poprawy jakości życia (*quality of life*, QOL) [21,22].

Działania dotyczące odzyskiwania funkcji motorycznych (*motor recovery*) w ostatnich dekadach stały się przedmiotem badań nad mechanizmami plastyczności mózgu, która zapewnia adaptację organizmu do środowiska poprzez uczenie się i autonaprawę po uszkodzeniu [23,24]. Typowym przykładem plastyczności neuronalnej jest proces rekonwalescencji po udarze niedokrwiennym mózgu, który inicjuje reorganizację OUN i przejęcie niektórych funkcji przez nieuszkodzone części struktur mózgowych. Reorganizacja obejmuje również poszerzanie obszarów korowych, które stanowią neuronalne podłoże dla odzyskania lub adaptacji czynności ruchowych po uszkodzeniu [25]. Wyniki badań nad plastycznością mózgu umożliwiły rozwój neurorehabilitacji, która znajduje odzwierciedlenie w różnych metodach fizjoterapeutycznych, w tym proprioceptywnego nerwowo-mięśniowego torowania (*proprioceptive neuromuscular facilitation*, PNF) i terapii lustrzanej (*mirror therapy*, MT) [26–30].

Nie bez znaczenia jest także rola biomarkerów definiowanych jako czynników biologicznych, które są obiektywnie mierzone i oceniane jako wskaźniki normalnych procesów biologicznych, procesów patologicznych lub odpowiedzi ustrojowej na interwencję terapeutyczną [31]. Bez wątpienia jednym z takich czynników w kontekście udaru mózgu staje się białko C-reaktywne

(*C-reactive protein*, CRP). CRP jest biomarkerem stanu zapalnego i może odzwierciedlać progresję choroby naczyniowej. Cały proces produkcji tego białka odbywa się w odpowiedzi na cytokiny prozapalne i inne mediatory zapalenia [32]. Szczegółowy mechanizm obniżonego wyniku funkcjonalnego i tempa powrotu do sprawności po udarze niedokrwiennym mózgu nie jest jeszcze w pełni wyjaśniony i wiąże się ze złożonym cyklem powiązanych ze sobą mechanizmów molekularnych i komórkowych. Niektóre badania wskazują, że proces zapalny w fazie przetrwałej po udarze może promować naprawę tkanek i regenerację funkcjonalną [33].

W badaniach dotyczących przewidywania długoterminowych wyników funkcjonalnych u pacjentów po udarze mózgu wykazano, że poziom CRP w ciągu 12-24 godzin od wystąpienia objawów udaru był niezależnym predyktorem niekorzystnych wyników funkcjonalnych po 1 roku obserwacji. Poziom CRP mierzony w ciągu 24 do 48 godzin od wystąpienia objawów był jeszcze silniejszym predyktorem, ale ten przedział czasowy nie spełniał kryteriów włączenia, ponieważ nie mieści się w oknie czasowym oceny ostrego zapalenia [34].

Sprzeczne dowody sugerują, że CRP może być prognostycznym biomarkerem wyniku udaru niedokrwiennego mózgu. Jak wynika z piśmiennictwa, w większości badań, w których analizowano związek między CRP a wynikami udaru niedokrwiennego mózgu, jako pierwotną miarę wynikową stosowano śmiertelność lub kolejne zdarzenia naczyniowe. Jednak biorąc pod uwagę, że prawie połowa pacjentów po udarze mózgu doświadcza umiarkowanego lub ciężkiego upośledzenia funkcji, wykorzystanie biomarkera, takiego jak CRP, do przewidywania powrotu do zdrowia, a nie śmiertelności, może mieć wartość kliniczną podczas rehabilitacji [35].

Również niedobór witaminy D opisywany jest jako stan współwystępujący w wielu chorobach, takich jak ostry udar niedokrwienny mózgu, zaburzenia neurorozwojowe i niepełnosprawność intelektualna oraz ryzyko sercowo-naczyniowe, a także wiąże się ze zwiększoną śmiertelnością [36,37]. Co więcej, warto podkreślić, że niedobór witaminy D jest obecnie powszechnie znanym problemem zdrowia publicznego, który dotyczy prawie 1 na 2 osoby na świecie [38,39]. Ostatnie dowody z wielu badań populacyjnych wskazują, że niedobór witaminy D jest predyktorem przyszłych udarów mózgu [40,41].

Witamina D jest znanym hormonem neurosteroidowym, który odgrywa ważną rolę w modulacji procesów poznawczych i regulacji neurotroficznej sygnalizacji dla zapewnienia neuroprotekcji i neuromodulacji [42]. Odgrywa także zasadniczą rolę w regulacji procesów zapalnych [43,44] oraz naczyniowych czynników ryzyka udaru mózgu [45–47].

Wnioski płynące z przeglądu systematycznego i metaanalizy, potwierdziły hipotezę, że niskie stężenie witaminy D wiąże się ze zwiększonym ryzykiem wystąpienia udaru niedokrwiennego mózgu, co wskazuje, że jest to możliwy czynnik ryzyka udaru. Natomiast wyższe stężenie witaminy D istotnie chroni przed udarem mózgu [48]. W wielu dotychczasowych badaniach oceniano związek witaminy D z ryzykiem wystąpienia udaru mózgu [49,50]. W niewielu badaniach oceniano związek między stężeniem witaminy D w surowicy, a poziomem sprawności funkcjonalnej chorych po przebytym udarze mózgu; również mając na uwadze stopień niepełnosprawności.

Bez wątpienia, konieczne jest dalsze poszukiwanie skutecznych metod neurorehabilitacyjnych potrzebnych do kompleksowego i holistycznego usprawniania pacjentów po udarach. Istnieje potrzeba poddawania stałej empirycznej weryfikacji efektywności zastosowania tych metod w oparciu o badania z zastosowaniem silnych protokołów zapewniających wiarygodność danych naukowych w myśl zasad Medycyny Opartej na Dowodach Naukowych (*Evidence-Based Medicine*, EBM). Ważne jest identyfikowanie i analizowanie czynników biologicznie aktywnych jako potencjalnych biomarkerów skuteczności prowadzonej rehabilitacji i predyktorów powrotu sprawności funkcjonalnej, szczególnie w tak kluczowym dla potencjału rehabilitacyjnego pacjenta etapie regeneracyjno-kompensacyjnym po udarze niedokrwiennym mózgu.

6. Cele pracy

Cel ogólny:

- Kompleksowa ocena wpływu treningu usprawniającego pacjentów po udarze niedokrwiennym mózgu na poziom wybranych czynników wzrostu i plastyczności neuronalnej, mięśniowej i naczyniowej.

Cele szczegółowe:

- Porównanie wpływu dwóch metod neurorehabilitacji z zastosowaniem metody PNF lub MT na powrót zdolności funkcjonalnych w okresie regeneracyjno-kompensacyjnym u pacjentów z przebytym pierwszym udarze niedokrwiennym mózgu.
- Ewaluacja czynników wpływających na poziom CRP w surowicy krwi u pacjentów po udarze niedokrwiennym mózgu wraz z oceną przydatności CRP jako potencjalnego biomarkera skuteczności rehabilitacji i powrotu sprawności funkcjonalnej.
- Ocena związku pomiędzy stężeniem witaminy D w surowicy krwi a wynikami sprawności fizycznej i poziomu niepełnosprawności pacjentów poddanych rehabilitacji medycznej po udarze niedokrwiennym mózgu.
- Komplementarna analiza literatury i krytyczny przegląd badań naukowych dotyczących wykorzystania CRP jako potencjalnego biomarkera związanego z udarem mózgu i wpływającego na osiąganie postępów neurorehabilitacji u pacjentów po udarze.

7. Materiał i metody

7.1. Grupa badana

Wszyscy pacjenci biorący udział w projekcie badawczym byli usprawniani w Zamiejscowym Oddziale Rehabilitacji Neurologicznej Wojewódzkiego Szpitala Specjalistycznego we Wrocławiu, Ośrodka Badawczo-Rozwojowego, w okresie od stycznia 2020 do września 2022.

W pierwszym prospektywnym i interwencyjnym randomizowanym badaniu zaprezentowanym w oryginalnej pracy badawczej *Proprioceptive Neuromuscular Facilitation and Mirror Therapy Methods Are Comparable Methods of Rehabilitation After a First-Ever Ischemic Stroke: A Randomized Study* [51] udział wzięło 50 pacjentów (34 mężczyzn i 16 kobiet) w średnim wieku 65.5 ± 9.4 lat z pierwszym udarem niedokrwiennym mózgu w fazie regeneracyjno-kompensacji i przyjętych do oddziału w celu wczesnej rehabilitacji po udarze. Pacjentów losowo podzielono na dwie grupy pod względem stosowanej metody rehabilitacji: PNF (n=26) lub MT (n=24). Do oceny stanu funkcjonalnego na poziomie wyjściowym (M0) oraz po 3 (M1) i 6 tygodniach (M2) od interwencji zastosowano wskaźnik Barthel (*Barthel Index*, BI), a do oceny stopnia niepełnosprawności na poziomie wyjściowym (M0) oraz po 6 tygodniach (M2) od interwencji zastosowano zmodyfikowaną skalę Rankina (*modified Rankin Scale*, mRS).

Do udziału w drugim badania z protokołem retrospektywnej analizy prospektywnie zebranych danych ukazanym na łamach oryginalnej pracy badawczej *Assessment of Changes in Serum C-Reactive Protein Levels in Patients After Ischemic Stroke Undergoing Rehabilitation – A Retrospective Observational Study* [52] zakwalifikowano grupę 52 pacjentów (34 mężczyzn i 18 kobiet) po przebytym pierwszym udarze niedokrwiennym mózgu z następowym niedowładem połowiczym w średnim wieku 65.8 ± 9.33 lat. Rehabilitację z wykorzystaniem metod neurofizjologicznych stosowano pięć dni w tygodniu (każda sesja trwała 60 minut, a cały okres 42 dni). Poziom CRP w surowicy oznaczono podczas badań laboratoryjnych krwi. Do oceny wyników funkcjonalnych zastosowano mRS oraz wskaźnik BI.

W trzecim badaniu interwencyjnym badaniu opublikowanym w formie oryginalnej pracy badawczej *Association Between Serum Vitamin D Levels and Physical Outcomes of Patients Who Underwent Rehabilitation Following Ischemic Stroke* [60] przewidziano grupę 94 pacjentów, natomiast finalnie kryteria włączenia spełniło 80 pacjentów (55 mężczyzn i 25 kobiet) po udarze mózgu w średnim wieku 61,8 ± 6,9 lat. Zostali oni poddani 6-tygodniowej rehabilitacji z wykorzystaniem metody PNF (60 min dziennie), MT (30 min dziennie) oraz terapii zajęciowej (*occupational therapy*, OT; 45 min dziennie). Do oceny funkcjonalnej zastosowano wskaźnik BI i skalę mRS. Wykonano laboratoryjne badania krwi na poziom witaminy D i insulinopodobnego czynnika wzrostu 1 (*insulin-like growth factor 1*, IGF-1) w surowicy.

7.2. Narzędzia badawcze

Do pomiaru postępów terapeutycznych zastosowano walidowane i standaryzowane narzędzia klinimetryczne. Do oceny stanu funkcjonalnego użyto wskaźnika BI, a do oceny stopnia niepełnosprawności skali mRS. Skale długoterminowych wyników funkcjonalnych, takie jak mRS i BI, są powszechnie stosowane do pomiaru stopnia zależności fizycznej i charakteryzują się wysoką rzetelnością międzyosobniczą [53]. W drugim badaniu oceniano związek między punktacją BI, a wartościami CRP w trzech punktach czasowych oraz związek między mRS a poziomem CRP w dwóch punktach czasowych po udarze niedokrwiennym mózgu w okresie regeneracyjno-kompensacyjnym. W trzecim badaniu oceniano związek między poziomem witaminy D u pacjentów przyjętych na rehabilitację a wynikami funkcjonalnymi osiągniętymi podczas kompleksowego usprawniania fizjoterapeutycznego. Badania laboratoryjne były wykonywane w Laboratorium Naukowym Ośrodka Badawczo-Rozwojowego przy Wojewódzkim Szpitalu Specjalistycznym we Wrocławiu.

7.2.1. Wskaźnik Barthel (*Barthel Index,* BI)

Wskaźnik BI służy do oceny stopnia niezależności w wykonywaniu dziesięciu czynności życia codziennego u pacjentów poddawanych fizjoterapii po udarze niedokrwiennym mózgu. Mierzy zdolność pacjenta do wykonywania ADLs, takich jak kąpiel, ubieranie się, jedzenie i poruszanie się. Wskaźnik BI jest wykorzystywany do monitorowania postępów pacjenta w czasie oraz do określenia odpowiednich interwencji rehabilitacyjnych. Wykazano, że ma ona dobrą ważność, rzetelność i responsywność diagnostyczną, co czyni ją użytecznym narzędziem w praktyce klinicznej. Wskaźnik BI jest również często stosowany w badaniach naukowych nad udarem mózgu w celu pomiaru skuteczności interwencji i porównania wyników w różnych populacjach. BI jest cennym narzędziem do oceny stanu funkcjonalnego pacjentów po udarze niedokrwiennym mózgu i może pomóc w implementowaniu działań w zakresie rehabilitacji i powrotu do zdrowia. Zakres punktacji BI wynosi 0-20 pkt: ≤ 4 pkt (bardzo ciężka niepełnosprawność); 5-9 pkt (ciężka niepełnosprawność); 10-14 pkt (umiarkowane nasilenie niepełnosprawności); 15-19 pkt (lekka niepełnosprawność); 20 pkt (pełna niezależność) [54,55].

7.2.2. Zmodyfikowana Skala Rankina (*modified Rankin Scale*, mRS)

Wskaźnik mRS służy do przedstawienia uproszczonego opisu poziomu samodzielnego funkcjonowania. Dotyczy głównie funkcji lokomocyjnych oraz stopnia zależności od osób

trzecich i jest przydatna we wstępnej ogólnej ocenie pacjenta. Skala mRS jest powszechnie stosowanym narzędziem do oceny funkcjonalnej niepełnosprawności i powrotu do zdrowia pacjentów, który przebyli udar niedokrwienny mózgu. Mierzy ona stopień niepełnosprawności lub zależności w codziennych czynnościach, takich jak samoopieka, mobilność i zdolność do wykonywania zwykłych czynności. Skala jest wykorzystywana do oceny ogólnego stanu zdrowia pacjenta i rokowania, a także do kierowania decyzjami dotyczącymi leczenia i interwencji rehabilitacyjnych. Skala mRS ma dobrą rzetelność i ważność, a jej stosowanie jest zalecane przez wytyczne praktyki klinicznej i podczas prowadzenia badań naukowych. Zakres punktacji mRS mieści się w przedziale od 0 do 5 punktów: 0 (brak objawów); 1 (brak istotnej niepełnosprawności); 2 (lekka niepełnosprawność); 3 (umiarkowana niepełnosprawność); 4 (umiarkowanie ciężka niepełnosprawność); 5 (ciężka niepełnosprawność) [56,57].

7.2.3. Badania laboratoryjne stężenia CRP (*laboratory blood tests of CRP*)

Pacjenci mieli rutynowo pobieraną krew z żyły głównej co dwa tygodnie, tj. przy przyjęciu na oddział, po dwóch, czterech i sześciu tygodniach terapii. Krew do badań laboratoryjnych pobierano zawsze o tej samej porze, tj. o 6:30 rano na czczo. Badacze mieli na uwadze, że na poziom CRP i leukocytów mogły wpływać również środki pobierane w różnych warunkach klinicznych, np. o innej porze dnia lub po spożyciu pokarmu. Aby zminimalizować błędy i wyeliminować czynniki zakłócające, wszyscy pacjenci w naszym badaniu mieli pobieraną krew zawsze o tej samej porze, o godzinie 6:30, i nie przyjmowali niesteroidowych leków przeciwzapalnych. Ponadto oznaczono poziom CRP we krwi. Oceny CRP w surowicy dokonano przy użyciu testu Alinity c CRP Vario firmy Abbott (Chicago, Illinois, USA). Jest to test immunochemiczny, który wykorzystuje cząsteczki lateksu do dokładnego i precyzyjnego pomiaru poziomu CRP w surowicy i osoczu. Gdy dochodzi do reakcji antygen-przeciwciało pomiędzy białkiem CRP obecnym w badanej próbce a przeciwciałem przeciwko białku CRP zaadsorbowanym na cząstkach lateksowych, następuje proces aglutynacji. Proces aglutynacji jest wykrywany jako zmiana absorbancji (572 nm), przy czym szybkość zmiany jest proporcjonalna do ilości CRP obecnego w próbce [58].

7.2.4. Badania laboratoryjne poziomu witaminy D (*laboratory blood tests of vitamin D*)

Pacjentom rutynowo pobierano krew z żyły łokciowej na podstawowe badania laboratoryjne, takie jak pełna morfologia krwi (*complete blood count*, CBC) i badanie moczu. Oznaczono następujące stężenia: poziom witaminy D i IGF-1. Poziomy tych substancji w surowicy oznaczono przy przyjęciu na oddział oraz po 6 tygodniach treningu rehabilitacyjnego. U

każdego pacjenta pobierano krew z żyły łokciowej, zawsze o tej samej porze, o godzinie 6:30, na czczo. Wykonanie badań biochemicznych w tym samym czasie, przy użyciu odczynników z jednej serii produkcyjnej oraz zapewnienie takich samych warunków pomiaru miało na celu zminimalizowanie wystąpienia zewnętrznych, losowych błędów, które mogłyby zmienić wyniki analiz biochemicznych. Badania wykonywano w laboratorium na analizatorze Alinity ci z użyciem odczynników firmy Abbott (Chicago, Illinois, USA). Jest to szeroko stosowany, standaryzowany test immunochemiczny wykorzystujący chemiluminescencyjny test immunologiczny z mikrocząsteczkami (*chemiluminescent microparticle immunoassay*, CMIA) stosowany do ilościowego oznaczania 25(OH)D w ludzkiej surowicy i osoczu na analizatorze Alinity ci. Test Alinity ci 25-OH Vitamin D został wystandaryzowany względem National Institute of Standards & Technology Standard Reference Material 2972 (NIST SRM 2972). Do badanej próbki dodano mikrocząstki paramagnetyczne opłaszczone przeciwciałami przeciwko witaminie D oraz rozcieńczalnik do oznaczeń, a całą mieszaninę poddano inkubacji. Obecna w próbce 25-hydroksywitamina D była usuwana z białka wiążącego witaminę D, a następnie wiązała się z przeciwciałami przeciwko witaminie D, opłaszczając mikrocząstki. Koniugat zawierający witaminę D znakowaną akrydyną był dodawany w celu utworzenia mieszaniny reakcyjnej. Mieszanina reakcyjna była inkubowana. Po cyklu mycia dodawano roztwór Pre-Trigger oraz roztwór wyzwalający reakcję Trigger Solution. Intensywność sygnału powstałego w wyniku reakcji chemiluminescencji mierzono we względnych jednostkach światła (RLU), na podstawie zależności między ilością 25-hydroksywitaminy D w próbce a wartościami RLU mierzonymi przez układ optyczny. Prawidłowy poziom witaminy D w surowicy był definiowany jako stężenie 25(OH)D >30 ng/ml. Niedobór witaminy D definiowano jako stężenie 25(OH)D <30 ng/ml [59].

7.3. Wymogi etyczne

Niniejszy projekt badawczy uzyskał pozytywną rekomendację niezależnej komisji Bioetycznej Uniwersytetu Medycznego we Wrocławiu z numerem zgody KB-813/2020). Badanie zostało prospektywnie zarejestrowane na platformie *International Standard Randomised Controlled Trial Number* (ISRCTN) z numerem rejestracyjnym ISRCTN16891871. Badanie przeprowadzono zgodnie z zasadami Deklaracji Helsińskiej i Dobrej Praktyki Klinicznej. Wszyscy uczestnicy badania wyrazili pisemną, dobrowolną i świadomą zgodę przed udziałem w badaniu. Każda osoba przed podpisaniem zgody na udział w badaniu została poinformowana i poinstruowana o przebiegu oraz o możliwości zadawania pytań celem uzyskania wyjaśnienia dotyczącego badania. Wszyscy uczestnicy badania zostali poinformowani o możliwości przerwania udziału w projekcie w przypadku problemów zdrowotnych lub z innych powodów, bez ponoszenia żadnych konsekwencji.

7.4. Analiza statystyczna

Analizę statystyczną przeprowadzono przy użyciu oprogramowania Statistica 13 (TIBCO, Inc., Palo Alto, USA). Dla zmiennych mierzalnych obliczano średnie arytmetyczne i odchylenia standardowe lub mediany, górny i dolny kwartyl oraz zakres zmienności (wartość minimalna i maksymalna). Dla zmiennych jakościowych obliczono częstość występowania (%). Wszystkie badane zmienne ilościowe zweryfikowano za pomocą testu Shapiro-Wilka w celu określenia typu rozkładu. W pierwszej pracy porównania wewnątrzgrupowe pomiędzy wynikami uzyskanymi w miarach 1 (M1) i 2 (M2) przeprowadzono za pomocą testu Wilcoxona, natomiast w miarach 1-4 (M1-4) za pomocą analizy wariancji ANOVA Friedmana i testu post-hoc (test Dunna); natomiast porównanie międzygrupowe oceniono za pomocą testu U-Manna-Whitneya. W drugiej pracy porównania wyników przed i po terapii dokonano za pomocą testu t dla prób niezależnych; wykonano analizę korelacji Pearsona pomiędzy wybranymi zmiennymi oraz analizę wpływu wybranych czynników na wynik BI z wykorzystaniem regresji liniowej; kolejnym krokiem było zbudowanie modelu wieloczynnikowego z wykorzystaniem regresji krokowej postępującej. W trzeciej pracy porównania między punktacją przed i po rehabilitacji przeprowadzono za pomocą nieparametrycznego testu Wilcoxona; analizę wpływu wybranych zmiennych na czynności życia codziennego (BI) oraz niezależność w wykonywaniu codziennych czynności (mRS) przeprowadzono z wykorzystaniem regresji liniowej (model jednoczynnikowy); wyznaczono niestandaryzowane i standaryzowane współczynniki regresji, a kolejnym krokiem było opracowanie modelu wieloczynnikowego (metoda progresywna krokowa). Do wszystkich porównań przyjęto poziom $\alpha=0,05$.

8. Wyniki

Za nadrzędny cel pierwszej pracy badawczej *Proprioceptive Neuromuscular Facilitation and Mirror Therapy Methods Are Comparable Methods of Rehabilitation After a First-Ever Ischemic Stroke: A Randomized Study* [51] postawiono porównanie wpływu dwóch metod neurorehabilitacji z zastosowaniem metody PNF lub MT na powrót zdolności funkcjonalnych w okresie regeneracyjno-kompensacyjnym u pacjentów po pierwszym przebytym udarze niedokrwiennym mózgu. Po zakończeniu badania odnotowano, że istotne statystycznie różnice w obu grupach badawczych w ocenie przy użyciu wskaźnika BI (efekt główny: $p<0,05$). W grupie MT nastąpiła poprawa pomiędzy M1 i M2 o 3,6 punktu, M1 i M3 o 6,9 punktu oraz M2 i M3 o 6,9 punktu. Dla grupy PNF wystąpiły różnice pomiędzy M1 i M2 o 4,1 punktu, M1 i M3 o 7,2 punktu oraz M2 i M3 o 3,1 punktu. Również w obu grupach odnotowano istotne statystycznie różnice w ocenie za pomocą mRS (efekt główny: $p<0,05$). W grupie MT nastąpił spadek o 2,2 punktu pomiędzy pomiarami M1 i M2. W przypadku grupy PNF wystąpiły różnice pomiędzy M1 i M2 o 2,3 punktu. Nie było istotnych statystycznie różnic pomiędzy grupami MT i PNF zarówno w punktacji BI jak i mRS ($p<0,05$).

Z kolei, głównym celem drugiej pracy badawczej *Assessment of Changes in Serum C-Reactive Protein Levels in Patients After Ischemic Stroke Undergoing Rehabilitation – A Retrospective Observational Study* [52] było przeanalizowanie czynników wpływających na poziom CRP w surowicy krwi u pacjentów po udarze niedokrwiennym mózgu w okresie regeneracyjno-kompensacyjnym z uwzględnieniem oceny przydatności CRP jako potencjalnego biomarkera skuteczności rehabilitacji i powrotu sprawności funkcjonalnej. W toku realizacji projektu, w pierwszym badaniu poziomu CRP w surowicy krwi stwierdzono wyniki powyżej normy (5mg/l) u 19 pacjentów, w drugim badaniu u 12 pacjentów, w trzecim badaniu u 5 pacjentów, a w czwartym badaniu u 9 pacjentów. Tylko u trzech pacjentów wartości były wyższe niż 5mg/l we wszystkich kolejnych ocenach ($p>0,05$). Zaobserwowano istotny statystycznie wzrost punktacji wskaźnika BI po terapii ($p<0,001$), a także spadek punktacji skali mRS o 2,2 punktu ($p<0,001$), wartości CRP o 5,02 mg/l ($p=0,019$) oraz poziomu kortyzolu o 2,5 nmol/l ($p=0,002$). Zaobserwowano istotne statystycznie zależności pomiędzy poziomem CRP po przeprowadzonym postepowaniu rehabilitacyjnym, a odpowiadającą mu punktacją w skali mRS ($rs=0,29$, $p=0,038$). Wykazano również wpływ wskaźnika masy ciała (*body mass index*, BMI) na poziom CRP ($B=0,20$, $p=0,038$).

Natomiast zasadniczym celem trzeciej pracy badawczej *Association Between Serum Vitamin D Levels and Physical Outcomes of Patients Who Underwent Rehabilitation Following Ischemic Stroke* [60] było zbadanie związku pomiędzy stężeniem witaminy D w surowicy krwi a wynikami sprawności fizycznej pacjentów poddanych rehabilitacji ruchowej po udarze

niedokrwiennym mózgu. Wyniki uzyskane podczas przeprowadzonego badania wskazują na istotny wzrost punktacji wskaźnika BI (mediana różnicy = 2,0 pkt ; p<0,001) oraz poziomu IGF (mediana różnicy = 124,6 ng/ml; p<0,001) po przeprowadzonej rehabilitacji z zastosowaniem metod PNF, MT oraz OT. Nastąpiło istotne zmniejszenie punktacji w skali mRS (mediana różnicy = 7,0 pkt; p<0,001), ale nie było istotnej różnicy w poziomie witaminy D (p=0,40). Wykazano wpływ wieku (B=-0,01, p=0,04) i poziomu witaminy D w surowicy (B=-0,02, p=0,01) na wynik wskaźnika BI. Zaobserwowano wpływ wyników BMI (B=-0,07, p=0,02) na wynik uzyskane za pomocą skali mRS.

Przytoczyć należy również założenia czwartej pracy o charakterze poglądowym *C-Reactive protein as a biomarker affecting neurorehabilitation outcomes in post-stroke patients: state of knowledge and global trends in research* [61], której celem była komplementarna analizy literatury i krytyczny przegląd badań naukowych dotyczących wykorzystania CRP jako potencjalnego biomarkera związanego z udarem mózgu i wpływającego na osiąganie postępów neurorehabilitacji u pacjentów po udarze. Wykazano, że dostrzeżenie roli czynników zapalnych i immunologicznych w rozwoju miażdżycy i wystąpieniu udaru niedokrwiennego mózgu stwarza pole do poszukiwania nowych metod oceny ryzyka wystąpienia udaru mózgu oraz opracowania nowych metod jego prewencji. Przeprowadzone dotychczas badania zakwalifikowane do niniejszego przeglądu ujawniły istotną rolę mechanizmów zapalnych i poziomu stężenia CRP w dynamice rozwoju ogniska udarowego. W odpowiedzi na obecność tkanek martwiczych (uwalnianych z nich antygenów) rozwija się ostra odpowiedź zapalna, która przyczynia się do powiększenia obszaru martwicy i znajduje odzwierciedlenie w pogorszeniu stanu neurologicznego. Wpływa to również znacząco na późniejsze rokowanie pacjenta po udarze i ma bezpośrednie przełożenie na skuteczność rehabilitacji medycznej oraz postępy, jakie osiąga chory w odzyskiwaniu funkcji ruchowych utraconych w wyniku udaru. Konieczna jest dalsza empiryczna weryfikacja i jednoznaczne wykazanie znaczenia CRP jako potencjalnego biomarkera wpływającego na stan zdrowia pacjenta po udarze mózgu w celu zapewnienia jak odpowiednie rehabilitacji ruchowej i odzyskania możliwie jak największego poziomu zdolności do samodzielnego funkcjonowania w zakresie wszystkich czynności życia codziennego [61].

9. Podsumowanie

Syntetyczna interpretacja niniejszych wyników i rozważenie ich znaczenia w świetle dostępnej literatury wskazuje, że ćwiczenia fizyczne u pacjentów po udarze mózgu mogły wywołać mechanizmy neuroplastyczności, które doprowadziły do poprawy funkcji OUN u rehabilitowanych pacjentów po pierwszym udarze niedokrwiennym. Procesy te prawdopodobnie zachodzą na wielu poziomach, rozpoczynając od poziomu komórkowego i postępując na drodze neuroprzekaźnictwa do sieci neuronalnych budujących funkcjonalne połączenia pomiędzy współpracującymi obszarami mózgu [25].

Przedstawione wyniki nie rozstrzygają o skuteczności danej formy terapii w całościowym procesie rehabilitacji. Jednak w obu grupach pacjentów nastąpiła znacząca poprawa stanu funkcjonalnego w ocenie adekwatnymi narzędziami klinimetrycznymi takimi jak BI i mRS. Terapia prowadzona koncepcją PNF oraz MT pozwala na wykorzystanie zjawiska plastyczności OUN do aktywizacji receptorów układu ruchu [62,63]. Analiza testów funkcjonalnych pacjentów poddanych rehabilitacji wykazała poprawę stanu funkcjonalnego u wszystkich pacjentów niezależnie od rodzaju zastosowanej terapii (MT lub PNF).

Odnosząc wyniki MT (mimo znacznej liczby prac i przeglądów systematycznych dotyczących zastosowania tej metody w celu oceny skuteczności tej prostej i taniej metody o charakterze terapii skoncentrowanej na pacjencie po udarze, która może poprawić funkcję kończyny górnej) do innych prac badawczych, należy pamiętać, że jest to dość trudne, gdyż dokonując przeglądu piśmiennictwa, nie znaleziono podobnych badań jak w naszym projekcie oceniających skuteczność MT. Na podstawie przeglądu piśmiennictwa na temat MT wdrożonej u pacjentów po przebytym po raz pierwszy udarze niedokrwiennym mózgu można zauważyć, że większość badań nie spełnia rzetelnej jakości metodologicznej i prezentuje ograniczony poziom dowodów. Utrudnia to włączenie skuteczności klinicznej MT do codziennej praktyki neurorehabilitacyjnej. W pracach tych nie stosowano ustalonego protokołu kwalifikacyjnego ani właściwej randomizacji, a badania często prowadzono jedynie w oparciu o subiektywne kwestionariusze i skale odczuwania bólu (brak metod pomiarowych obiektywizujących postępy leczenia).

Jak wynika z powyższej dyskusji, uzasadnione było przeprowadzenie badania w tym zakresie obejmującego zarówno metody PNF, jak i MT, randomizację, spójny materiał badawczy, ścisły protokół kwalifikacji, subiektywne i obiektywne narzędzia pomiarowe oraz wczesne wyniki. W celu dalszego wzmocnienia dowodów naukowych zaleca się, aby zebrane dane zostały niezależnie potwierdzone przez inne instytucje. W ostatnim czasie nadal istnieją ograniczone dowody o dużej wartości naukowej, aby jednoznacznie przesądzić o skuteczności terapii PNF

nad MT lub odwrotnie u pacjentów po pierwszym udarze niedokrwiennym mózgu. W chwili obecnej wyniki dotychczasowych badań są obiecujące, ale fakt ten wymaga dalszej weryfikacji.

Bez wątpienia, kompleksowa rehabilitacja jest podstawowym elementem postępowania terapeutycznego, dzięki któremu pacjenci osiągają poprawę funkcjonalną i niezależność. Ponadto rehabilitacja prowadzona przez interdyscyplinarny zespół stanowi kluczowy element zmniejszający ryzyko zgonu, ciężkiej niepełnosprawności oraz stresu związanego z koniecznością przystosowania się do życia w warunkach zmienionych przez chorobę. Odnośnie badania poziomu CRP, nowością zaprezentowanej pracy jest pogłębiona ocena poziomu CRP u pacjentów po udarze niedokrwiennym mózgu poddanych rehabilitacji neurologicznej w ramach badania opartego na ścisłym protokole, z jednoznacznymi kryteriami włączenia i wyłączenia, z wykorzystaniem zarówno obiektywnych pomiarów, jak i subiektywnych skal zalecanych w literaturze, z jednolitą konstrukcją statystyczną. Jak wynika z dostępnego piśmiennictwa, podejmowano liczne próby oceny zarówno poziomu CRP u pacjentów po udarze mózgu w fazie ostrej, jak i wpływu udaru na wynik funkcjonalny tej grupy chorych, natomiast niewiele jest prac dotyczących korelacji poziomu CRP i jego wpływu na wynik funkcjonalny pacjentów po udarze niedokrwiennym mózgu w okresie regeneracyjno-kompensacyjnym.

Odnośnie badania nad witaminą D, w naszym projekcie oceniano poziom witaminy D w surowicy u pacjentów z pierwszorazowym udarem niedokrwiennym przy przyjęciu na oddział rehabilitacji. Niedobór witaminy D definiowano jako stężenie 25(OH)D w osoczu <30 ng/ml. W badanej grupie stwierdzono, że 67,5% pacjentów (54 chorych) miało niedobór witaminy D3. Niedobory witaminy D są obecnie powszechnie znanym problemem zdrowia publicznego, który dotyczy prawie 1 na 2 osoby na świecie. Ostatnie dowody z wielu badań populacyjnych wskazują, że niedobór witaminy D jest predyktorem przyszłych udarów mózgu. Ta "pandemia" niedoboru witaminy D jest niepokojąca, ponieważ niskie poziomy witaminy D w surowicy są związane z chorobami sercowo-naczyniowymi, mięśniowo-szkieletowymi, zakaźnymi, autoimmunologicznymi i złośliwymi.

Ponieważ udar mózgu jest wiodącą przyczyną niepełnosprawności, a osoby starsze mają często poważne niedobory witaminy D, należy rozszerzyć badania oceniające skuteczność suplementacji witaminą D. Przedstawione powyżej wyniki zawierają wiele interesujących i istotnych informacji, które mają znaczenie poznawcze i praktyczne dla planowania rehabilitacji u pacjentów po udarze niedokrwiennym mózgu w okresie rekonwalescencji i kompensacji, jednak do wdrożenia tej wiedzy w praktyce klinicznej potrzebne są dalsze badania.

9.1. Ograniczenia badań własnych

Do ograniczeń metodologicznych zaliczyć można brak grupy kontrolnej złożonej z pacjentów poddawanych jedynie standardowej neurorehabilitacji (bez PNF i MT), jak również brak zaślepienia próby względem zastosowanych interwencji rehabilitacyjnych. W przyszłych badaniach istnieje potrzeba zastosowania innych obiektywnych metod pomiaru oraz kontynuowania projektu z większą liczbą uczestników i przez dłuższy okres (follow-up). Ważnym aspektem jest ustalenie standaryzowanych parametrów leczenia, które mogłyby zostać zweryfikowane przez innych badaczy. Korzystne byłoby również rozszerzenie oceny niepełnosprawności o inne kwestionariusze i skale, takie jak Pomiar Niezależności Funkcjonalnej (*Functional Independence Measure*, FIM) czy polski Wskaźnik Funkcjonalny Repty (*Repty Functional Index*, RFI).

Ponadto nasze wyniki dotyczyły tylko pacjentów z jednego ośrodka i nie mogą być generalizowane na większą populację. Dlatego też związek między wartościami CRP w osoczu a wynikami funkcjonalnymi po udarze niedokrwiennym mózgu w okresie regeneracyjno-kompensacyjnym powinien być dalej weryfikowany w innych populacjach pacjentów. Podkreślić należy, że zmieniony stan psychiczny i towarzysząca depresja są ważnymi problemami klinicznymi związanymi z udarem mózgu, a w niektórych badaniach wykazano korelację między zmienionym stanem psychicznym po udarze a podwyższonym CRP. Bardziej holistyczna ocena wyników przy użyciu skal uwzględniających zarówno fizyczne, jak i psychiczne samopoczucie może lepiej scharakteryzować ogólną niepełnosprawność po udarze pod względem długoterminowych wyników.

W przyszłości wskazane byłoby przeprowadzenie wieloośrodkowego badania w celu walidacji poziomu witaminy D w innych kohortach. Nie możemy bezpośrednio odnieść naszych wyników do powyższych badań ze względu na fakt, że nasza grupa badawcza obejmowała wyłącznie pacjentów po udarze niedokrwiennym mózgu, ale nieleczonych terapią trombolityczną. Przyszłe badania, które planujemy rozszerzyć na większą populację pacjentów, powinny uwzględniać ten aspekt. Ponadto nie było możliwości wykluczenia błędów związanych ze zmiennymi, które nie były mierzalne w tym badaniu obserwacyjnym, takimi jak ekspozycja na słońce, dieta, aktywność fizyczna czy poziom parathormonu. Nie przeprowadzono pogłębionej analizy stanu odżywienia jak również przyszłych badaniach należy rozważyć, czy suplementacja witaminą D u pacjentów poddawanych rehabilitacji poprawia wyniki funkcjonalne u pacjentów z niedokrwiennym udarem mózgu.

9.2. Implikacje dla praktyki klinicznej

Przedstawione powyżej wyniki dostarczają wielu ciekawych i istotnych informacji, które mają znaczenie poznawcze i praktyczne dla planowania rehabilitacji u pacjentów po udarze niedokrwiennym mózgu w okresie regeneracyjno-kompensacyjnym. Wdrożenie tej wiedzy do praktyki klinicznej wymaga jednak dalszych dobrze zaplanowanych i wieloośrodkowych badań. W celu dalszego wzmocnienia dowodów naukowych zaleca się, aby zebrane dane zostały niezależnie potwierdzone przez inne ośrodki badawcze. W ostatnim czasie nadal istnieją ograniczone dowody o dużej wartości naukowej, aby jednoznacznie przesądzić o skuteczności terapii PNF nad MT, przewagi jednej metody nad drugą stosowanych oddzielnie u pacjentów po pierwszym udarze niedokrwiennym mózgu.

Ciekawym rozwiązaniem w celu obserwacji potencjalnego skumulowanego efektu terapeutycznego, byłoby połączeniu oby tych metod i jednoczesne ich zastosowanie w rehabilitacji usprawniającej. Ponadto, kliniczna przydatność stężenia CRP w rehabilitacji pacjentów po udarze niedokrwiennym mózgu w okresie regeneracyjno-kompensacyjnym podczas leczenia problemów z poruszaniem się powinna być brana pod uwagę podczas rutynowej oceny efektów terapii.

Natomiast zgodnie z wynikami naszego badania wskazującymi, że niższe stężenie witaminy D w surowicy i bardziej zaawansowany wiek mogą być związane z gorszymi wynikami funkcjonalnymi u pacjentów z pierwszym w życiu udarem niedokrwiennym; istnieje potrzeba włączenia oznaczenia stężenia witaminy D jako czynnika rokowniczego w zakresie efektywności prowadzonych działań usprawniających w kontekście uzyskiwanego poziomu poprawy sprawności fizycznej.

10. Wnioski

1) Zarówno metody neurorehabilitacji PNF, jak i MT mogą być przydatne w poprawie stanu funkcjonalnego i zmniejszeniu poziomu niepełnosprawności u pacjentów po pierwszym udarze mózgu w fazie regeneracyjno-kompensacyjnej.
2) Pomimo wykazania istotnego związku między poziomem CRP i punktacją mRS, samo CRP może być niewystarczającym predyktorem długoterminowych wyników funkcjonalnych rehabilitowanych pacjentów z udarem niedokrwiennym mózgu.
3) Niższe stężenie witaminy D w surowicy i starszy wiek pacjentów mogą być związane z gorszym poziomem funkcjonowania pacjentów z przebytym pierwszym udarem niedokrwiennym mózgu.
4) Konieczna jest dalsza empiryczna weryfikacja i jednoznaczne wykazanie potencjału stężenia CRP oraz witaminy D jako predyktorów warunkujących stan zdrowia pacjenta po udarze mózgu, aby zapewnić możliwie największy poziom powrotu do sprawności ruchowej i zdolności do samodzielnego funkcjonowania pacjentów w zakresie wszystkich czynności życia codziennego.

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12. Streszczenie

Wpływ treningu usprawniającego pacjentów po udarze niedokrwiennym mózgu na poziom wybranych czynników wzrostu i plastyczności neuronalnej, mięśniowej i naczyniowej

Wstęp: Udary mózgu dotyczą milionów ludzi na całym świecie, a roczna zapadalność stale rośnie. Skuteczne postępowanie diagnostyczne i terapeutyczne, ale także prognostyczne dotyczące powrotu sprawności ruchowej po udarze pozostają ważnym interdyscyplinarnym problemem medycznym. Głównym celem współczesnej rehabilitacji medycznej pacjentów po udarze mózgu z zastosowaniem takich metod jak proprioceptywne nerwowo-mięśniowego torowanie (PNF) i terapia lustrzana (MT) jest dążenie do odzyskania utraconych funkcji poprzez aktywowanie mechanizmów reorganizacji neuronalnej. Działania dotyczące odzyskiwania funkcji motorycznych w ostatnich dekadach stały się przedmiotem badań nad mechanizmami plastyczności mózgu. Nie bez znaczenia jest także rola biomarkerów, które są obiektywnie mierzalne i swoiste dla uszkodzeń układu nerwowego i mogą być powiązane z interwencję terapeutyczną. Jednym z takich czynników jest białko C-reaktywne (CRP) typowe dla procesów zapalnych, które także w fazie przetrwałej po udarze może promować naprawę tkanek i regenerację funkcjonalną. Również witamina D odgrywa ważną rolę w modulacji procesów poznawczych, neuroprotekcji i neuromodulacją. W wielu badaniach oceniano związek witaminy D z ryzykiem wystąpienia udaru mózgu nie mniej jednak brakuje badań oceniających związek między stężeniem witaminy D, a poziomem sprawności funkcjonalnej chorych po przebytym udarze mózgu.

Cele: Celem głównym projektu badawczego była kompleksowa ocena wpływu treningu usprawniającego pacjentów po udarze niedokrwiennym mózgu na poziom wybranych czynników wzrostu i plastyczności neuronalnej, mięśniowej i naczyniowej. Wyróżniono następujące cztery cele szczegółowe: (1) porównanie wpływu dwóch metod neurorehabilitacji z zastosowaniem metody PNF lub MT na powrót zdolności funkcjonalnych w okresie regeneracyjno-kompensacyjnym u pacjentów z przebytym pierwszym udarze niedokrwiennym mózgu; (2) ewaluacja czynników wpływających na poziom CRP w surowicy krwi u pacjentów po udarze niedokrwiennym mózgu wraz z oceną przydatności CRP jako potencjalnego biomarkera skuteczności rehabilitacji i powrotu sprawności funkcjonalnej; (3) ocena związku pomiędzy stężeniem witaminy D w surowicy krwi a wynikami sprawności fizycznej i poziomu niepełnosprawności pacjentów poddanych rehabilitacji medycznej po udarze niedokrwiennym mózgu; oraz (4) komplementarna analiza literatury i krytyczny przegląd badań naukowych dotyczących wykorzystania CRP jako potencjalnego biomarkera związanego z udarem mózgu i wpływającego na osiąganie postępów neurorehabilitacji u pacjentów po udarze.

Materiał i metody: Niniejszy projekt badawczy uzyskał pozytywną rekomendację niezależnej komisji Bioetycznej Uniwersytetu Medycznego we Wrocławiu (KB-813/2020). W ramach niniejszego projektu badawczego zakwalifikowano dorosłych pacjentów po przebytym pierwszym udarze niedokrwiennym mózgu będących w okresie regeneracyjno-kompensacyjnym. Zakwalifikowanych do badania pacjentów rehabilitowano z wykorzystaniem metod neurofizjologicznych PNF lub MT uzupełnionych o terapię zajęciową (OT). W pierwszym badaniu udział wzięło 50 pacjentów (34 mężczyzn i 16 kobiet) w średnim wieku 65.5 ± 9.4 lat; pacjentów losowo podzielono na dwie grupy pod względem stosowanej metody rehabilitacji: PNF (n=26) lub MT (n=24). Do drugiego badania zakwalifikowano grupę 52 pacjentów (34 mężczyzn i 18 kobiet) w średnim wieku 65.8 ± 9.33 lat; poziom CRP w surowicy oznaczono podczas badań laboratoryjnych krwi. Natomiast w trzecim badaniu kryteria włączenia spełniło 80 pacjentów (55 mężczyzn i 25 kobiet) w średnim wieku 61,8 ± 6,9 lat; wykonano laboratoryjne badania krwi na poziom witaminy D i insulinopodobnego czynnika wzrostu 1 (IGF-1). W każdym z trzech badań, do oceny stanu funkcjonalnego zastosowano wskaźnik Barthel (BI), a ocenę stopnia niepełnosprawności weryfikowano zmodyfikowaną skalę Rankina (mRS). Analizę statystyczną przeprowadzono przy użyciu oprogramowania Statistica 13; do wszystkich porównań przyjęto poziom $\alpha=0,05$.

Wyniki: Pierwsza praca badawcza z cyklu: Odnotowano istotne statystycznie różnice w obu grupach badawczych w ocenie przy użyciu wskaźnika BI (efekt główny: <0,05); jak również wykazano istotne statystycznie różnice w ocenie za pomocą mRS (efekt główny: $p<0,05$). Nie zaobserwowano istotnych statystycznie różnic pomiędzy grupami MT i PNF w punktacji BI oraz mRS ($p<0,05$). Druga praca badawcza z cyklu: Zaobserwowano istotny statystycznie wzrost punktacji BI po frehabilitacji ($p<0,001$), a także spadek punktacji mRS o 2,2 punktu ($p<0,001$), spadek wartości CRP o 5,02 mg/l ($p=0,019$) oraz spadek poziomu kortyzolu o 2,5 nmol/l ($p=0,002$). Po rehabilitacji, wykazano istotne statystycznie zależności pomiędzy poziomem CRP w skali mRS ($rs=0,29$, $p=0,038$). Wykazano również wpływ BMI na poziom CRP ($B=0,20$, $p=0,038$). Trzecia praca badawcza z cyklu: Odnotowano istotny wzrost punktacji BI ($p<0,001$) oraz poziomu IGF ($p<0,001$) po rehabilitacji. Nastąpiło istotne zmniejszenie punktacji w skali mRS (7,0 pkt; $p<0,001$), ale nie było istotnej różnicy w poziomie witaminy D ($p=0,40$). Wykazano wpływ wieku ($B=-0,01$, $p=0,04$) i poziomu witaminy D ($B=-0,02$, $P=0,01$) i na wynik BI. Wykazano wpływ wyników BMI ($B=-0,07$, $p=0,02$) na wynik mRS. Czwarta praca poglądowa z cyklu: Przeprowadzone dotychczas badania zakwalifikowane do niniejszego przeglądu ujawniły istotną rolę mechanizmów zapalnych i poziomu stężenia CRP w dynamice rozwoju ogniska udarowego. W odpowiedzi na obecność tkanek martwiczych dochodzi do rozwijania się ostrej odpowiedzi zapalnej, która przyczynia się do powiększenia obszaru martwicy i znajduje odzwierciedlenie w pogorszeniu stanu neurologicznego pacjentów.

Wnioski: (1) Metody neurorehabilitacji PNF i MT mogą być przydatne w poprawie stanu funkcjonalnego i zmniejszeniu poziomu niepełnosprawności u pacjentów po pierwszym udarze mózgu. (2) Pomimo wykazania istotnego związku między poziomem CRP i punktacją mRS, samo CRP może być niewystarczającym predyktorem długoterminowych wyników funkcjonalnych. (3) Niższe stężenie witaminy D w surowicy i starszy wiek pacjentów mogą być związane z gorszym poziomem funkcjonowania pacjentów po udarze; (4) Konieczna jest dalsza empiryczna weryfikacja i jednoznaczne wykazanie potencjału stężenia CRP oraz witaminy D jako predyktorów warunkujących stan zdrowia pacjenta po udarze mózgu.

Słowa kluczowe: badania laboratoryjne; biomarkery; C-reaktywna proteina; ocena funkcjonalna; okres regeneracyjno-kompensacyjny; proprioceptywne nerwowo-mięśniowe torowanie; regeneracja po udarze; rehabilitacja neurologiczna; rekonwalescencja; Skala Udarów Narodowego Instytutu Zdrowia; terapia lustrzana; terapia zajęciowa; udar niedokrwienny mózg; witamina D; wskaźnik Barthel; wyniki funkcjonalne; zdrowie; zmodyfikowana Skala Rankina.

13. Abstract

Effect of rehabilitation training of patients after ischemic stroke on the level of selected growth factors and neuronal, muscular and vascular plasticity

Background: Brain strokes affect millions of people worldwide, and the annual incidence continues to rise. Effective diagnostic and therapeutic, but also prognostic management of motor recovery after stroke remains an important interdisciplinary medical problem. The main goal of modern medical rehabilitation of post-stroke patients using methods such as proprioceptive neuromuscular facilitation (PNF) and mirror therapy (MT) is to strive to regain lost function by activating mechanisms of neuronal reorganization. Motor function recovery efforts in recent decades have become a focus of research on brain plasticity mechanisms. The role of biomarkers that are objectively measurable and specific for nervous system damage and can be linked to therapeutic intervention is also not insignificant. One such factor is C-reactive protein (CRP), typical of inflammatory processes, which, even in the surviving phase after stroke, can promote tissue repair and functional regeneration. Also, vitamin D plays an important role in the modulation of cognitive processes, neuroprotection and neuromodulation. A number of studies have evaluated the association of vitamin D with the risk of stroke, however, there is a lack of studies evaluating the relationship between vitamin D levels and the level of functional performance of post-stroke patients.

Aims: The main aim of the research project was to comprehensively evaluate the effect of improvement training of ischemic stroke patients on the levels of selected growth factors and neuronal, muscular, and vascular plasticity. The following four specific objectives were identified: (1) to compare the effects of two methods of neurorehabilitation using PNF or MT on the return of functional capacity during the recovery-compensation period in patients with a history of first ischemic stroke; (2) to evaluate the factors affecting serum CRP levels in patients after ischemic stroke, together with an assessment of the usefulness of CRP as a potential biomarker of rehabilitation effectiveness and return of functional capacity; (3) evaluation of the relationship between serum vitamin D levels and physical performance and disability levels of patients undergoing medical rehabilitation after ischemic stroke; and (4) complementary analysis of the literature and critical review of scientific studies on the use of CRP as a potential biomarker associated with stroke and affecting the achievement of neurorehabilitation progress in post-stroke patients.

Material and methods: This research project received a positive approval from the independent Bioethics Committee of the Wroclaw Medical University (KB-813/2020). Within the framework of the present research project, adult patients after a first ischemic stroke who are in the recovery-compensation period were qualified. Eligible patients were rehabilitated using PNF or MT neurophysiological methods supplemented with occupational therapy (OT). The first study included 50 patients (34 men and 16 women) with a mean age of 65.5 ± 9.4 years; patients were randomly divided into two groups according to the rehabilitation method used: PNF (n=26) or MT (n=24). A group of 52 patients (34 men and 18 women) with a mean age of 65.8 ± 9.33 years were enrolled in the second study; serum CRP levels were determined during blood laboratory tests. And in the third study, the inclusion criteria were met by 80 patients (55 men and 25 women) with a mean age of 61.8 ± 6.9 years; laboratory blood tests for vitamin D and insulin-like growth factor 1 (IGF-1) levels were performed. In each of the three studies, the Barthel Index (BI) was used to assess functional status, and the modified Rankin Scale (mRS) was used to evaluate the degree of disability. Statistical analysis was performed using Statistica 13 software; α =0.05 was used for all comparisons.

Results: First research paper in the cycle: There were statistically significant differences between the two study groups in the BI score (main effect: <0.05); as well as statistically significant differences in the mRS score (main effect: p<0.05). No statistically significant differences were observed between the MT and PNF groups in BI and mRS scores (p<0.05). Second research paper in the cycle: A statistically significant increase in BI scores was observed after rehabilitation (p<0.001), as well as a decrease in mRS scores by 2.2 points (p<0.001), a decrease in CRP values by 5.02 mg/dL (p=0.019) and a decrease in cortisol levels by 2.5 nmol/L (p=0.002). After rehabilitation, statistically significant correlations were shown between CRP levels on the mRS scale (rs=0.29, p=0.038). The effect of BMI on CRP levels was also demonstrated (B=0.20, p=0.038). Third research paper in the cycle: There was a significant increase in BI scores (p<0.001) and IGF levels (p<0.001) after rehabilitation. There was a significant reduction in mRS scores (7.0 points; p<0.001), but no significant difference in vitamin D levels (p=0.40). There was an effect of age (B=-0.01, p=0.04) and vitamin D level (B=-0.02, P=0.01) and on BI score. There was an effect of BMI score (B=-0.07, p=0.02) on mRS score. Fourth review paper in the cycle: Studies conducted until now, which were qualified for this review, have revealed the important role of inflammatory mechanisms and CRP levels in the dynamics of stroke focus development. In response to the presence of necrotic tissue, an acute inflammatory response develops, which contributes to the enlargement of the necrotic area and is reflected in the deterioration of the patients' neurological condition.

Conclusions: (1) PNF and MT neurorehabilitation methods may be useful in improving functional status and reducing the level of disability in patients after a first stroke. (2) Despite demonstrating a significant association between CRP levels and mRS scores, CRP alone may not be a sufficient predictor of long-term functional outcomes. (3) Lower serum vitamin D levels and older age of patients may be associated with poorer functional outcomes in post-stroke patients; (4) Further empirical verification and clear demonstration of the potential of CRP levels and vitamin D levels as predictors of post-stroke patient health status are needed.

Key words: laboratory blood tests; biomarkers; C-reactive protein; functional assessment; recovery-compensation stage; proprioceptive neuromuscular facilitation; post-stroke recovery; neurological rehabilitation; reconvalescence; National Institutes of Health Stroke Scale; mirror therapy; occupational therapy; ischaemic stroke; vitamin D; Barthel Index; functional outcomes; health; modified Rankin Scale.

14. Załączniki

Załącznik 1. Pierwsza praca z cyklu.

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Proprioceptive Neuromuscular Facilitation and Mirror Therapy Methods Are Comparable Methods of Rehabilitation after a First-Ever Ischemic Stroke: A Randomized Study

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Abstract: Stroke is a serious cause of premature death among adults and the reason for much long-term disability. Understanding the mechanisms of disability and the potential for recovery of stroke patients should be one of the highest priorities of the health care system. Neurorehabilitation of post-stroke patients focuses on functional recovery by activating mechanisms of natural reorganization. Proprioceptive neuromuscular facilitation (PNF) and mirror therapy (MT) are neurorehabilitation methods activating brain plasticity, and their clinical utility for stroke survivors is still under studied. This study compared two neurorehabilitation methods using PNF or MT on functional recovery in patients after a first-ever ischemic stroke. This prospective and interventional randomized clinical study involved a group of 50 patients (34 males and 16 females) with first-ever ischemic stroke, aged 48–82 years being in the recovery-compensation stage and admitted to the unit for early post-stroke rehabilitation. Patients were randomly enrolled into two groups in terms of rehabilitation method used: PNF (n = 26) or MT (n = 24). Barthel Index (BI) was used for assessing functional status at baseline (M0), and 3 (M1) and 6 weeks (M2) after intervention), and modified Rankin Scale (mRS) was used for assessing a disability level at baseline (M0), and 6 weeks (M2) after the intervention. Statistically significant differences were noted in the two study groups in BI (main effect: <0.05). There was an improvement in the MT group between M1 and M2 by 3.6 points, M1 and M3 by 6.9 points, and M2 and M3 by 6.9 points. For the PNF group, there were differences between M1 and M2 by 4.1 points, M1 and M3 by 7.2 points, and M2 and M3 by 3.1 points. Moreover, statistically significant differences were noted in both groups in mRS (main effect: $p < 0.05$). There was a decrease of 2.2 points in the MT group between M1 and M2 measurements. For the PNF group, there were differences between M1 and M2 by 2.3 points. There were no statistically significant differences between the MT and PNF groups in both BI and mRS scores ($p < 0.05$). In conclusion, both PNF and MT neurorehabilitation methods could be useful for improving functional status and reducing disability level in patients after first-ever stroke during the regenerative-compensatory stage.

Keywords: stroke; rehabilitation; functional recovery; health; proprioceptive neuromuscular facilitation; mirror therapy

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1. Introduction

Stroke is a major cardiovascular diseases worldwide; it is the second leading cause of death and the third leading cause of death and disability combined [1]. Stroke is also one of the major public health problems. Data from the World Health Organization (WHO) determine that globally 15 million people each year experience a stroke, of which about one-third suffer from disability [2]. In Poland, there are 60–70 thousand new stroke cases each year [3]. According to European demographic forecasts, the number of new cases will

increase. The incidence of stroke is estimated to rise by 37% and 38% for men and women, respectively, between 2005 and 2025 [4].

Approximately 75% of all strokes affect the population over the age of 65, and its prevalence will rise systematically due to demographic changes [5]. This phenomenon is expected to lead to increased demand for rehabilitation protocols aimed at improving the functional status and quality of life of patients. Therefore, understanding the mechanisms of disability and the potential for recovery of stroke patients should be one of the highest priorities of the health care system. Currently, in Poland and around the world, more and more novel physiotherapy methods based on natural principles of central nervous system (CNS) reorganization are being applied in dealing with stroke patients. Physiotherapy is employed when there is a disturbance in the automatic, free, or reflex organization of movement, which manifests as paresis, impaired motor coordination, and muscle tone control, i.e., typical signs of a cerebrovascular event [6].

The main goal of modern rehabilitation of post-stroke patients is to strive to recover lost functions by activating mechanisms of natural functional reorganization. Appropriate interactions, among others in the rehabilitation program, induce CNS remodeling [7–9]. Physiotherapy in the management of post-stroke patients is conditional on the type and severity of motor and cognitive deficits as well as disease stage [10]. The individual therapeutic goals run from restoring the patients as fully as possible to their functions and social roles to achieving a relatively high quality of life [11,12].

Some well-evidenced neuroprotective strategies may be complementary to neurorehabilitation management, especially in post-stroke patients. One such method inducing neuroprotective action can be oxygen therapy in the form of normobaric oxygen (NBO) and hyperbaric oxygen (HBO), which improve reperfusion rate and makes favorable changes in brain metabolism [13]. Moreover, reperfusion therapies such as remote ischemic conditioning (RIC) can be clinically useful in the prevention of the progression of ischemic necrosis after stroke and limit ischemia-reperfusion injury of the brain [14]. It should be noted that interventions reducing the harmful effect of oxidative stress by decreasing reactive oxygen species (ROS) can be found. An antioxidant strategy using vitamins (C and E), resveratrol, or allopurinol may have a beneficial effect on preventing brain tissue damage and enhancing outcomes after stroke [15].

Activities concerning the recovery of motor function over the past decades have become the focus of research by scientists dedicated to developing the topic of brain plasticity, which ensures that the subject adapts to the environment by learning and self-repairing after damage [16,17]. A typical example of neural plasticity is the healing process after an ischemic stroke, which initiates CNS reorganization and the assumption of some functions by undamaged parts of the brain structures. The reorganization also involves expanding cortical areas that provide the neuronal substrate for recovery or adaptation of motor activities after damage [18]. The results of research on brain plasticity have enabled the development of neurorehabilitation, which is reflected in various physiotherapeutic methods, including proprioceptive neuromuscular facilitation (PNF) and mirror therapy (MT) [19–23].

This study aimed to compare the effects two neurorehabilitation methods using PNF or MT on functional recovery in patients after a first-ever ischemic stroke during the regenerative-compensatory period.

2. Materials and Methods

2.1. Participants and Design

This prospective and interventional randomized clinical study was carried out in the Department of Neurological Rehabilitation from January 2021 to December 2021. Patients were qualified for the project by a team consisting of a medical rehabilitation physician, neurologist, neurologopedist, clinical psychologist, and physiotherapist. Eligibility criteria for all participants included status after a first-ever ischemic stroke confirmed by MRI or CT scan, with upper limb hemiparesis, consent to participate in the study, and consent

from the supervising physician. The exclusion criteria were: (1) complete lack of movement of the upper limb, (2) highly functional upper limb, (3) time since stroke longer than 30 days, (4) complete lack of cooperation from the patient (global aphasia, lack of patient consent), (5) complete stiffness of the shoulder joint, (6) history of myocardial infarction, (7) chronic respiratory disease (asthma, COPD), and (8) previously established permanent musculoskeletal impairment.

A group of 62 patients after their first-ever ischemic stroke was assessed for eligibility. All patients were admitted directly from the neurology department to the neurorehabilitation department and screened for inclusion. During this stage, 12 patients were excluded: discontinuation of rehabilitation due to the onset of COVID-19 ($n = 4$) and the occurrence of complications in the form of a second stroke ($n = 4$), as well as the inability to participate in follow-up assessments ($n = 4$). The study finally included a group of 50 patients (34 males and 16 females) with first-ever ischemic stroke, aged 48–82 years, in the recovery-compensation stage, admitted to the unit for early post-stroke rehabilitation.

Hemiparetic patients were randomly assigned to two groups in terms of rehabilitation method: PNF ($n = 26$) or MT ($n = 24$). Patients signed their informed consent to participate in the study. In addition, they were informed and instructed about their options for discontinuing participation in the experiment in case of health problems or other reasons.

2.2. Ethical Considerations

This research project obtained a positive recommendation of the Independent Bioethics Committee of the Wroclaw Medical University in Poland (no. KB-813/2020). The trial was prospectively registered on the ISRCTN platform (no. ISRCTN16891871). The study was conducted under the principles of Declaration of Helsinki and Good Clinical Practice. All study participants gave their written informed consent before participating in the study.

2.3. Randomization Procedure

The study was designed as a randomized trial. Participants who were screened successfully for eligibility were randomly assigned to one of two groups (rehabilitated with MT and PNF methods) using a computerized random number generator (simple 1:1 randomization). Patients in both groups had sessions with a clinical psychologist and a neurologist and attended occupational therapy. Assignment to a particular group was independent of those implementing the therapy and analyzing the results. The same physician administered all tests and questionnaires.

2.4. Interventions

Patients enrolled in the study group were rehabilitated using either the PNF concept [24–26] or MT method [27–29]. The exercise schedule was set at five times each week. With each improvement session lasting 60 min. Heart rate (HR) and blood pressure (BP) were taken before each exercise session for patients in the study group who met the inclusion criteria. The rehabilitation training was always individualized for each patient, according to the current physical capabilities and needs. Its intensity was analyzed based on HR, which simultaneously provided up-to-date information that characterized the patient's emotional state and fatigue level. Each patient was rehabilitated for 6 weeks, or 36 days (based on a Monday–Saturday schedule). In addition, the following 90-min sessions were continued for 5 days a week: occupational therapy (30 min a day), psychologist visit (30 min a day), and neurologist visit (30 min a day). Due to significant differences in functional status, an individualization of the rehabilitation program was applied in each randomly selected group.

2.5. Measurements

Validated scales were used to measure therapeutic progress. The Barthel Index (BI) was used for assessing a functional status, and the modified Rankin Scale (mRS) was used for evaluating a disability level.

The BI assesses independence in performing ten activities of daily living in patients undergoing physiotherapy after an ischemic stroke. It measures deficits in self-care, mobility, and sphincter control. BI score range of 0–20 pts.: ≤4 pts. (very severe disability); 5–9 pts. (severe disability); 10–14 pts. (moderate severity of disability); 15–19 pts. (mild disability); and 20 pts. (full independence) [30,31]. The BI was performed 3 times (before MT or PNF interventions, 3 and 6 weeks after completing the program).

The mRS is used to provide a simple description of the level of independent functioning. It mainly deals with locomotor function and the degree of dependence on third parties and is simple to use and useful in the initial general assessment of the patient [32,33]. It allows an assessment of the patient's disability. mRS score range of 0–5: 0 (no symptoms); 1 (no significant disability); 2 (slight disability); 3 (moderate disability); 4 (moderately severe disability); and 5 (severe disability). The mRS was performed twice (before MT or PNF interventions and 6 weeks after completing the program).

2.6. Statistical Analysis

Statistica 13.1 software (TIBCO Inc., Palo Alto, CA, United States) was used to perform all statistical analyses. The Shapiro–Wilk test was used to determine the type of distribution of quantitative variables. Arithmetic means, medians, standard deviations, quartiles, and range of variation (extreme values) were calculated for measurable variables. Frequencies (percentages) were calculated for qualitative variables. Comparisons of qualitative variables between groups were made using the chi-square test (χ^2). Intra-group comparisons between the results obtained in measures 1 (M1) and 2 (M2) were made using the Wilcoxon test, while in measures 1–4 (M1-4) were made using Friedman's ANOVA analysis of variance and post-hoc test (Dunn's test). An inter-group comparison was assessed using the U-Mann–Whitney test. All comparisons were assumed to be statistically significant at $\alpha = 0.05$.

3. Results

Patients in both study groups were homogeneous in terms of the baseline characteristics of the population studies. Table 1 shows the characteristics of the study groups in terms of selected variables. Both groups were homogenous and no statistically significant differences ($p > 0.05$) were found between the study groups at baseline (Table 1).

Table 1. Study group characteristics.

Variable	MT (*n* = 24)							PNF (*n* = 26)							*p*-Value
	$\bar{x}$	Me	Min	Max	Q1	Q3	SD	$\bar{x}$	Me	Min	Max	Q1	Q3	SD	
Age [years]	65.5	68.1	48.1	82.0	59.7	72.3	9.4	66.9	65.5	53.2	82.0	60.2	75.3	8.7	0.590 [a]
Body height [cm]	169.0	171.0	150.0	180.0	163.5	175.5	8.0	166.8	168.0	150.0	186.0	161.0	172.0	9.3	0.371 [a]
Body mass [kg]	74.1	73.5	46.0	108.0	57.5	88.0	17.6	73.4	73.5	50.0	92.0	67.0	82.0	11.0	0.853 [a]
BMI [kg/m^2]	25.9	26.0	16.3	35.4	21.6	29.0	5.2	26.3	26.2	20.5	31.2	23.7	29.7	3.2	0.669 [a]
Stroke onset (days)	23.6	22.5	19.0	29.0	22.0	25.0	2.55	24.1	24.0	18.0	30.0	22.0	25.0	2.97	0.636 [a]
NIHSS score (pts.)	17.0	17.0	16.0	19.0	16.0	18.0	1.04	17.2	17.0	16.0	19.0	16.0	18.0	1.12	0.546 [a]
Sex	F–n = 8; 33.3% M–n = 16; 66.7%							F–n = 8; 30.8% M–n = 18; 69.2%							0.846 [b]
Tabaco smoke	No–n = 15; 62.5% Yes–n = 9; 37.5%							No–n = 16; 61.5% Yes–n = 10; 38.5%							0.944 [b]
Diabetes mellitus	No–n = 16; 66.7% Yes–n = 8; 33.3%							No–n = 16; 61.5% Yes–n = 10; 38.5%							0.706 [b]
Hypertension	No–n = 5; 20.8% Yes–n = 19; 79.2%							No–n = 7; 26.9% Yes–n = 19; 73.1%							0.614 [b]

Table 1. *Cont.*

Variable	MT (n = 24)							PNF (n = 26)							p-Value
	$\bar{x}$	Me	Min	Max	Q1	Q3	SD	$\bar{x}$	Me	Min	Max	Q1	Q3	SD	
Hypolipidemic drugs (Atorvasterol)	40 mg–n = 22; 91.7% 60 mg–n = 2; 8.3%							40 mg–n = 24; 92.3% 60 mg–n = 2; 7.7%							0.933 [a]
Anticoagulant drugs (Clexane)	40 mg/0.4 mL–n = 22; 91.7% 60 mg/0.6 mL–n = 2; 8.3%							40 mg/0.4 mL–n = 24; 92.3% 60 mg/0.6 mL–n = 2; 7.7%							0.933 [a]

Notes: [a] Mann-Whitney U test; [b] chi-square test. Abbreviations: MT, mirror therapy; PNF, proprioceptive neuromuscular facilitation; n, number of participants; F, female; M, male; $\bar{x}$, mean; Me, median; Min, minimal value; Max, maximal value; Q1, lower quartile; Q3, upper quartile; SD, standard deviation.

Table 2 shows a comparison of changes in BI scores in the MT and PNF groups in three consecutive measurements (M1, M2, M3). Statistically significant differences were noted in the two study groups (main effect: $p < 0.05$). There was an improvement in BI scores in the MT group between M1 and M2 by 3.6 points, between M1 and M3 by 6.9 points, and between M2 and M3 by 6.9 points. For the PNF group, there were differences between M1 and M2 by 4.1 points, M1 and M3 by 7.2 points, and M2 and M3 by 3.1 points (Table 2).

Table 2. Comparison of changes in BI scores on three measurements (M1, M2, and M3) in the MT and PNF groups.

Variable	M	MT (n = 24)							PNF (n = 26)						
		$\bar{x}$	Me	Min	Max	Q1	Q3	SD	$\bar{x}$	Me	Min	Max	Q1	Q3	SD
BI	M1	9.7	9.0	7.0	13.0	8.5	11.0	1.6	9.5	9.0	7.0	13.0	9.0	10.0	1.6
	M2	13.3	13.0	12.0	16.0	12.5	14.0	1.2	13.6	13.0	12.0	16.0	12.0	15.0	1.4
	M3	16.6	17.0	15.0	18.0	16.0	17.0	1.0	16.7	16.5	14.0	19.0	16.0	17.0	1.3
p-value (main effect) [a]		<0.001							<0.001						
p-value (multiple comparisons) [b]		M1 vs. M2: $p < 0.001$ M1 vs. M3: $p < 0.001$ M2 vs. M3: $p < 0.001$							M1 vs. M2: $p < 0.001$ M1 vs. M3: $p < 0.001$ M2 vs. M3: $p < 0.001$						

Notes: [a] Friedman's ANOVA; [b] Dunn's test. Abbreviations: BI, Barthel Index, MT, mirror therapy; PNF, proprioceptive neuromuscular facilitation; n, number of participants; $\bar{x}$, mean; Me, median; Min, minimal value; Max, maximal value; Q1, lower quartile; Q3, upper quartile; SD, standard deviation.

Table 3 shows a comparison of changes in mRS scores in the groups undergoing MT and PNF methods in two consecutive measurements (M1, M2). Statistically significant differences were noted in both groups (main effect: $p < 0.05$). There was a decrease of 2.2 points in mRS scores in the MT group between M1 and M2 measurements. For the PNF group, there were differences between M1 and M2 by 2.3 points (Table 3).

Table 3. Comparison of changes in RS scores on two measurements (M1 and M2) in the MT and PNF groups.

Variable	M	MT (n = 24)							PNF (n = 26)						
		$\bar{x}$	Me	Min	Max	Q1	Q3	SD	$\bar{x}$	Me	Min	Max	Q1	Q3	SD
mRS	M1	3.5	3.5	3.0	4.0	3.0	4.0	0.5	3.5	3.0	3.0	4.0	3.0	4.0	0.5
	M2	1.3	1.0	1.0	2.0	1.0	2.0	0.5	1.2	1.0	1.0	2.0	1.0	1.0	0.4
p-value (main effect) [a]		<0.001							<0.001						

Notes: [a] Wilcoxon test. Abbreviations: mRS, modified Rankin Scale, MT, mirror therapy; PNF, proprioceptive neuromuscular facilitation; n, number of participants; $\bar{x}$, mean; Me, median; Min, minimal value; Max, maximal value; Q1, lower quartile; Q3, upper quartile; SD, standard deviation.

In addition, a comparison of BI scores on three measurements (M1, M2, M3) between the MT and PNF groups were analyzed (Figure 1). Again, no statistically significant differences were observed ($p > 0.05$). Moreover, a comparison of mRS scores on two measurements (M1, M2) between the MT and PNF groups was analyzed (Figure 1). No statistically significant differences were observed ($p > 0.05$).

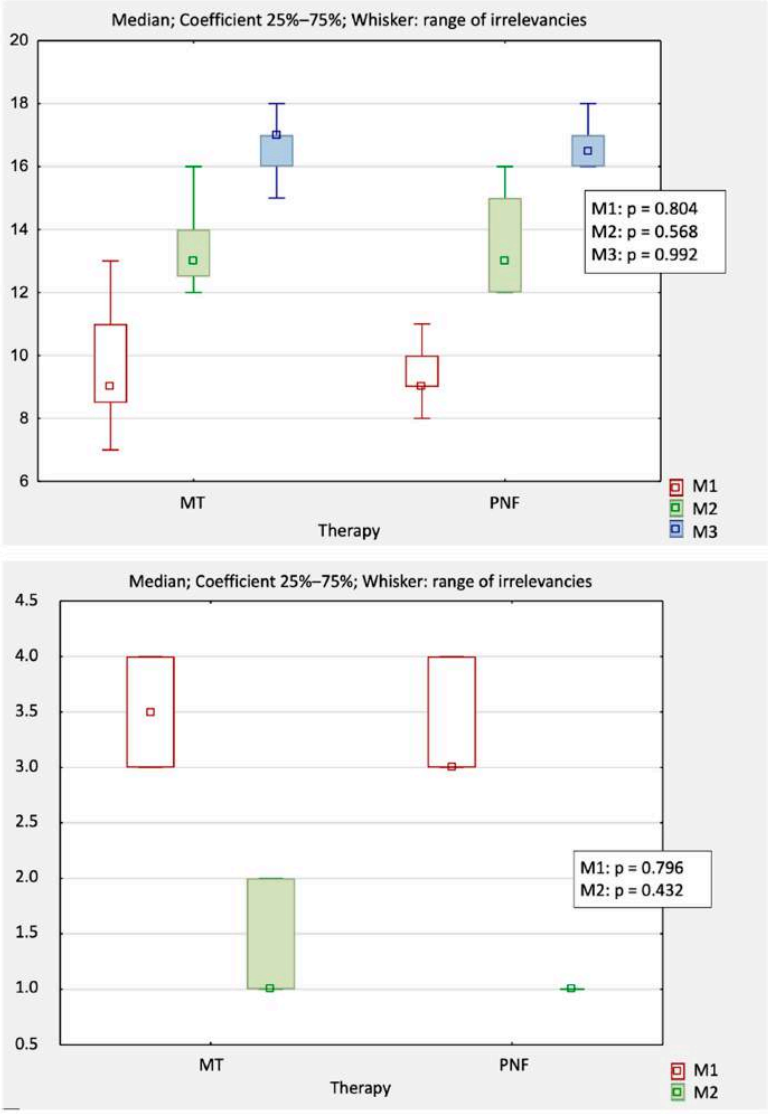

Figure 1. Comparison between MT and PNF groups. regarding changes in BI scores on three measurements (M1, M2, and M3) and in mRS scores on two measurements (M1 and M2).

4. Discussion

Synthesizing the interpretation of the present results and considering their significance in the light of the available literature indicates that physical exercise in post-stroke patients may have induced neuroplasticity mechanisms that led to improved CNS function in rehabilitated patients after their first ischemic stroke. These processes are likely to occur at multiple levels, beginning at the cellular level and progressing via neurotransmission to neuronal networks that build functional connections between co-operating brain areas [18].

The results presented are not conclusive about the effectiveness of a particular form of therapy in the overall rehabilitation process. However, the functional status of both patient groups improved significantly in the BI and RS. Therapy conducted with the PNF concept and MT allows using the phenomenon of CNS plasticity to activate the receptors of the movement system [34,35].

Analysis of functional tests of patients undergoing rehabilitation showed improvement in functional status in all patients regardless of the type of therapy used (MT or PNF). Similar results were obtained by Rynkiewicz et al. [36]; their study group consisted of 85 ischemic stroke patients aged from 28 to 92 years (mean age 65). They also used the BI and mRS to assess rehabilitated patients' functional status changes. According to the authors, the results obtained from the mRS show a very highly statistically significant ($p < 0.001$) improvement in the patients' functional abilities. In the first study, patients obtained an average of 4.07 points, and in the second study, an average of 3.24 points.

Moreover, Starosta et al. [37] evaluated the effectiveness of a specific psychomotor rehabilitation program after first-ever ischemic stroke patients underwent 25 days of rehabilitation. Functional status was assessed in 57 patients based on the ADL and mRS tools. Functional improvement based on the ADL scale was observed by 32% and on the mRS by 22% (with a mean score of 4.1 points at admission and 3.2 points at discharge). Our study recorded scores of 3.5 and 1.3 points in MT and 3.5 and 1.2 points in PNF therapy, respectively.

Our results are difficult to compare to the preceding research because the authors did not identify the sort of exercise therapy employed, how many days per week, or for how long. Nevertheless, the presented studies support the thesis that comprehensive rehabilitation conducted by an interdisciplinary team is necessary and significantly improves functional status, thus reducing the degree of disability. However, in summary—despite methodological differences—the conclusions are similar.

Przysada et al. [38] emphasize that the BI which was also used in our study to measure the state and effects of rehabilitation of patients after stroke, reliably shows increasing independence in fundamental ADLs under the influence of rehabilitation. In our study, patients who were qualified for MT on the day of admission averaged 9.7 points and 16.5 points after 6 weeks of rehabilitation; similarly to our research project, patients rehabilitated with the PNF method averaged 9.5 points on admission and 16.7 points after 6 weeks.

In the PNF concept, special attention is paid to the patient's motivation and positive attitude towards therapy, achievable through an individualized approach to the patient's needs. Wolny et al. [39] stressed the need to individualize improvement programs for each patient. There is substantial literature on the relationship between serotonin system deregulation [14] and post-stroke depression, where the negative impact of depression on stroke-related outcomes includes slower recovery, presence of recurrent vascular accidents, lower quality of life, and higher mortality [40].

All the time, the search is ongoing for methods that will respond to the expectations of patients and their relatives while at the same time working multifacetedly using all the possible reserves of the body.

Mosiejczuk et al. [41] showed that significantly better results were obtained in patients participating in the full rehabilitation program after stroke for 4 weeks than patients participating in therapeutic sessions for 2 weeks. Rehabilitation using the PNF method is an effective form of achieving functional improvement in patients after stroke. However, these results cannot be fully applied to our study since, although the age range of the

patients was similar, the daily dose of rehabilitation was not specified. It was also shown that the rehabilitation led to significant functional improvement and that better results were obtained by patients after 6 weeks than after 3 weeks of rehabilitation, demonstrating the need for prolonged improvement.

On the other hand, Kaniewski et al. [42] proved that the PNF method improves the condition of patients in the acute phase of stroke and that the degree of disability assessed by the mRS significantly decreased. Furthermore, significant improvement was observed in the patients' overall disability score after the PNF method compared to the pre-therapy results (3.65 vs. 1.8; $p < 0.05$). This was corroborated in our study, where patients scored by the mRS had an average of 3.5 points, and after 6 weeks, an average of 1.2 points.

Olak et al. [43] evaluated the dynamics of motor recovery in acute and subacute ischemic stroke patients undergoing the PNF method using Rivermead Motor Assessment (RMA), National Institutes of Health Stroke Scale (NIHSS), BI, and RS. They observed statistically significant improvement for the study group in functional assessment and independence. The summary scores according to the BI at the beginning of therapy were: 9.30 ± 6.80, and at the end of therapy, 16.86 ± 4.32 points. mRS score 3.78 ± 0.76 vs. 2.45 ± 0.86. It should be noted that our findings are difficult to relate explicitly to the findings by Olak et al. [43], since the patients were rehabilitated in the acute and subacute periods in this study (regenerative-compensatory period). In addition, the participants in our project underwent a full rehabilitation program lasting 42 days (6 weeks) rather than 56 days or longer. The daily dose of exercise therapy, occupational therapy, and classes with a psychologist and a neurologist were identical to those in the discussed publication by Olak et al. [43]. However, in summary—despite the methodological differences—the conclusions are similar. Moreover, in our study, even though the patients' improvement time was only 42 days, functional status and independence improvements were achieved.

Our study shows that post-stroke patients rehabilitated in our project (PNF and MT methods) achieved significant improvement in functional status as assessed with BI. Similar results were obtained by Starosta et al. [37], who noted that the applied program of comprehensive neurorehabilitation led to functional improvement based on the ADL scale by 32% (36% in women, 30% in men) and on the mRS by 22% (22% in women, 21% in men).

The presented results of our study correspond with the study by Jankowska et al. [44], who evaluated the effectiveness of comprehensive in-hospital neurorehabilitation of ischemic stroke patients who achieved significantly greater improvements in functional status compared to patients who improved in an ambulatory setting. Everyday rehabilitation of patients using both the PNF and MT methods for 6 weeks after ischemic strokes affects the recovery of lost motor functions. An interdisciplinary team provides intensive, individualized neurological physiotherapy results in better functional therapy outcomes.

In addressing the results of MT (despite the considerable number of papers and systematic reviews on the use of this method to evaluate the effectiveness of this simple and low-cost method with a post-stroke patient-centered treatment that can improve upper limb function) to other research papers, it should be kept in mind that this is quite difficult, as in reviewing the literature, no similar studies as in our project evaluating the effectiveness of MT were found. Based on the literature review on MT implemented in patients after a first-ever ischemic stroke, it can be noted that most studies do not meet the fair methodological quality and present limited level of evidence. It makes difficult to incorporate the clinical efficacy of MT in daily neurorehabilitation practice. These papers did not use a well-established qualification protocol or proper randomization, and the studies were often conducted based only on subjective questionnaires and pain sensation scales (no measurement methods to objectify treatment progress).

In a review article, Thieme et al. [28] emphasized the potential of MT to aid in the motor recovery of post-stroke patients, which would in turn improve ADL quality, decrease their level of pain, and lessen the impact of visuospatial neglect. The authors analyzed 14 articles on the MT effectiveness among a group of 567 post-stroke participants. It was confirmed that the use of MT affected motor recovery in post-stroke patients and facilitated

ADL performance. In contrast, the authors noted that visuospatial neglect in post-stroke patients was not significantly improved.

In the available literature on the subject discussed, only one Polish paper can be found. Radajewska et al. [22] evaluated the use of an MT in hand rehabilitation in 60 patients with upper limb hemiparesis after stroke. The study patients were divided into two groups of 30 patients each: one received comprehensive neurorehabilitation and second received additional MT (five days a week, two 15-min sessions a day for 21 days). The function of the upper limb paresis was assessed using two functional tests: Frenchay Arm Test (FAT) and the "Repty" Functional Index (RFI), performed at admission and after 21 days. It was shown that patients who underwent MT presented greater degree of hand function recovery. In our study, patients were rehabilitated during the recovery-compensation period. In addition, the participants in our study underwent a complete rehabilitation program lasting 42 days (6 weeks) rather than 21 days. The BI scores in the MT group in three consecutive measurements (M1, M2, M3) were statistically significant differences (main effect: $p < 0.05$). There was an improvement in BI scores in the MT group between measurements M1 and M2 by 3.6 points, M1 and M3 by 6.9 points, and M2 and M3 by 6.9 points. In the above-mentioned study, the measurements of M1 vs. M2 were made at admission and after 3 weeks of rehabilitation; however, our results indicate that the rehabilitation period should last 6 weeks.

As can be seen from the above discussion, a study in this field including both PNF and MT methods, randomization, consistent study material, a strict protocol for qualification, subjective and objective measurement tools, and early results were warranted. To further strengthen the scientific evidence, it is recommended that the collected data be independently confirmed by other institutions. Recently, there are still limited evidence of high scientific merit to unequivocally prejudge the effectiveness of PNF therapy over MT or vice versa in patients after a first ischemic stroke. At the moment, the results of the studies so far are promising, but this fact needs further verification.

Study Limitations

There are several limitations of this study to be explained. First of all, the absence on negative control group consisted of patients undergoing only standard neurorehabilitation management (with no PNF and MT) is an important limitation. The absence of blinding does not exclude that the results are affected by observer bias. In future studies, there is a need for the use other objective measurement methods and continue the project with a larger number of participants and for a more extended period (follow-up). An important aspect is to establish standardized treatment parameters other research studies can verify. Moreover, it would also be beneficial to expand the assessment of disability to include other questionnaires and scales, such as FIM or RFI.

5. Conclusions

Both PNF and MT neurorehabilitation methods could be useful for improving functional status and reducing disability level in patients after first-ever stroke during the regenerative-compensatory stage.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Załącznik 2. Druga praca z cyklu.

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Assessment of Changes in Serum C-Reactive Protein Levels in Patients after Ischemic Stroke Undergoing Rehabilitation—A Retrospective Observational Study

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Abstract: Inflammation plays a key role in the pathogenesis and prognosis of ischemic stroke. C-reactive protein (CRP) is an inflammatory biomarker of inflammation and may reflect the progression of vascular disease. Using a biomarker such as CRP to predict recovery rather than mortality may present clinical value in providing rehabilitation. The primary aim of the study was to analyze changes in serum CRP levels in patients after ischemic stroke during the regenerative-compensatory period and to assess the usefulness of CRP as a potential biomarker during the rehabilitation period. The project was carried out as a retrospective analysis of prospectively collected data from post-stroke patients from the Department of Neurological Rehabilitation of the Regional Specialist Hospital in Wrocław. A group of 52 patients, after their first-ever ischemic stroke with subsequent hemiplegia, was finally qualified to participate in the study. Serum CRP levels were determined during blood laboratory tests. The Modified Rankin Scale (mRS) and Barthel Index (BI) were used to assess functional outcomes. Rehabilitation using neurophysiological methods was applied five days a week (each session lasted 60 min, and the entire period was 42 days). At the first test, serum CRP levels were found to be above 5 mg/L in 19 patients, the second test in 12 patients, the third test in five patients, and the fourth test in 9 patients. Only three patients had values higher than 5 mg/L in all consecutive assessments ($p > 0.05$). There was a statistically significant increase in BI scores after therapy ($p < 0.001$) as well as a decrease in the mRS score by 2.2 points ($p < 0.001$), in CRP values by 5.02 mg/L ($p = 0.019$), and in cortisol levels by 2.5 nmol/L ($p = 0.002$). Statistically significant relationships were observed between the CRP levels after rehabilitation and the corresponding mRS scores (rs = 0.29, $p = 0.038$). Furthermore, the effect of BMI on CRP levels was demonstrated (B = 0.20, $p = 0.038$). In conclusion, despite demonstrating a significant relationship between CRP levels and corresponding mRS scores, CRP levels alone may not serve as an independent predictor of long-term functional outcomes in ischemic stroke patients undergoing rehabilitation.

Keywords: stroke; biomarkers; C-reactive protein; functional outcomes; rehabilitation

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1. Introduction

Stroke is the third leading cause of death in the adult population, following heart disease and cancer. Post-stroke mortality rates in Poland are higher than in other European countries and the USA. Long-term disability is a serious problem among survivors. Studies have shown that almost 15–30% of people are permanently disabled after a stroke, with more than 20% of those requiring institutional support three months after a stroke [1]. Given the high burden of disability after stroke, there is a need to identify clinical biomarkers

so that individualized treatment regimens can be developed after ischemic stroke and targeted to maximize function and quality of life [2]. Inflammation plays a key role in the pathogenesis and prognosis of ischemic stroke [3].

C-reactive protein (CRP) is an inflammatory biomarker of inflammation and may reflect the progression of vascular disease. The entire production process of this protein takes place in response to pro-inflammatory cytokines and other inflammatory mediators. Conflicting evidence implies that CRP may be a prognostic biomarker of ischemic stroke outcome. As reported in the literature, most studies that analyzed the relationship between CRP and ischemic stroke outcomes used mortality or subsequent vascular events as the primary outcome measure. However, given that almost half of the post-stroke patients experience moderate to severe functional impairment, using a biomarker such as CRP to predict recovery rather than mortality may present clinical value during rehabilitation [4].

CRP enhances nerve cell damage by increasing the activation of the complement system. There is a proven close relationship between the increase in CRP levels and complement components in the blood of patients in the acute phase of stroke and the size of the infarct focus. The progression or enlargement of the zones of damage to brain tissue following stroke is a consequence of the deterioration of local microcirculatory conditions. In addition, a cascade of destructive phenomena associated with inflammatory and immunological reactions in response to ischemic damage to neural tissue is observed. It is important to approach this problem in the context of the development of stroke focal damages and the potential possibilities of modulating the inflammatory response in acute focal cerebral ischemia. Therefore, more effective treatment methods for patients in the acute phase of stroke and post-stroke rehabilitation will be developed [5].

The primary aim of the study was to analyze factors affecting serum CRP levels in patients after ischemic stroke during the regenerative-compensatory period. The secondary aim was to assess the usefulness of CRP as a potential biomarker during rehabilitation, including the relationship between CRP levels and the functional assessment of post-stroke patients.

2. Materials and Methods

2.1. Ethical Consideration

The study was approved by the Bioethics Committee of the Wrocław Medical University (KB–813/2020) and conducted in accordance with the Good Clinical Practice Guidelines and the Declaration of Helsinki. All project participants were informed of the purpose of the study and how it would be conducted, and gave their written consent to participation in the study and the processing of their personal data. Moreover, the study was registered under the number ISRCTN16891871.

2.2. Participants and Design

The project was carried out as a retrospective analysis of prospectively collected data from 62 patients from the Department of Neurological Rehabilitation of the Regional Specialist Hospital in Wrocław. The study included a group of 62 first-ever ischemic stroke survivors discharged from neurology or internal medicine wards with a recommendation for rehabilitation no later than 14 days after discharge from the stroke unit. All patients were Caucasian and were rehabilitated from 2 January 2021 to 22 December 2021. The patients were treated for mobility issues for 42 days. Patients were qualified for the project by an interdisciplinary team consisting of a neurologist, a specialist in medical rehabilitation, and a physiotherapist. The selection of patients to participate in the study was purposive.

2.3. Qualification Procedure

The eligibility criteria for all participants included first-ever ischemic stroke confirmed by MRI or CT, subsequent hemiplegia, functional disability assessed on the day of admission on the modified Rankin Scale (mRS) > 3, consent to participate in the study, consent from the attending physician, the absence of infection, which was defined by excluding

patients with fever, signs of infection on physical examination, or those who needed antibiotic therapy during subsequent hospitalization. Furthermore, all patients underwent a routine chest X-ray, urinalysis, and consultation with a specialist in internal medicine within the first two days of admission. Furthermore, a follow-up internist consultation was conducted when CRP values increased above 10 mg/L before discharge from the ward. Exclusion criteria comprised patients with sensory aphasia identified by anamnesis and medical examination, a history of myocardial infarction, chronic respiratory disease (bronchial asthma, COPD), previously diagnosed persistent musculoskeletal dysfunction, active infection (chest X-ray, general urinalysis, full results of physical examination), and patients who did not give their consent to participate.

A group of 52 patients who met the inclusion criteria was finally qualified to participate in the study. The group included 18 women (aged 67.00 ± 8.70) and 34 men (aged 62.00 ± 9.00). The patients underwent neurological rehabilitation for six weeks. At two-week intervals, the patients had their blood drawn for routine tests, and selected biochemical parameters were determined in the remaining blood. All tests and surveys were carried out by the same physician.

2.4. Outcome Measures

Patients had their blood drawn from a basilic vein every fortnight, i.e., on admission to the ward, and after two, four, and six weeks of therapy. Blood for the laboratory tests was always taken at the same time, i.e., at 6:30 a.m. and on an empty stomach. The researchers kept in mind that the CRP and leukocyte levels could also be affected by measures taken under different clinical conditions, such as different times of day or after consuming food. To minimize errors and eliminate confounding factors, all patients in our study always had their blood drawn at the same time (6:30 a.m.), and had not taken non-steroidal anti-inflammatory drugs.

Furthermore, CRP levels were determined in the blood. Serum CRP assessments were performed using the Alinity c CRP Vario assay. It is an immunochemical test that uses latex particles to measure serum and plasma CRP levels in an accurate and precise manner. When an antigen-antibody reaction occurs between the CRP protein present in the test sample and an antibody against the CRP protein adsorbed on latex particles, the agglutination process takes place. The agglutination process is detected as a change in absorbance (572 nm), with the rate of change being proportional to the amount of CRP present in the sample [6].

Patients' functional outcomes were assessed using the modified Rankin Scale (mRS) [7,8] and Barthel Index (BI) [9,10], the most commonly used clinimetric tools for measuring disability after stroke. Long-term functional outcome scales, such as mRS and BI, are commonly used for measuring the degree of physical dependence and have high inter-rater reliability compared to other scales [11]. Therefore, both scales were used in the project. BI was performed on the day of admission to the ward and after 21 days of rehabilitation and after 42 days of treatment for mobility issues. In contrast, mRS was performed only on the day of admission to the ward and after six weeks. Functional disability was defined as an mRS score > 3. This study assessed the relationship between BI scores and CRP values at three-time points after ischemic stroke in the regenerative-compensatory period, and the relationship between mRS and CRP levels at two-time points.

2.5. Neurological Rehabilitation

After stabilizing the patient's condition during the early neurological rehabilitation period, rehabilitation using neurophysiological methods was applied five days a week in patients whose dysfunctions had not diminished. Each session of neurorehabilitation lasted 60 min, and the entire period was 42 days. Blood pressure and heart rate were measured before each kinesitherapy unit for patient safety reasons. Treatment for mobility issues has always been selected individually for each person, taking into account the patient's capabilities.

2.6. Statistical Analysis

The statistical analysis was performed using Statistica 13.1 software (TIBCO, Inc., Palo Alto, CA, USA). The sample size was assessed based on the available results in the unit's database (n = 12). Means and standard deviations of CRP results (before and after rehabilitation) were used in the analysis of estimating the sample size. The estimated sample size was calculated by a paired-means test (paired t-test). The alpha level was set at 0.05, and the power of the test at 0.8. It also assumed no correlation of evaluated variables and adopted a two-sided null hypothesis. On the basis of the parameters, the estimated sample size was obtained for 49 patients.

Arithmetic means, standard deviations, and the range of variability (extreme values) were calculated for measurable variables. Prevalence (%) was calculated for qualitative variables. All studied quantitative variables were verified using the Shapiro-Wilk test to determine distribution type. Comparisons between pre- and post-therapy results were made using the t-test for independent samples. Moreover, a Pearson correlation analysis was performed between the selected variables. In addition, an analysis of the effect of selected factors on the BI score was performed using linear regression. The next step was to build a multivariate model. The model-building process was conducted using progressive stepwise regression. The level of $\alpha = 0.05$ was used for all comparisons.

3. Results

Table 1 shows the characteristics of the group, including age, height, weight, BMI, number of days since stroke diagnosis, NIHSS score, sex, smoking, and history of chronic disease.

Table 1. Characteristics of the study group.

Variable	Study Group (n = 52)			
	$\overline{x}$	SD	Min	Max
Age [years]	65.8	9.33	48.0	83.0
Height [cm]	167.86	8.67	150.00	186.00
Body weight [kg]	73.74	14.40	46.00	108.00
BMI [kg/m^2]	26.12	4.21	16.33	35.44
Time since stroke onset [days]	23.9	2.76	18.0	30.0
NIHSS [score]	17.1	1.08	16.0	19.0
Sex	F—n = 18; 32.7% M—n = 34; 67.3%			
Hypertension	No—n = 13; 24.0% Yes—n = 39; 76.0%			
Diabetes	No—n = 33; 64.0% Yes—n = 19; 36.0%			
Smoking	No—n = 32; 62.0% Yes—n = 20; 38.0%			

Abbreviations: n, number of participants; $\overline{x}$, mean; SD, standard deviation; Min, minimum value; Max, maximum value; F, Female; M, Male; BMI, body mass index, NIHSS, National Institutes of Health Stroke Scale.

Table 2 shows the results of CRP tests in each measurement. The results were not statistically significantly different ($p > 0.05$). At the first test, serum CRP levels were found to be above 5 mg/L in 19 patients, the second test in 12 patients, the third test in five patients, and the fourth test in nine patients. Only three patients had values higher than 5 mg/L in all consecutive assessments.

Table 3 shows a comparison of results before and after rehabilitation. There was a statistically significant increase in BI scores after therapy ($p < 0.001$). Moreover, there was a statistically significant decrease in the mRS score by 2.2 points ($p < 0.001$), in CRP values by 5.02 mg/L ($p = 0.019$), and in cortisol levels by an average of 2.5 nmol/L ($p = 0.002$).

Table 2. Numerical characteristics of the results of individual CRP sampling.

Sample Number	*n*	Min–Max [mg/L]	$\bar{x}$ [mg/L]	SD [mg/L]
Admission Test 1	52	0.4–70.3	8.1	14.6
After 2 weeks Test 2	52	0.4–31.9	4.3	5.88
After 4 weeks Test 3	52	0.4–26.7	3.0	4.09
After 6 weeks Test 4	52	0.4–12.7	3.1	2.88
p-value	0.94 *			

Abbreviations: *n*, number of participants; $\bar{x}$, mean; SD, standard deviation; Min, minimum value; Max, maximum value. * one-way ANOVA.

Table 3. Comparisons of results before and after rehabilitation.

	Before				After				Difference				*p*-Value
	$\bar{x}$	SD	Min	Max	$\bar{x}$	SD	Min	Max	$\bar{x}$	SD	Min	Max	
BI	9.6	1.58	7.0	13.0	16.62	1.12	14.0	19.0	7.02	1.19	5.0	10.0	<0.001
mRS	3.48	0.5	3.0	4.0	1.28	0.45	1.0	2.0	−2.2	0.45	−3.0	−1.0	<0.001
CRP [mg/L]	8.08	14.59	0.4	70.3	3.06	2.88	0.40	12.7	−5.02	13.97	−63.9	8.7	0.019
COR [nmol/L]	15.92	4.7	6.4	29.7	13.42	3.13	7.20	20.6	−2.5	3.85	−11.3	6.0	0.002
Hemoglobin [g/dL]	13.93	1.64	10.7	17.2	13.99	1.37	10.6	16.0	0.06	1.09	−2.5	3.3	0.835
RBC [T/L]	4.48	0.51	3.45	5.98	4.6	0.49	3.57	5.56	0.13	0.34	−0.5	0.9	0.208
WBC [thous./µL]	7.39	2.3	3.96	14.05	6.95	1.91	4.42	14.2	−0.44	2.22	−7.1	3.9	0.296
PLT [thous./µL]	242.48	67.42	103.0	472.0	260.14	67.72	119.0	410.0	17.66	59.76	−136.0	173.0	0.194
HCT [%]	40.6	4.14	30.7	50.3	40.79	3.83	32.40	49.1	0.19	2.41	−6.7	6.2	0.816

Abbreviations: *n*, number of participants; $\bar{x}$, mean; SD, standard deviation; Min, minimum value; Max, maximum value; BI, Barthel Index; mRS, modified Rankin Scale; CRP, C-reactive protein; COR, cortisol; RBC, red blood cell; WBC, white blood cell; PLT, plates; HCT, hematocrit. All significant values are marked in bold.

Furthermore, a correlation analysis of the results of CRP levels and other variables was also performed, as shown in Table 4. Statistically significant relationships were observed between the results of CRP levels after rehabilitation and the corresponding mRS scores ($r_s = 0.29$, $p = 0.038$) plus platelet (PLT) values ($r_s = 0.30$, $p = 0.036$).

Table 4. Correlations between CRP levels and other variables.

			mRS	BI	COR	HB	RBC	WBC	PLT	HTC
CRP	Before treatment	coefficient r	0.18	−0.13	0.16	−0.26	−0.18	0.13	−0.01	−0.20
		p-value	0.221	0.372	0.261	0.066	0.202	0.369	0.946	0.170
	After treatment	coefficient r	0.29	−0.06	0.07	−0.09	0.12	0.13	0.30	−0.01
		p-value	0.038	0.686	0.640	0.514	0.412	0.384	0.036	0.943
	Difference	coefficient r	0.19	−0.04	0.08	0.00	0.06	0.20	0.07	0.07
		p-value	0.194	0.800	0.577	0.995	0.688	0.164	0.612	0.627

Abbreviations: CRP, C-reactive protein; BI, Barthel Index; mRS, modified Rankin Scale; COR, cortisol; RBC, red blood cell; WBC, white blood cell; PLT, plates; HCT, hematocrit.

The effect of the selected parameters on final CRP levels (a univariate model of the predictors included in the analysis) was also assessed after the completion of the treatment

for mobility issues. The unstandardized and standardized regression coefficients, standard error, and level of statistical significance were determined. The following variables were included in the analysis: age, sex, BMI, smoking, history of diabetes, hypertension, mRS (before and after rehabilitation) and BI (before and after) scores, and blood biochemical parameters (before and after).

Table 5 shows the linear regression analysis in the univariate model. The effect of BMI (B = 0.20, $p = 0.038$) on CRP levels was demonstrated. The linear regression analysis in a multivariate model (stepwise, progressive) revealed an effect of BMI (B = 0.26, $p = 0.005$), cortisol value (B = 0.28, $p = 0.023$) and mRS score (B = 2.43, $p = 0.005$) on CRP levels. Moreover, Table S1 presents univariate logistic regression analyses assessing the effect of selected variables on CRP score (≤5 vs. >5). Table S2 presents multivariate logistic regression analyses assessing the effect of selected variables on CRP scores (≤5 vs. >5).

Table 5. Linear regression analyses assessing the effect of selected variables on CRP score.

		Univariate Linear Regression Analysis					Multivariate Linear Regression Analysis				
		B	SE	t	*p*-Value	ß	B	SE	t	*p*-Value	ß
Age		0.00	0.05	−0.06	0.95	−0.01	-	-	-	-	-
BMI *		0.20	0.09	2.14	0.038	0.29	0.26	0.09	2.94	0.005	0.38
Time since stroke onset		0.07	0.73	0.10	0.920	0.02	-	-	-	-	-
NIHSS		2.29	1.84	1.25	0.22	0.18	-	-	-	-	-
Sex	M	Ref.					-				
	F	−0.11	0.45	−0.24	0.81	−0.04	-	-	-	-	-
Hypertension	No	Ref.					-				
	Yes *	−0.78	0.47	−1.66	0.10	−0.23	-	-	-	-	-
Diabetes	No	Ref.					-				
	Yes	0.11	0.43	0.27	0.79	0.04	-	-	-	-	-
Smoking	No	Ref.					-				
	Yes	−0.06	0.42	−0.13	0.90	−0.02	-	-	-	-	-
mRS–before		0.64	0.82	0.78	0.44	0.11	-	-	-	-	-
mRS–after *		1.61	0.89	1.81	0.08	0.25	2.43	0.83	2.94	0.005	0.38
BI–before		−0.23	0.26	−0.86	0.39	−0.12	-	-	-	-	-
BI–after		−0.02	0.37	−0.05	0.96	−0.01	-	-	-	-	-
COR [nmol/L]–before		0.07	0.09	0.80	0.43	0.11	-	-	-	-	-
COR [nmol/L]–after *		0.21	0.13	1.62	0.11	0.23	0.28	0.12	2.36	0.023	0.30
HGB [g/dL] *–before		−0.25	0.25	−1.00	0.32	−0.14	-	-	-	-	-
HGB [g/dL] *–after		−0.07	0.30	−0.24	0.81	−0.03	-	-	-	-	-
RBC [T/L]–before		−0.25	0.82	−0.30	0.76	−0.04	-	-	-	-	-
RBC [T/L]–after *		0.90	0.85	1.06	0.29	0.15	-	-	-	-	-
WBC [thous./µL]–before		0.30	0.18	1.71	0.09	0.24	-	-	-	-	-
WBC [thous./µL]–after *		0.38	0.21	1.81	0.08	0.25	-	-	-	-	-
PLT [thous./µL]–before		0.00	0.01	−0.17	0.86	−0.02	-	-	-	-	-
PLT [thous./µL]–after *		0.01	0.01	2.07	0.054	0.29	-	-	-	-	-
HTC [%]–before		0.00	0.10	−0.01	0.99	0.00	-	-	-	-	-
HTC [%]–after		0.04	0.11	0.38	0.71	0.05	-	-	-	-	-

Abbreviations: BMI, body mass index, NIHSS, National Institutes of Health Stroke Scale; M, Male; F, Female; BI, Barthel Index; mRS, modified Rankin Scale; COR, cortisol; HGB, hemoglobin, RBC, red blood cell; WBC, white blood cell; PLT, plates; HCT, hematocrit. *Notes:* B—unstandardized regression coefficient B; SE—standard error; t: B/standard error; ß—standardized regression coefficient ß; * variables included in a multivariate model (criterion: $p < 0.3$ in a univariate model).

4. Discussion

Comprehensive rehabilitation is a fundamental component of therapeutic management, through which patients achieve functional improvement and independence. In addition, rehabilitation provided by an interdisciplinary team forms a key element in reducing the risk of death, severe disability, and the stress associated with the need to adapt to life under conditions altered by the disease.

According to the authors, the novelty of this study is the in-depth assessment of CRP levels in first-ever ischemic stroke patients in the regenerative-compensatory period undergoing neurological rehabilitation as part of a clinical trial based on a strict protocol of inclusion and exclusion criteria, using both objective measurements and subjective scales recommended in the literature, with a uniform statistical design.

According to the available literature, there have been numerous attempts to assess both CRP levels in post-stroke patients in the acute phase and the impact of stroke on the functional outcome of this group of patients, whereas there are few papers on the correlation of CRP levels and its effect on the functional outcome of patients after ischemic stroke in the regenerative-compensatory period.

Wnuk et al. [12] observed that non-infectious CRP values are an independent risk factor for poor short- and long-term functional outcomes with ischemic stroke patients undergoing thrombolytic treatment. Those authors found that a poor functional outcome, as assessed by mRS >3, was achieved by patients with CRP levels >8.65 mg/L compared to those with CRP levels below 5 mg/L. In our project, we assessed a similar to the above-mentioned report relationship between CRP levels on admission and functional outcome assessed by mRS on the admission of patients to the ward and a follow-up measurement after 42 days of the treatment for mobility issues. We defined functional disability as a mRS score >3; the group size was smaller, but the age range was comparable. We observed statistical relationships between the results of CRP levels after 42 days of rehabilitation and the corresponding mRS scores ($r_s = 0.29$, $p = 0.038$) plus platelet (PLT) values ($r_s = 0.30$, $p = 0.036$), which may reflect the complex interactions of the induction and progression processes occurring between vascular wall cells (endothelial cells, tunica media myocytes) and blood cells (leukocytes and platelets) plus plasma lipoproteins.

As highlighted by Masztalewicz et al. [13], the contribution of inflammatory and immunological factors to ischemic stroke is mainly considered in terms of their effect on the development of atherosclerosis and the destabilization of atherosclerotic plaques within the arteries supplying the brain. As the literature supports the view that elevated leukocyte values may also be a predictor of poorer functional outcomes, the authors of this project attempted to verify this finding. These authors [13] emphasize the important role of inflammatory mechanisms in the dynamics of stroke focus development. An acute inflammatory response develops in response to the necrotic tissues, or, more specifically, to the antigens released from them, which contributes to the enlargement of the infarcted area as reflected in the neurological deterioration, and significantly affects the subsequent prognosis of the stroke patient. Microglia cells, astrocytes, T lymphocytes, endothelial cells, perivascular cells (macrophages), and neurons located in the ischemic area are involved in this reaction. Peripheral blood leukocytes (neutrophils, monocytes, T lymphocytes), flowing into the vicinity of the developing lesions are also involved in this reaction. The influx of leukocytes is determined by the reperfusion of the cerebral vessels in the ischemic area. The increased adhesion of these cells to the endothelial surface impairs local blood flow. Again, there is a reduction in the oxygen and glucose supply to the brain area affected by stroke and, consequently, a worsening of the damage associated with ischemia. Animal experiments have proven that counteracting leukocyte adhesion to the endothelium results in beneficial therapeutic effects in animals in the form of a reduction in brain infarct volume and associated edema and a reduction in a neurological deficit. The migration of leukocytes into the central nervous system (CNS) exacerbates inflammation-related damage to ischemic brain tissues, as these cells are a source of free radical substances, proteolytic enzymes, neurotoxic cytokines, and neurotoxic nitric oxide [13]. In this study, we found

no significant statistical relationship between elevated white blood cell counts and poorer functional outcomes as assessed by BI and mRS.

To date, there is no universally accepted cut-off point in the literature for the infectious CRP levels in studies on ischemic stroke [14]. Although a specific cut-off value (>6 mg/L) was used to rule out a possible comorbid infection in the study by Montaner et al. [15], they emphasize that clinical assessment plays a more important role in ruling out infection. Therefore, previous studies may have produced inconsistent results regarding the prognostic role of CRP in ischemic stroke patients due to the variable and inadequate CRP threshold. It should be borne in mind that CRP and leukocyte values may also be affected by measurements that took place under different clinical conditions, such as a different time of day, after food intake and under the influence of non-steroidal anti-inflammatory drugs. For example, fasting is associated with a significant decrease in CRP levels, as highlighted by Alam et al. [16] in their study, whereas leukocyte counts increase by almost 10% two hours after eating a meal [12].

In our study, to minimize errors, all patients had their blood drawn at the same time (6.30 a.m.) and were not taking non-steroidal anti-inflammatory drugs. This was our way of trying to eliminate confounding factors. For example, high blood pressure (hypertension) is a major global problem; it is the second risk factor after age that can lead to stroke [17].

Peng et al. [18] found in their studies that increased CRP levels tended to be a more significant risk factor for stroke among women than men, which they confirmed by the multivariate logistic analysis. Chinese researchers obtained different results and found that elevated CRP levels significantly affected male patients but not female patients [19]. The inconsistent findings on sex differences may have been partly due to genetic and hormonal differences between men and women. The above-mentioned processes need to be clarified; consequently, further research is needed to work out the phenomenon. In this study, due to the small group size, there was no breakdown by sex.

Rajeshwar et al. [20] revealed that higher levels of hs-CRP were significantly associated with poor outcomes after considering several confounding variables. Similarly, a study by Winbeck et al. [21] revealed that CRP levels within 12 to 24 h at the onset of stroke symptoms were independently predictive of adverse functional outcomes after one year of follow-up. CRP levels measured 24 to 48 h after the onset of symptoms were even stronger predictors; however, the timeframe did not meet the inclusion criteria, as it falls outside the time window for assessing acute inflammation.

Elevated CRP levels revealed positively significant associations with long-term, >30 days, adverse functional outcomes. Song et al. [22] found that CRP levels were significantly and positively correlated with functional outcomes, assessed by mRS after 1, 3, 6, and 12 months of follow-up, with increasingly strong observational associations as time increased. A significant highlight was that CRP values measured seven days after admission showed a stronger statistical correlation with mRS scores after 12 months than CRP values measured within 24 h of admission.

The detailed mechanism of reduced functional outcome after ischemic stroke is not yet fully understood and is related to a complex cycle of interconnected molecular and cellular mechanisms. However, some studies by, among others, Jayaraj et al. [23], point out that inflammation in the surviving phase after stroke can promote tissue repair and functional regeneration.

Ye et al. [24] found elevated CRP values as an independent predictor of functional disability after one year in both sexes, in men ($p = 0.017$) and in women ($p = 0.042$). In contrast, Ahmadi Ahangar et al. [25] found that serum CRP values were positive in 122 cases (57%). Out of 122 cases of positive CRP, 64 cases (52%) involved women, and the remaining 58 cases (48%) involved men ($p = 0.21$). The results of this study revealed that positive serum CRP values were associated with ischemic stroke severity and poor prognosis. In contrast, Totan et al. [17] examined the correlation between CRP values and the degree of motor deficit in mRS. Motor deficits were prevalent in the study group, with CRP values

in the range of 5–50 mg/dL. There were no significant differences in the cases studied between patients with severe disabilities and patients with moderate disabilities.

The effectiveness and need for the patients' mobilization are evidenced by the obtained functional outcomes of the study group of patients before and after rehabilitation (shown in Table 4). This study revealed a statistically significant increase in BI scores after therapy ($p < 0.001$). Moreover, there was a statistically significant decrease in the mRS score by 2.2 points ($p < 0.001$), in CRP values by 5.02 mg/L ($p = 0.019$), and in cortisol levels by an average of 2.5 nmol/L ($p = 0.002$).

In this study, we used a multivariate analysis to determine whether CRP values were an independent predictor of long-term functional outcomes while controlling for confounding variables. The linear regression analysis in a univariate model revealed an effect of BMI (B = 0.20, $p = 0.038$) on CRP values. The linear regression analysis in a multivariate model (stepwise, progressive) revealed an effect of BMI (B = 0.26, $p = 0.005$), cortisol level (B = 0.28, $p = 0.023$) and mRS score (B = 2.43, $p = 0.005$) on CRP values.

Chinese researchers Gu Hong-Qiu et al. [3] found that less than 20% of poor functional outcomes could be explained by recurrent stroke, meaning that more than 80% of functional damage is due to disability. Therefore, typical secondary prevention strategies to prevent stroke recurrence, which include rehabilitation, are very important. Pawluk et al. [26] pointed out that the precise and reliable process of reduced functional outcome after ischemic stroke is not yet fully understood and is related to a complex cycle of interconnected molecular and cellular mechanisms. As they point out, inflammation contributes to cell death, brain damage, and blood-brain barrier disruption. Furthermore, inflammation plays a role in pathogenesis and progression, increases the risk of stroke, and only later causes functional disability. In contrast, Jayaraj et al. [23] emphasized that chronic inflammation could promote tissue repair and functional regeneration in the chronic phase after stroke.

The results presented above provide a lot of interesting and relevant information, which has cognitive and practical relevance for rehabilitation planning in patients after ischemic stroke in the regenerative-compensatory period. However, further research is required to implement this knowledge in clinical practice.

Study Limitations

A limitation of this study was that our results might also be biased by unidentified confounding factors that were not adapted. In addition, our results concerned only patients from one facility and cannot be generalized to a larger population. Therefore, the relationship between plasma CRP values and functional outcomes after ischemic stroke during the regenerative-compensatory period should be further validated in other cohorts.

Long-term functional outcome rating scales, such as BI and mRS, are commonly used for measuring functional outcome assessment and have high inter-item reliability. There is no mandatory definition of good and unfavorable outcomes using BI and mRS. The subjective standards determining the outcome are set by the researcher. It should be borne in mind that psychological conditions such as post-stroke anxiety and depression are psychological effects that can affect functioning. Altered mental status and comorbid depression are known to affect the quality of life; however, they are not measured with these clinimetric tools. Altered mental status and comorbid depression are important clinical problems associated with stroke, and some studies report a correlation between altered mental status after stroke and elevated CRP. A more holistic assessment of outcomes using scales that take into account both physical and psychological well-being may better characterize the overall disability after stroke in terms of long-term outcomes

5. Conclusions

This study showed that despite demonstrating a significant relationship between CRP levels and corresponding mRS scores, CRP levels alone may not serve as an independent predictor of long-term functional outcomes in ischemic stroke patients undergoing rehabilitation. CRP levels in ischemic stroke patients in the regenerative-compensatory period

are affected by BMI, cortisol levels (stress hormone), and disability score assessed by mRS. The clinical utility of CRP levels in the rehabilitation of post-ischemic stroke patients in the regenerative-compensatory period during the treatment for mobility issues should be further validated based on multicenter trials regarding the care of post-ischemic stroke patients in the regenerative-compensatory period during the treatment for mobility issues.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12031029/s1, Table S1: Univariate logistic regression analyses assessing the effect of selected variables on CRP score (≤5 vs. >5). Table S2. Multivariate logistic regression analyses assessing the effect of selected variables on CRP score (≤5 vs. >5).

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Association Between Serum Vitamin D Levels and Physical Outcomes of Patients Who Underwent Rehabilitation Following Ischemic Stroke

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Background: Ischemic stroke is the most common cause of disability in adults. Deficiency of vitamin D in patients with cardiovascular diseases is increasing. Only a few studies have assessed the relationship between serum vitamin D levels and functional capacity and degree of disability. This study aimed to evaluate the association between serum vitamin D levels and physical outcomes of 94 patients who underwent physical rehabilitation following ischemic stroke.

Material/Methods: A group of 94 patients was enrolled; however, 80 patients (61.8±6.9 years) were included. They underwent a 6-week rehabilitation using proprioceptive neuromuscular facilitation (PNF, 60 min daily), mirror therapy (MT, 30 min daily), and occupational therapy (OT, 45 min daily). The Barthel Index (BI) and modified Rankin scale (mRS) were used for functional assessments. Laboratory blood tests for serum vitamin D and insulin-like growth factor 1 (IGF-1) levels were conducted.

Results: There was a significant increase in BI scores (median difference=2.0 points [pts]; $P<0.001$) and IGF levels (median difference=124.6 ng/ml; $P<0.001$) after rehabilitation. There was a significant decrease in mRS scores (median difference=7.0 pts; $P<0.001$), but there was no significant difference in vitamin D levels ($P=0.40$). The effect of age (B=-0.01, $P=0.04$) and serum vitamin D level (B=-0.02, $P=0.01$) on the BI score was demonstrated. The effect of body mass index (BMI) results (B=-0.07, $P=0.02$) on the mRS score was observed.

Conclusions: Lower serum vitamin D levels and more advanced age may be associated with worse functional outcomes in first-ever ischemic stroke patients.

Keywords: 25-hydroxyvitamin D • Functional Status • Ischemic Stroke • Neurological Rehabilitation

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Background

Ischemic stroke causes irreversible brain damage and affects people of all ages on all continents. It is the second leading cause of death [1], and it is the leading cause of disability in people aged over 45 years [2]. Despite significant improvements in primary prevention, stroke continues to affect more than 1.1 million Europeans [3] and Chinese [4] each year, which indicates the severity of the problem.

Established risk factors for ischemic stroke do not explain the occurrence of the disease in one-third of patients [5], warranting further exploration of potential risk factors. Serum vitamin D levels are positively associated with improved cardiovascular health, particularly with a reduced risk of stroke [6]. Recently, there has been an increased prevalence of vitamin D deficiency in patients with cardiovascular diseases, including post-stroke patients [7].

Vitamin D deficiency is described as a co-morbid condition in many diseases such as acute ischemic stroke, neurodevelopmental disorders and intellectual disability, and cardiovascular risk, and it is associated with increased mortality [8,9]. The discovery of the vitamin D receptor (VDR) made it possible to learn more about its effects on extraskeletal organs [10]. The identification of calcitriol (the active form of vitamin D) receptors in various tissues of the human body confirmed the pleiotropic, multidirectional effects of vitamin D [11].

Zhou et al [12], in their systematic review and meta-analysis, confirmed the hypothesis that low vitamin D levels are associated with an increased risk of ischemic stroke, which indicates they are a possible risk factor for stroke. In contrast, higher vitamin D concentrations significantly protect against stroke.

Vitamin D is a well-known neurosteroid hormone that plays an important role in modulating cognitive processes and regulating neurotrophic signaling [13] for neuroprotection, neuromodulation, vascular risk factors for stroke [14-16], and inflammation [17,18]. VitaminD, both from food and that synthesized in the skin, undergoes transformations that result in the formation of 2 metabolites. Hydroxylation to 25-hydroxyvitamin D (25(OH)D), a substrate for the synthesis of the biologically active 1,25 dihydroxyvitamin D ($1,25(OH)_2D$), occurs in liver cells, which takes place in the proximal cells of the kidneys. Both metabolites enter the bloodstream. Although $1,25(OH)_2$ is a biologically active form of vitamin D, its serum levels do not correlate with the state of the body's actual supply. A marker of vitamin D content is the measurement of 25(OH)D. The half-life of the circulating metabolite in the blood is approximately 21 days and is the best indicator of the total vitamin D content in the body. In contrast, the $1,25(OH)_2$ present in serum has a short half-life of approximately 4 hours and determination of its content is not used for assessing vitamin D deficiency.

Many studies in the literature have assessed the relationship between vitamin D in terms of stroke risk [6,19]. Few studies have assessed the relationship between serum vitamin D levels and the functional capacity of patients and the associated degree of disability. Therefore, there was an attempt to assess the relationship between vitamin D levels in patients admitted to rehabilitation and functional outcomes. Therefore, this study aimed to evaluate the association between serum vitamin D levels and physical outcomes of 94 patients who underwent physical rehabilitation following ischemic stroke.

Material and Methods

Ethical Considerations

The study was approved by the Ethics Committee of Wrocław Medical University (permission no. KB-813/2020). The study was conducted in accordance with the Good Clinical Practice Guidelines and the Declaration of Helsinki. Each person was briefed and instructed on the conduct of the experiment before signing the consent to participate. All study participants were informed of the possibility of discontinuing their participation in the project in the case of health problems or for other reasons.

Trial Registration

The study was conducted as part of the project "Effectiveness of various therapeutic forms and their influence on nervous, muscular and vascular plasticity in patients after ischemic stroke" in collaboration with Dr. Sílvia Rocha-Rodrigues (Research Centre in Physical Activity and Health, Faculty of Sport, University of Porto, Portugal). The project was registered in the International Standard Randomized Controlled Trial Number Registry Platform (registry no. ISRCTN16891871).

Participants

A group of 94 post-ischemic stroke patients undergoing rehabilitation at the Neurological Rehabilitation Unit of the Wrocław Regional Specialist Hospital were enrolled in the study. Patients were qualified to participate in the research by a team consisting of a physician-specialist in medical rehabilitation, a neurologist, a neurologopedist, a clinical psychologist, and a physiotherapist. Inclusion criteria for the study included first-ever ischemic stroke, time of onset 2 weeks before admission for early neurological rehabilitation, stroke confirmed by magnetic resonance imaging (MRI) or computed tomography (CT), age >18 years, no contraindications to participate in the experiment (consent of attending physician), no neurological comorbidities, and written informed consent of the patient to participate in the study. Exclusion criteria included patients with

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an infection in the past 2 weeks, patients who took vitamin D and its derivatives or calcium in the past 3 months, patients with liver and kidney disorders, patients with thyroid disorders, patients with aphasia, and patients who did not provide consent. A group of 80 patients met the criterion of participating in 2 follow-up examinations was finally qualified for the study. There were 25 women (31.3%) and 55 men (68.7%) in that group. Patients were provided with proprioceptive neuromuscular facilitation (PNF) and mirror therapy (MT) for 42 days. At 6-week intervals, patients had blood drawn for routine tests and selected biochemical parameters were determined in the remaining blood. All tests and surveys were carried out by the same physician.

Measurements

On the day of admission, all patients underwent standard neurological examination, basic anthropometric measurements, and stroke severity assessment using the National Institutes of Health Stroke Scale (NIHSS). In terms of primary outcomes, functional tests were performed using Barthel Index (BI) and modified Rankin scale (mRS).

Barthel Index

The BI is a commonly used scale to assess the level of functional independence in patients undergoing physiotherapy after stroke. The BI measures deficits in self-care, mobility, and sphincter control. Scores ranging from 0 to 20 points are interpreted as follows: ≤4 points – very severe disability; 5-9 points – severe disability; 10-14 points – moderate severity of disability; 15-19 points – mild disability; 20 points – full independence.

Modified Rankin scale

The mRS is a commonly used tool to assess functional outcome after a stroke. It assigns a score ranging from 0 (no symptoms) to 6 (death), with higher scores indicating more severe disability. The scale is often used to assess a patient's ability to carry out activities of daily living, such as eating, dressing, and mobility. The mRS has been shown to have good inter-rater reliability and validity, and is widely used in both clinical practice and stroke research.

Laboratory Blood Tests

Patients had their blood routinely drawn from the ulnar vein for basic laboratory tests such as complete blood count (CBC) and urinalysis. The following concentrations were determined: vitamin D and IGF-1 levels. The serum levels of those substances were determined on admission to the unit and after 6 weeks of rehabilitation training. Each patient had blood drawn from an ulnar vein, always at the same time, at 6: 30 a.m., on an empty stomach. Laboratory tests were performed at the Scientific Laboratory of the Research and Development Center at the Regional Specialized Hospital in Wrocław. Performing biochemical tests at the same time, using reagents from a single production batch, and ensuring the same measurement conditions was intended to minimize the occurrence of external, random errors that could alter the results of biochemical analyses. The tests were performed in the laboratory on an Alinity ci analyzer using reagents from Abbott (Chicago, Illinois, USA). This is a widely used, standardized immunochemical assay using a chemiluminescent microparticle immunoassay (CMIA) used to quantify 25(OH)D in human serum and plasma on an Alinity ci analyzer. The Alinity ci 25-OH Vitamin D test has been standardized against the National Institute of Standards & Technology Standard Reference Material 2972 (NIST SRM 2972). The test is used as an aid in assessing adequacy of vitamin D levels. It is a one-step immunochemical test with delayed conjugate addition, dedicated to the quantitative determination of 25-hydroxyvitamin D in human serum and plasma using microparticles and a chemiluminescent marker (CMIA). Paramagnetic microparticles coated with anti-vitamin D antibodies and assay diluent are added to the test sample, and the whole mixture was incubated. The 25-hydroxyvitamin D present in the sample was removed from the vitamin D-binding protein and then binds to the anti-vitamin D antibodies, coating the microparticles. A conjugate containing acridine-labeled vitamin D was added to form the reaction mixture. The reaction mixture was incubated. After a wash cycle, the Pre-Trigger Solution and the Trigger Solution that triggers the Trigger Solution reaction were added. The intensity of the signal produced by the chemiluminescence reaction was measured in relative light units (RLU), based on the relationship between the amount of 25-hydroxyvitamin D in the sample and the RLU values measured by the optical system. A normal serum vitamin D level was defined as a 25(OH)D concentration >30 ng/ml. Vitamin D deficiency was defined as a concentration of 25(OH)D <30 ng/ml.

Rehabilitation Procedures

Once stabilized during the early neurological rehabilitation period, post-ischemic stroke patients may develop a wide variety of disorders, the clinical picture of which will depend on the nature and extent of damaged brain tissues. Movement disorders are one of the most common clinical manifestations. Rehabilitation treatment (rehabilitation training) focuses on regaining motor function to a degree that enables patients to achieve and meet their self-care needs. Patients selected for the project were rehabilitated with neurophysiological methods (PNF and MT) for 5 days a week. Rehabilitation using the PNF method was oriented towards improvement of a specific lost function, not just a structure. The overriding aim of the therapy was to help the patient achieve the highest possible

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Table 1. Characteristics of the study group.

Variable	Study group (n=80)			
	$\bar{\chi}$	SD	Min	Max
Age [years]	61.8	6.9	36.3	71.9
Height [cm]	168.5	8.5	150.0	186.0
Body weight [kg]	74.1	14.9	46.0	108.0
BMI [kg/m^2]	26.0	4.3	16.3	35.4
Time since stroke onset [days]	21.9	3.8	14.0	30.0
NIHSS [points]	16.3	1.3	14.0	19.0
Sex	F – n=25; 31.3%			
	M – n=55; 68.7%			
Hypertension	No – n=26; 32.5%			
	Yes – n=54; 67.5%			
Diabetes mellitus	No – n=55; 68.8%			
	Yes – n=25; 31.3%			
Smoking	No – n=45; 56.3%			
	Yes – n=35; 43.7%			

n – number of participants; $\bar{\chi}$ – mean; SD – standard deviation; Min – minimum value; Max – maximum value; F – Female; M – Male; BMI – body mass index, NIHSS – National Institutes of Health Stroke Scale.

functional level. Each unit of treatment for mobility issues lasted 60 minutes. Moreover, each patient additionally had MT applied daily for 30 minutes. The rehabilitation training was 6 weeks long. Also, each patient had daily one-to-one sessions with a clinical psychologist for 30 minutes and an additional 45 minutes of occupational therapy (OT). For patient safety reasons, blood pressure and heart rate were measured before each kinesitherapy unit. Since patients with diabetes were also included in the study group, electroencephalography (ECG) changes indicative of myocardial hypoxia, which may also occur during exercise, were an absolute precondition for discontinuing the rehabilitation training. The rehabilitation training has always been individually tailored to each patient and their current abilities and needs, taking into account the patient's capabilities.

Sample Size

The sample size analysis was based on the main objective of the study, which was to assess changes in vitamin D levels before and after 6 weeks of rehabilitation. Before the start of the study, it was assumed that there would be an increase in vitamin D levels. The minimum sample size needed to detect a difference of 20% assuming alpha=5%, power=80% and confidence level=95% is 79 patients. The sample size analysis was performed using the G*Power software. Statistical power analyses were performed using G*Power 3.1

Statistical Analysis

Statistical analysis was performed using Statistica 13 software (TIBCO, Inc., Palo Alto, USA). Arithmetic means and standard deviations or medians, upper and lower quartiles and the range of variability (minimum and maximum value) were calculated for measurable variables. Prevalence (%) was calculated for qualitative variables. All studied quantitative variables were verified using the Shapiro-Wilk test to determine distribution type. Comparisons between pre- and post-rehabilitation scores were made using non-parametric Wilcoxon test. The level of α=0.05 was used for all comparisons. Moreover, the analysis of the impact of selected variables on activities of daily living (BI) and disability/dependence in the daily activities (mRS) was performed using a linear regression (univariate model). The unstandardized and standardized regression coefficients, standard error and level of statistical significance were determined. The next step was to develop a multivariate model (stepwise progressive method), taking into account variables whose *P* value in the univariate model was ≤0.30. A p value less than.05 was considered statistically significant.

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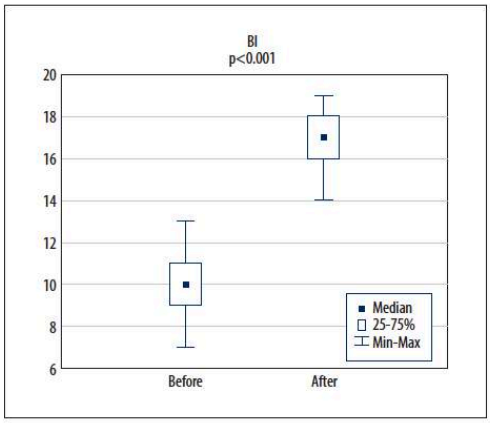

Figure 1. A comparison of BI results before and after rehabilitation. BI – Barthel Index.

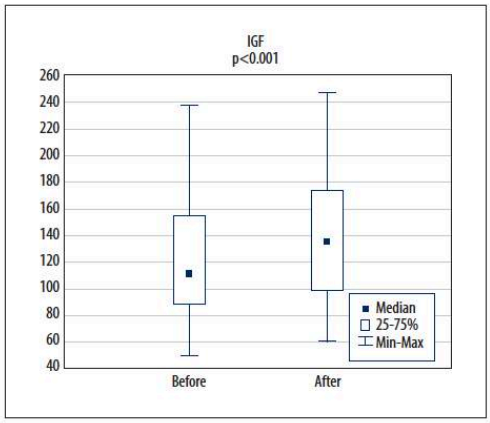

Figure 3. A comparison of IGF results before and after rehabilitation. IGF – insulin-growth factor.

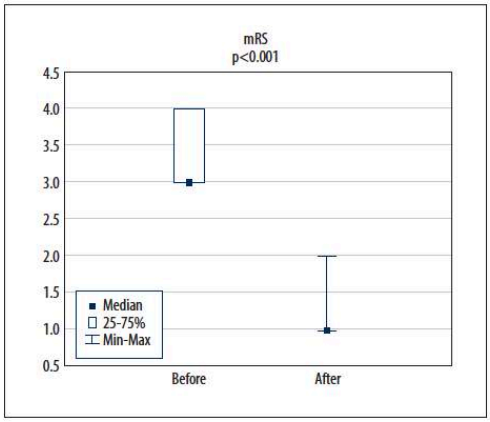

Figure 2. A comparison of mRS results before and after rehabilitation. mRS – modified Rankin scale.

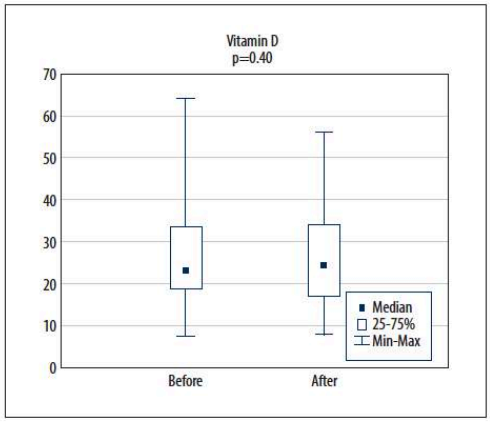

Figure 4. A comparison of vitamin D results before and after rehabilitation.

Results

Patients' Characteristics

The study ultimately included 80 patients meeting the participation criterion; the mean age of participants was 61.8±6.9. In this group, 68.7% were men (55 individuals). **Table 1** shows the characteristics of the group including age, height, weight, body mass index (BMI), number of days since stroke diagnosis, NIHSS score, sex, smoking, and history of chronic diseases.

Outcomes' Changes after Rehabilitation

Figures 1-4 show a comparison of BI, mRS, vitamin D, and insulin-like growth factor 1 (IGF-1) results before and after rehabilitation. After therapy, there was a statistically significant increase in BI scores (median difference is 2.0 points; *P*<0.001) and IGF levels (median difference is 124.6 ng/ml; *P*<0.001). There was also a statistically significant reduction in mRS scores (median difference is 7.0 points; *P*<0.001). There were no significant differences in vitamin D levels (*P*=0.40).

Variables Affecting Outcomes

Table 2 shows the assessment of the impact of selected variables on activities of daily living (BI) and disability/dependence in the daily activities (mRS) of post-stroke patients (linear regression analysis in the univariate model). The effect of age (B=-0.01, *P*=0.04) and serum vitamin D levels (B=-0.02,

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Table 2. The assessment of the impact of selected variables on activities of daily living (BI) and disability/dependence in the daily activities (mRS) of post-stroke patients.

		BI					mRS				
		B	SE	t	p-value	β	B	SE	t	p-value	β
Age [years]		**-0.01**	**0.01**	**-2.04**	**0.04**	**-0.23**	0.00	0.02	0.07	0.94	0.01
BMI [kg/m²]		0.00	0.01	-0.45	0.65	-0.05	**-0.07**	**0.03**	**-2.33**	**0.02**	**-0.25**
Time since stroke onset [days]		-0.01	0.01	-1.20	0.24	-0.13	-0.01	0.03	-0.18	0.86	-0.02
NIHSS [points]		-0.04	0.03	-1.43	0.16	-0.16	0.01	0.10	0.06	0.95	0.01
Sex [ref. M]	F	-0.02	0.04	-0.39	0.70	-0.04	0.11	0.14	0.76	0.45	0.09
Hypertension [ref. No]	Yes*	0.01	0.04	0.29	0.77	0.03	0.04	0.14	0.32	0.75	0.04
Diabetes mellitus [ref. No]	Yes	-0.02	0.04	-0.39	0.70	-0.04	-0.01	0.14	-0.08	0.94	-0.01
Smoking [ref. No]	Yes	0.02	0.04	0.53	0.60	0.06	-0.03	0.13	-0.22	0.83	-0.02
IGF [ng/ml]		0.00	0.00	-0.65	0.52	-0.07	0.00	0.00	-0.11	0.91	-0.01
Vitamin D [ng/ml]		0.02	0.01	2.51	0.01	0.27	-0.02	0.02	-0.74	0.46	-0.08

BMI – body mass index, NIHSS – National Institutes of Health Stroke Scale; M – Male; F – Female; BI – Barthel Index; mRS – modified Rankin Scale; IGF – insulin-like growth factor; B – unstandardized regression coefficient B; SE – standard error; t: B/standard error; β – standardized regression coefficient β.

P=0.01) on BI score was demonstrated. The effect of BMI results (B=-0.07, *P*=0.02) on mRS score was observed.

Discussion

Vitamin D deficiency is now a widely well-known public health problem that affects almost 1 in 2 people worldwide. Recent evidence from many population-based studies indicates that vitamin D deficiency is a predictor of future strokes. This "pandemic" of vitamin D deficiency is worrying because low serum vitamin D levels are linked to cardiovascular, musculoskeletal, infectious, autoimmune, and malignant diseases. Wu and He [20] found that 80% of patients who were admitted to the neurological rehabilitation unit immediately after an acute stroke incident had low serum vitamin D levels. Also, Manson et al [21] reported that 75% of patients hospitalized for ischemic stroke had vitamin D levels <20 ng/ml. We believe that the lower percentage of counts in our study may be dictated by the small group size (80 subjects).

In our study, serum vitamin D levels were assessed in patients with first-ever ischemic stroke on admission to a rehabilitation unit. Vitamin D deficiency was defined as plasma 25(OH)D levels <30 ng/ml. In the study group, it was found that 67.5% of patients (54 patients) had vitamin D3 deficiency. Functional outcomes were assessed using the BI and mRS. The BI is a standard scale that is used for measuring performance in daily activities (DAs). It measures 10 basic aspects of self-care and dependence in DAs. The normal score is 20 and lower scores indicate increasing disability. The BI score >12 corresponds to assisted independence in DAs and BI <8 corresponds to severe dependence in DAs.

mRS scores of 0-2 are defined as no symptoms up to minimal disability and are equivalent to a good outcome, while scores of 3-6 indicate moderate to severe disability or death and are equivalent to a poor outcome [22].

Markišić et al [23], while conducting a non-interventional prospective clinical study of 50 patients with first-ever ischemic stroke, assessed the relationship between early functional outcomes of acute ischemic stroke and serum vitamin D levels in patients undergoing rehabilitation. The study group of 50 patients was slightly older (mean age 71.9±11.3 years and ranged from 45 to 90 years) compared to that in this project. It should be noted that in the elderly (aged over 60 years), vitamin D levels gradually decrease due to the reduced ability of the skin to synthesize vitamin D in old age.

In the present study the mean age of participants was 61.8±6.9 and ranged from 36 to 72 years. The sex distribution was also slightly different. In the group studied by Markišić et al [23], women predominated, with 28 women (56%) and 22 men (44%). In the present study, men predominated, with 55 men (68.7%) and 25 women (31.3%). For functional assessment, we used BI and mRS. Markišić et al [23] conducted the functional assessment at 3 time points: on admission and 3 and 6

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months after stroke. On admission, the NIHSS was negatively correlated with vitamin D levels, which may indicate a relationship between neurological deficits and lower vitamin D levels, while the researchers did not detect a correlation between vitamin D levels and BI and mRS scores at both time points after adjusting for age and initial stroke severity.

The above results can be applied to the present results, as our clinical observations have shown that rehabilitation treatment for this group of patients is very important, resulting in significant functional improvement. After therapy, there was a statistically significant increase in BI scores (median difference of 2.0 points; $P<0.001$) and a statistically significant decreases in mRS scores (median difference of 7.0 points; $P<0.001$). Similar ro the study by Markišić et al [23], no significant differences in vitamin D levels were found in this study ($P=0.40$).

The linear regression analysis in a univariate model assessed the impact of selected variables on activities of daily living (BI) and disability (mRS). It was revealed that the older the person (B=-0.01, $P=0.04$), the worse the ability to perform activities of daily living (ADLs). In contrast, higher levels of vitamin D improved ADLs. It was also found that the higher the BMI (B=0.07, $P=0.02$) the lower the independence in DAs.

Similarly, Alfieri et al [8], who studied 168 patients with acute ischemic stroke, observed that lower 25(OH)D levels were negatively correlated with disability score as measured by mRS after 3 months of follow-up regardless of age, sex, and neurological deficits. Daubail et al [24] found that their patients with vitamin D deficiency with values of 25(OH)D <25.7 nmol/l had a worse functional prognosis compared to post-stroke patients with serum vitamin D levels of 25(OH)D >25.7 nmol/l.

Also, Zhang et al [25] investigated the relationship between vitamin D levels and clinical severity, as well as outcome at 3 months in post-stroke patients. Vitamin D concentration levels were measured at the beginning of the study. Patients' clinical status after ischemic stroke was assessed at admission using the NIHSS scale. Functional outcome was assessed 3 months after the onset of the disease using the modified Rankin scale (mRS) (like our study, the authors used the same scales). The study group included 377 patients. They performed multivariate analyses using logistic regression models. They showed that vitamin D deficiency was not associated with NIHSS risk at admission in all patients. In contrast, patients without hypertension had significantly higher vitamin D levels. Patients with lower vitamin D levels had higher NIHSS scores at admission and at 3 months mRS compared to those with vitamin D levels ≥50 nmol/l. The odds ratio (95% confidence interval) was 5.51 (1.83-16.60) and 4.63 (1.53-14.05) in the multivariate-adjusted model (P for linear trend <0.05). The authors concluded that low serum vitamin D level was an independent predictor of functional outcomes in non-hypertensive ischemic stroke patients.

In contrast, Wei and Kuang [26] concluded that vitamin D levels below 20 ng/ml contribute to a 3.2-fold increased risk of poor functional outcome in post-ischemic stroke patients without diabetes assessed at 1-year follow-up after a stroke incident.

Li et al [27], similar to our study, analyzed the relationship between vitamin D levels in patients after cerebral stroke and functional outcomes of patients undergoing rehabilitation. Sixty-nine men and 31 women aged 32-82 years (mean age 54.75 ±10.61) participated in the study. After 30 days of rehabilitation, they the effectiveness of rehabilitation was significantly positively correlated with serum vitamin D levels (r=0.562, $P<0.003$) and significantly negatively correlated with BMI (r=-0.347, $P<0.05$). Regarding the effectiveness of rehabilitation after the multivariate logistic regression analysis, Li et al [27] found that disease duration and NIHSS score were independent risk factors for the effectiveness of rehabilitation treatment ($P<0.05$), and vitamin D levels were a protective factor ($P<0.05$).

Park et al [28] also assessed whether baseline serum vitamin D levels affect functional outcome in patients with acute ischemic stroke. They used mRS and the relationship between baseline vitamin D levels and good functional outcome (mRS 0-2) after 3 months was analyzed using multiple logistic regression models. The study included 818 patients. The mean age was 66.2 (±12.9) years and 40.5% of the participants were women. The mean vitamin D level was 47.2±31.7 nmol/l, and the majority of patients had vitamin D deficiency status (<50 nmol/l; 68.8%), while the optimal vitamin D level (≥75 nmol/l) was present in only 13.6% of patients, and 436 (53.3%) patients showed a good functional outcome after 3 months. Serum vitamin D levels in patients with good results were significantly higher than in those with poor results (50.2±32.7 vs 43.9±30.0 nmol/l, $P=0.007$). The researchers found that serum vitamin D levels were an independent predictor of functional outcome in patients with acute ischemic stroke. They highlighted the need for further research to determine whether vitamin D supplementation can improve functional outcomes in patients with ischemic stroke.

Turetsky et al [29] investigated whether vitamin D was an independent predictor of cerebral infarct volume and poor outcome after 90 days (assessed by mRS >2) using multivariate linear and logistic regression analyses, finding that the risk of poor functional outcome (mRS >2) doubled with each 10-ng/ml reduction in serum 25(OH)D levels. They concluded that low serum vitamin D levels were independently associated with higher ischemic infarct volume, resulting in poorer functional outcomes for patients with vitamin D deficiency. Vitamin D

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deficiency in patients may increase susceptibility to brain ischemia and a tendency towards larger infarcts. As in this project, age was significantly correlated with serum vitamin D levels (r=0.398, *P*<0.01).

Siniscalchi et al [30] in their review highlighted the roles of vitamin D in post-stroke patients. They emphasized that low vitamin D levels are primarily associated with stroke of ischemic rather than hemorrhagic etiology. Vitamin D, as a neurosteroid with a neuroprotective role due to the presence of vitamin D receptors in neuronal and glial cells, has been proposed as a prognostic biomarker for functional outcomes in stroke patients. They pointed out that vitamin D deficiency causes changes in the vascular wall, and found no conclusive evidence that vitamin D supplementation in patients will translate into better functional outcomes.

In contrast, Daumas et al [31] evaluated the relationship between vitamin D levels in patients after ischemic stroke treated with thrombolytic therapy and functional outcome 3 months after the ischemic incident. The study group consisted of 325 patients mean age of 68.6±15.8 years, slightly outnumbered by women at 50.7%. Vitamin D levels were measured within 24 hours of hospital admission. On admission and at discharge, patients' clinical stroke severity was assessed using the NIHSS scale. The mean vitamin D level in the study group was 43.4±24.2 nmol/l, and the median was 37.9 nmol/l (24.2-58.6). Patients with low vitamin D levels had a higher mean NIHSS score at discharge than the functional score assessed by mRS. It was concluded that lower vitamin D concentrations are associated with poorer functional outcomes, emphasizing the need for further research to understand and explain unexplored beneficial phenomena such as promoting neuronal plasticity or preventing early reocclusion.

Vitamin D deficiency causes muscle weakness and muscle pain, especially in post-stroke patients with neurological disorders [32]. Holick [33] emphasizes that normal vitamin D levels affect muscle strength and balance, which contributes to the effectiveness of rehabilitation. Patients with vitamin D deficiency are reported to have reduced muscle strength and balance disorders. This was also confirmed in experimental studies carried out on rats; skeletal muscle atrophy and a decrease in muscle strength were observed in the absence of vitamin D while there was an increase in muscle diameter and strength gain after adequate vitamin D supplementation [34].

In a systematic review, Antoniak and Greig [35] found that the combination of rehabilitation exercises with vitamin D supplementation affects muscle strength by contributing to improved functional outcomes in patients. On the other hand, a randomized clinical trial by Momosaki et al [36] found that daily supplementation with 2000 IU of vitamin D3 in post-acute stroke patients applied for 8 weeks did no significantly improve BI scores in relation to the ability to perform DAs.

As Murphy and Corbett [37] stated, current concepts of biological recovery after stroke suggest a narrow window of opportunity to stimulate plasticity and repair of brain function, so early vitamin D supplementation may make an important contribution to the recovery in these patients, which requires further research.

As stroke is the leading cause of disability and the elderly have often severe vitamin D deficiencies, studies evaluating the effectiveness of vitamin D supplementation should be extended. The results presented above include much interesting and relevant information, which has cognitive and practical relevance for rehabilitation planning in post-ischemic stroke patients in the period of recovery and compensation, but further research is needed for the implementation of this knowledge in clinical practice.

Study Limitations

Firstly, a limitation of this study was that the trial was not randomized and it took place at a single center. In the future, it would be advisable to conduct a multicenter study for validation in other cohorts. We cannot directly relate our results to the above studies due to the fact that our study group included only patients after ischemic stroke but not treated with thrombolytic therapy. Future studies, which we plan to expand to a larger patient population, should take this aspect into account. Furthermore, there was no way to exclude errors related to variables that were not measurable in this observational study, such as sun exposure, diet, physical activity, or parathormone levels. No in-depth analysis of nutritional status was carried out and no information on nutritional conditions was collected. Future research should consider whether vitamin D supplementation in patients undergoing rehabilitation improves functional outcomes in ischemic stroke patients. The BI and mRS tools used are recommended for functional assessment and have high inter-rater reliability. Nevertheless, there is no mandatory definition of a good score, and it is the researcher who sets the standards that determine the score. Neither scale takes into account the patient's mental state, and anxiety or post-stroke depression can affect a patient's functioning and quality of life. Future studies should also use other objective measurement methods that take into account all aspects of life, both physical and mental.

Conclusions

In conclusion, lower serum vitamin D levels and older age may be associated with worse functional outcome in first-ever

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ischemic stroke patients. It is urgent to evaluate in a prospective, randomized trial with a placebo group whether vitamin D supplementation in appropriate doses can improve prognosis and functional outcomes in first-ever ischemic stroke patients undergoing rehabilitation treatment.

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Załącznik 4. Czwarta praca z cyklu.

BOROWICZ, Wojciech, SZCZEPAŃSKA, Marta & ROSIŃCZUK, Joanna. C-Reactive protein as a biomarker affecting neurorehabilitation outcomes in post-stroke patients: state of knowledge and global trends in research. Journal of Education, Health and Sport. 2023;13(4):92-107. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2023.13.04.010
https://apcz.umk.pl/JEHS/article/view/41951
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C-Reactive protein as a biomarker affecting neurorehabilitation outcomes in post-stroke patients: state of knowledge and global trends in research

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Abstract

Background: Stroke-related cerebrovascular diseases affect millions of people worldwide and the annual incidence rate is steadily increasing. The role of biomarkers is inevitably reflected in technological advances but also in the development of molecular methods in the field of laboratory diagnostics. C-reactive protein (CRP) is a commonly determined biomarker of inflammation and may reflect the progression of a vascular disease. CRP values within 12 to 24 hours of stroke symptom onset are an independent predictor of adverse functional outcome in terms of the level of motor recovery in the first year of follow-up.

Objective: This study aims to provide a complementary analysis of the scientific literature and critically review studies on the use of CRP as a potential biomarker associated with stroke and affecting the achievement of neurorehabilitation progress in post-stroke patients.

Methods: This critical review of the literature was prepared based on the international recommendations of the Scale for the Assessment of Narrative Review Articles (SANRA). Inclusion criteria included (1) original research-oriented publications, (2) studies indexed in PubMed, Scopus and PEDro databases, (3) full-text articles in English, (4) recent papers published in 2012 – 2022, (5) papers addressing the use of PCR assay as a biomarker of rehabilitation effectiveness, and (6) papers discussing the role in prognosis of post-stroke patients.

Results: Based on a review of PubMed, Scopus and PEDro databases, 47, 56 and 9 papers, respectively, were selected based on precisely selected keywords and included in full for further full text review. In this review, the most important scientific rationale was included in response to the aim of this paper.

Summary: Recognition of the role of inflammatory and immunological factors in the development of atherosclerosis and the occurrence of ischaemic stroke provides scope for the search for new methods of stroke risk assessment and the development of new methods to prevent stroke. Further empirical validation and unequivocal demonstration of the levels of CRP as a potential marker that affects the health status of a post-stroke patient are needed to ensure the greatest possible level of motor recovery and ability to function independently in terms of all activities of daily living.

Keywords: stroke, C-reactive protein, biomarker, neurorehabilitation, functional outcomes, state of knowledge, critical review

Introduction

Problematics of stroke

Stroke-related cerebrovascular diseases affect millions of people worldwide and the annual incidence rate is steadily increasing. In an ageing society with multiple risk factors, strokes and subsequent neurological deficits as a result of damage to central nervous system (CNS) structures will constitute an increasing challenge for the entire healthcare system [1,2]. Effective diagnostic and therapeutic management, but also prognostic management in terms of the prognosis of motor recovery after stroke remain an important interdisciplinary medical problem [3].

Stroke is characterised by a neurological deficit associated with acute focal CNS damage in vascular disorders, including cerebral infarction, intracerebral haemorrhage, and subarachnoid haemorrhage, excluding any other aetiology [4]. According to the American Heart Association (AHA) and the American Stroke Association (ASA), the definition of stroke needs consistent specification for the multidimensional needs of clinical practice, research and public health. The terminology should be based on advances in basic science, neuropathology and neuroimaging that enable a detailed observation and understanding of the complex mechanisms of stroke in ischaemia and cerebral haemorrhage [5].

Epidemiology of stroke

According to the World Health Organization (WHO), stroke is the second most fatal syndrome affecting people aged 60 years and older, with the incidence steadily increasing [6]. Approximately 15-17 million people worldwide suffer from strokes annually, with as many as 5 million cases resulting in death, while another 5 million are associated with permanent disability, indirectly involving the families of those affected as well as society as a whole [7,8].

According to data from a population-based study involving more than one million patients as part of the international EROS project [9], there is a slightly higher incidence of stroke among women (51.4%), the average age for peak incidence was found to be 73 years and the age range 75-84 years has the highest incidence, affecting almost 33% of individuals. It was revealed that the mean annual incidence of stroke in the European population is 101.2 per 100,000, with the highest incidence in Lithuania at 239.3 per 100,000 and the lowest in Italy at 101.2 per 100,000, and in Poland at 147.2 per 100,000 [9].

Consequences of stroke

It is worth drawing attention to the systemic European Stroke Action Plan (ESAP) 2018-2030 being implemented by the European Stroke Organisation (ESO) in collaboration with the Stroke Alliance for Europe (SAFE). The plan has 4 overarching goals for 2030: (1) to reduce the absolute number of strokes in Europe by 10%, (2) to treat 90% or more of all stroke patients in Europe in a dedicated stroke unit as the first level of care, (3) to have national stroke plans covering the whole chain of care, and (4) to fully implement national strategies for multi-sectoral public health interventions [10].

A cohort study conducted as part of the ARIC project involving nearly 500 post-stroke patients described the specific symptoms of cerebrovascular incidents according to prevalence, which included hemiparesis, facial muscle paralysis, limb muscle paralysis, unilateral and contralateral sensory abnormalities, speech impairment, non-specific headache, gait and balance impairment, loss of half of the visual field, dizziness and seizures [11].

In stroke, there is a reduction in conscious, coordinated and fine motor skills [12,13], as well as a significant deterioration in overall levels of activities of daily living (ADLs) and social participation, resulting in a negative impact on patients' health-related quality of life (HRQOL) [14,15].

The role of biomarkers in medicine

According to the Biomarkers Definitions Working Group (BDWG) [16], the role of biomarkers in the assessment and prediction of many conditions, including stroke, is inevitably reflected in technological advances related to the collection and processing of medical data, but also in the development of molecular methods in the field of laboratory diagnostics. This opens up great opportunities and creates hitherto unattainable potential for the search for specific substances linked to the risk of various conditions for preventive or predictive purposes. One approach to achieving faster and more informative therapeutic trials is to use precise clinical measurement tools to determine disease progression and the effects of therapeutic interventions. Another approach is to use a wide range of analytical tools to assess biological parameters, which are referred to as biomarkers. A biomarker is thus defined as a biological factor that is objectively measured and assessed as an indicator of normal biological processes, pathological processes or pharmacological responses to a therapeutic intervention [16].

The search for increasingly specific, sensitive and specific biomarkers to improve the assessment of patients' prognosis of survival and their motor recovery and thus their return to work and active social life is of no little importance [17]. Biomarkers are crucial to ensure the sustainability of medical therapies; however, there is still considerable variation in the underlying concepts and terms associated with their use in research and clinical practice, particularly in the fields of chronic disease and nutrition [18]. CRP becomes one such factor in respect of stroke. The detailed mechanism of reduced functional outcome after ischaemic stroke is not yet fully elucidated and is related to a complex cycle of interconnected molecular and cellular mechanisms. Some studies point out that inflammation in the persistent phase after stroke may promote tissue repair and functional regeneration [19].

Potential of CRP in stroke

CRP is a commonly measured biomarker of inflammation and may reflect the progression of vascular disease. CRP was first discovered by Tiller and Francis in 1930 [20]. It plays an important role in the pathogenesis of atherosclerosis; high-sensitivity CRP (hs-CRP) correlates with the extent of atherosclerosis, and high triglyceride levels and BMI are closely associated with high hs-CRP levels in dyslipidemic patients [21]. CRP is a glycoprotein whose synthesis occurs mainly in hepatocytes of the liver and smooth muscles. The gene for CRP is located within chromosome 1 in a single copy. Normal CRP levels in healthy individuals should not exceed 5 mg/l. In inflammatory conditions, CRP levels are usually reached after 24-48 hours and may increase even 1000-fold. In contrast, CRP levels return to baseline values within 7 to 12 days [22].

The recognition of the role of inflammatory and immunological factors associated with the occurrence of ischaemic stroke provides room to explore new methods of assessing stroke risk and developing new methods to prevent stroke. In studies on predicting long-term functional outcomes of post-stroke patients, it was revealed that CRP levels within 12 to 24 hours of stroke symptom onset were independently predictive of adverse functional outcome after 1 year of follow-up. CRP levels measured 24 to 48 hours after symptom onset were even stronger predictors, but the time frame did not meet the inclusion criteria as it falls outside the time window for assessing acute inflammation [23].

Elevated CRP levels showed positively significant associations with long-term, >30 days, adverse functional outcome. Researchers in previous reports found that CRP levels were significantly and positively correlated with functional outcomes assessed by the Modified Rankin Scale (mRS) at 1, 3, 6 and 12 months of follow-up, with increasingly stronger observational associations as the time increased. An important highlight was that CRP levels measured 7 days after admission revealed a stronger statistical correlation with mRS scores at 12 months than CRP levels measured within 24 hours of admission [24].

Other studies also confirmed the association between ischaemic stroke and elevated CRP levels. Researchers found that high plasma CRP levels obtained in their study, independent of other risk factors for cardiovascular diseases, can be used as a predictor of transient ischaemic attack (TIA) and ischaemic stroke risk for the elderly group, i.e. those over 65 years of age [25]. As highlighted by Sproston and Ashworth [26], although elevations in inflammatory markers are usually observed in infections, increases in CRP levels in ischaemic stroke may reflect

non-infectious inflammation induced by ischaemia, contributing to a hypercoagulable state and extensive tissue damage.

Objectives

This study aims to provide a complementary analysis of scientific literature and a critical review of studies on the use of CRP as a potential biomarker associated with stroke and affecting the achievement of neurorehabilitation progress in post-stroke patients. The objective will also be to analyse the global trend in the publication of papers on the subject during the period under study, i.e., the last decade (2012–2022).

Methods

Methodological quality

This critical review of the literature was prepared based on the SANRA (Scale for the Assessment of Narrative Review Articles) international recommendations for assessing the methodological quality of such papers [27]. The PICO strategy [28] was used for the formulation of a guiding question and review of the literature for the following components: Patient (ischaemic stroke), Intervention (diagnosis, prognosis, rehabilitation), Control (not applicable), and Outcomes (CRP biomarker). The Narrative Review Checklist (NRC) was also used in the development of the publication in terms of the appropriate standard of content, form and structure of the paper [29]. Descriptors were selected according to the current MeSH terminology [30] and a combination of the following keywords was used: stroke, post-stroke patients, PCR biomarker, motor recovery, rehabilitation, neurorehabilitation.

Qualification procedure

Inclusion criteria included (1) original publications with a research and clinical focus, (2) studies indexed in PubMed, Scopus and PEDro databases, (3) full-text articles in English, (4) recent papers published in the last decade, i.e., 2012– 2022, (5) papers addressing the use of the PCR assay as a biomarker of rehabilitation effectiveness, and (6) papers discussing the role in post-stroke patient's prognosis.

Exclusion criteria included (1) review publications in the nature of systematic reviews, meta-analyses, as well as narrative reviews and range of literature, (2) studies indexed in medical databases other than those indicated above, (3) articles available only as abstracts or post-conference reports, (4) papers published before 2012, (5) publications significantly deviating from the target topic of this article and in languages other than English.

Results

Database search

In the PubMed database, 3,855 records were retrieved after using the initial keyword combination "stroke AND C-reactive protein". After changing the keywords to "ischemic stroke AND C-reactive protein", 1,239 records were retrieved. In the next step, the final keyword combination "ischemic stroke AND C-reactive protein AND rehabilitation" was used, where 58 records were found. Subsequently, after narrowing the scope of the search to the years 2012-2022, 47 papers were retrieved, of which 41 papers in English were available in the full-text version and were included in this review (Fig.1a and 1b).

In the Scopus database, after using the initial keyword combination "stroke AND C-reactive protein", 8,896 records were retrieved. After changing the keywords to "ischemic stroke AND C-reactive protein", 3,566 records were retrieved. In the next step, the final keyword combination "ischemic stroke AND C-reactive protein AND rehabilitation" was used, where 66 records were found. Subsequently, after narrowing the temporal scope of the search to 2012-2022, 56 papers were retrieved, of which 53 papers in English were available in the full-text version and were included in this review (Fig. 2a and 2b). In contrast, in the PEDro database, after using the initial keyword combination "stroke AND C-reactive protein", only 9 records were retrieved, all of which were included for further full-text review (Fig. 3).

It should be emphasised that from the biological point of view, on the one hand, the post-stroke CRP biomarker will cause cell death, brain damage and disruption of the blood-brain barrier (BBD), which directly contributes to damage and worse functional outcome, but on the other hand, it can exacerbate atherosclerosis via atherosclerotic plaque rupture, platelet aggregation and intravascular thrombosis [31,32]. Various biological mechanisms underlying stroke disorders are presented, the understanding and elucidation of which may contribute to a faster and more complete diagnosis. This can also guide both pharmacological and rehabilitation therapy as a whole treatment process led by an interdisciplinary team. All of these coordinated actions aim to increase the effectiveness of patients' functional recovery and thus reduce the marginalisation of this patient group. The following review considers the most important scientific rationale in response to the objective set out in this paper.

In their study, Wnuk et al. [33] observed that non-infectious CRP levels are an independent risk factor for poor short- and long-term functional outcomes with ischaemic stroke undergoing thrombolytic treatment. In their study, conducted as a retrospective analysis of prospective data, they included a group of 158 patients with a mean age of 72 years (63-82). They used mRS to assess functional outcome. They considered a functional outcome to be poor when the value obtained in the score assessment 90 days after the ischaemic incident was greater than three points. They found that a poor functional outcome assessed using mRS 3 was obtained by patients with CRP levels > 8.65 mg/l compared to patients with CRP levels below 5 mg/l.

Geng et al. [34] prospectively investigated 301 patients with acute ischaemic stroke and assessed CRP levels as an inflammatory marker associated with stroke severity and long-term outcome. Patient demographic and clinical data were collected and assessed on admission. Adverse patient outcomes at hospital discharge were assessed using mRS > 2. The researchers conclude that the CRP levels measured at admission proved to be an independent predictor of adverse outcome at hospital discharge.

Tu et al. [35] investigated 189 patients with acute ischaemic stroke who were admitted to hospital within 24 hours of symptom onset. They observed that serum hs-CRP levels were significantly higher in stroke patients compared with controls ($p < 0.0001$). The conclusion was that hs-CRP may be one of the independent predictors of short-term outcome and mortality in acute ischaemic stroke.

Nozoe et al. [36] investigated the link between changes in quadriceps muscle thickness as a component of lower limb motor function and the severity of the condition, nutritional status as well as CRP levels among patients with acute intracerebral haemorrhage or ischaemic stroke. It was revealed that quadriceps muscle thickness was more reduced in CRP-positive patients (≥ 0.3 mg/dL) than in CRP-negative patients (< 0.3 mg/dL) in the limb not affected by paresis. The results indicate that positive CRP on admission was significantly correlated with reduced quadriceps muscle thickness after acute stroke which may be indicative of a lower level of lower limb motor function.

In October 2003 – December 2011, Karlinski et al. [37] investigated the link between routine CRP measurement within 24 hours of admission and outcome in ischaemic stroke patients treated with intravenous thrombolysis, taking into account a history of recent infection. It was observed that patients with elevated CRP levels (135/341, 42.5%) were significantly older compared to patients with normal CRP levels and more likely to present with pre-existing disability, comorbidities and they suffered more severe strokes. That group of patients also had a higher rate of symptomatic intracranial bleeding according to the European Cooperative Acute Stroke Study (ECASS) II classification (7.2% vs. 1.6%, $p = 0.010$), higher 3-month mortality (25.6% vs 11.3%, $p = 0.001$) and was significantly less independent at 3 months (45.9% vs 63.7%, $p = 0.002$).

In contrast, Jiménez et al. [38] observed that the risk of higher CRP levels and worse functional outcome were associated with hypertension in men who had ischaemic stroke in the past compared to men without hypertension as a comorbidity. Moreover, they emphasise that carotid atherosclerosis may be associated with elevated serum CRP levels in patients with internal carotid artery stenosis, resulting in carotid artery obstruction and subsequent large-artery atherosclerotic (LAA) stroke [39].

Matsuo et al. [40] assessed the link between CRP levels and functional outcomes in their prospective studies conducted from June 2007 to May 2014. They used mRS to assess the functional outcome (as in this study). Poor functional outcome of 3> mRS was defined as a disability at 3 months after stroke, and was tested using the logistic regression analysis. The mean age of the participants was 70.8 ± 12.2 years. Matsuo et al. found that CRP levels were independently associated with adverse functional outcomes. Those Japanese researchers proved

that elevated CRP levels increased with age and that functional outcome after stroke was generally poorer in the elderly.

Also, Peña Sánchez et al. [41] emphasised that the age of patients should be taken into account when assessing the usefulness of CRP and other blood biomarkers as clinical tools for predicting long-term or short-term neurological outcomes and, consequently, functional performance outcomes in ischaemic stroke patients. According to the authors of the above-mentioned report, CRP levels only increase in patients older than 55 years. The authors concluded that CRP levels and age were directly correlated in stroke patients, and older age correlates with more severe neurological impairment.

Peng et al. [42] evaluated links between CRP levels and the occurrence of stroke in their cross-sectional studies involving U.S. resident population. They enrolled 32,408 participants, including 15,495 men and 16,913 women. Multivariate analyses stratified by sex revealed a non-significant link between higher CRP levels and stroke in men. In the overall population, 13% of stroke cases could be attributed to higher CRP levels (> 5 mg/l). The authors found that higher CRP levels tended to be a more significant risk factor for stroke among women than men, as they confirmed by the multivariate logistic analysis.

Those findings were consistent with an earlier Framingham study [43], which revealed that the highest quartile CRP levels were associated with a significant increase in ischaemic stroke or TIA in women (risk ratio = 2.1; 95% CI: 1.19-3.83), while the association disappeared in men (risk ratio = 1.6; 95% CI: 0.87-3.13). Different results were obtained by Chinese researchers, who observed that elevated CRP levels had a significant effect in male patients, but not in female patients [44]. Those inconsistent findings regarding sex differences may have been partly due to genetic and hormonal differences between men and women; the above-mentioned processes need to be clarified and thus further studies to dissect this phenomenon need to be performed.

Rajeshwar et al. [45] by using the multiple logistic regression showed that higher levels of hs-CRP were significantly associated with poor outcomes in their sample of 581 patients after taking into account several confounding variables. They examined the link between CRP levels and poor outcome (>2 mRS and <5 on the Glasgow Coma Scale Extended, GCS-E). There was a significant link between elevated hs-CRP levels and nitric oxide (NO) levels with stroke occurrence. The regression analysis confirmed those results after adjusting for potential confounders for hs-CRP (adjusted OR = 2.890; 95% CI = 1.603-5.011; $p < 0.01$) and NO (adjusted OR = 2.364; 95% CI = 1.312-3.998; $p < 0.01$). After adjusting for potential confounders, patients with high CRP levels had a significantly increased risk of poor clinical outcome (adjusted OR = 3.50; 95% CI = 1.312-6.365; $p < 0.001$). The researchers conclude that hs-CRP and NO biomarker levels predict the occurrence of ischaemic stroke and, additionally, hs-CRP is an independent predictor of poor outcome at 3 months after stroke onset.

Imaging studies have revealed that the progression of infarct evolution is not further altered after approximately 30 days, which correlates with the patient's overall disability originating from ischaemic stroke. The most current evidence questions and emphasises that blood biomarkers may be as effective in predicting functional outcome as imaging biomarkers; however, this needs to be confirmed by further studies on the effectiveness of blood biomarkers in predicting recovery while monitoring imaging results. As highlighted by Van Gilder et al. [46], long-term functional outcome scales such as the Barthel Index (BI) and mRS are commonly used to measure dependence in activities of daily living and assessing disability and have high inter-rater reliability compared to other scales.

In their studies, Ye et al. [47] evaluated whether CRP levels in acute ischaemic stroke could act as a prognostic marker of long-term functional disability. In their project, they prospectively studied patients with first ischaemic stroke registered in the Nanijing Stroke Registry in the period from January 2012 and June 2014. For analyses, venous blood was collected from 625 patients within 14 days of stroke onset. Patients were followed up for one year. There were 458 men and 167 women in the study group. Elevated CRP as an independent predictor of functional disability was found in both sexes after one year, in men ($p=0.017$) and in women ($p=0.042$). The authors emphasise that elevated CRP levels are associated with greater motor disability.

In contrast, Ahmadi Ahangar et al. [48] conducted a cross-sectional analytical study among 214 patients after neuroimaging-confirmed ischaemic stroke (CT or MRI). Stroke severity was determined by NIHSS (National Institutes of Health Stroke Scale) criteria: score ≤ 8 mild stroke; 9-15 moderate stroke, ≥ 16 severe stroke. Serum CRP levels were measured using the Latex Agglutination Test. In this method, anti-CRP sensitised latex particles adjacent to CRP that is present in the serum sample causes agglutination. In that study, CRP levels greater than 5 mg/dl of serum were considered positive and lower values were considered normal. The authors found that serum CRP levels were positive in 122 cases (57%). Out of 122 cases of positive CRP, 64 cases (52%)

included women and the remaining 58 cases (48%) included men (p=0.21). The results of this study revealed that positive serum CRP levels were associated with ischaemic stroke severity and poor prognosis.

Totan et al. [49] also conducted a retrospective study in which they enrolled 81 patients diagnosed with ischaemic stroke. The mean age of the patients included in the study was 73.49 years (45-95). Seventy-nine per cent of the patients had elevated CRP levels, 56% of the patients had CRP levels between 5 and 50 mg/dl and 23% of the patients had CRP levels above 50 mg/dl. The authors examined the correlation between CRP levels and the degree of motor deficit. The degree of motor impairment was measured using mRS and was assessed in all patients included in the study. Motor deficits predominated in the study group, with CRP levels in the range of 5-50 mg/dl. There were no significant differences in terms of the cases studied between patients with severe motor impairment and those with moderate motor impairment. Since the most important risk factors present in the patients included in the above-mentioned study were hypertension and atherosclerosis, the authors also investigated the correlations between these risk factors and CRP levels. The majority of patients with those two risk factors had average CRP levels (5-50 mg/l).

Chinese researchers Hong-Qiu et al. [50] conducted a randomised, observational study. They assessed the link between CRP levels in patients after first ischaemic stroke and recurrent stroke plus functional disability, which they defined as a score assessed by mRS >2 (as in this project) at a follow-up of 90 days after the incident. The mean age of the participants was 62.3±11.3 years. Factors known to be associated with stroke recurrence and functional outcomes were included as confounders in analyses and included demographic data (age, sex, BMI), smoking, hypertension, diabetes. The analysis of the results revealed that less than 20% of the poor functional outcome could be explained by recurrent stroke, meaning that more than 80% of the functional damage was due to disability. Therefore, typical secondary prevention strategies, e.g., rehabilitation, are very important for preventing stroke recurrence.

Among all the studies cited, three reports questioned the use of CRP as a marker for predicting the level of motor function after stroke. Therefore, Taheraghdam et al. [51], in their prospective study involving 102 patients hospitalised for their first ischaemic stroke, report critical results and conclude that CRP is not an appropriate marker for predicting the severity of short-term functional disability as measured by mRS and may not be useful as a clinical factor for predicting treatment outcome.

In contrast, Ozkan et al. [52] assessed the predictive value of hs-CRP and ferritin levels for functional disability in patients with acute ischaemic stroke at 3-month follow-up. Plasma hs-CRP and ferritin measurements were obtained from patients within 48 hours after stroke onset and at 3-month follow-up in two groups of patients: elevated serum hs-CRP ≥0.5 mg/dl and normal serum hs-CRP<0.5 mg/dl. Treatment outcomes were assessed using the NIHSS and Functional Independence Measure (FIM) scales. According to the researchers, hs-CRP levels could not predict functional disability 3 months after stroke onset.

Åberg et al. [53] assessed the value of serum biomarkers such as CRP, D-dimers, fibrinogen and S100β protein in predicting the 3-month functional performance outcome on the mRS in 131 acute ischaemic stroke patients. Peripheral blood levels of the biomarkers studied were determined on admission (CRP, D-dimers and fibrinogen) or 48 hours after stroke (S100β). It was proven that although S100β protein levels were significantly associated with mRS scores at 3-month follow-up (p <.001), this association was not apparent for the other biomarkers assessed, including CRP.

Zhao et al. [54] conducted an interesting randomised trial to evaluate the effect of different doses of clopidogrel in combination with early rehabilitation on motor function and inflammatory markers in patients with ischaemic stroke. Patients' motor function-related outcomes were collected, including scores of scales such as BI, NIHSS, Fugl-Meyer Scale (FMS), scores of inflammatory markers such as hs-CRP, interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), and the rate of adverse events. It was revealed that high-dose clopidogrel and early rehabilitation were superior to low-dose treatment to effectively attenuate the inflammatory response by promoting restoration of neurological function, improving the level of motor function in patients with ischaemic stroke.

It should be mentioned that there is a link between CRP levels and the occurrence of post-stroke depression. Cheng et al. [55] investigated changes in hs-CRP and homocysteine levels in acute ischaemic stroke and assessed the link of those two risk factors with long-term post-stroke depression (PSD). They examined 259 patients, who were classified based on depressive symptoms according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for depression at 1 year after stroke. It was found that 94 patients (36.3%) were diagnosed with PSD. On the other hand, the multivariate logistic regression analysis revealed that the third and fourth quartiles of hs-CRP or homocysteine levels were significantly associated with PSD (p <

0.05), confirming the hypothesis that elevated serum levels of hs-CRP were related to a higher risk of developing PSD one year after stroke.

Summary

The recognition of the role of inflammatory and immunological factors in the development of atherosclerosis and the occurrence of ischaemic stroke provides room for the search for new methods to assess stroke risk and develop new methods to prevent stroke. The studies revealed the important role of inflammatory mechanisms in the dynamics of the development of stroke focus. In response to necrotic tissues (antigens released from them), an acute inflammatory response develops, which contributes to the enlargement of the infarct area and is reflected in neurological deterioration. This also significantly affects the subsequent prognosis of the stroke patient and has a direct bearing on the effectiveness of therapeutic rehabilitation and the progress the patient makes in the recovery of motor functions lost due to stroke. Further empirical verification and unequivocal demonstration of CRP levels as a potential marker that affects the health status of a post-stroke patient is needed to ensure the greatest possible level of motor recovery and ability to function independently in terms of all activities of daily living.

Abbreviations

ADL	activities of daily living
AHA	American Heart Association
ASA	American Stroke Association
BDWG	Biomarkers Definitions Working Group
BI	Barthel Index
CNS	central nervous system
CRP	C-reactive protein
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV
ECASS II	European Cooperative Acute Stroke Study II
ESAP	European Stroke Action Plan
ESO	European Stroke Organization
FIM	Functional Independence Measure
FMS	Fugl-Meyer scale
GCS	Glasgow Coma Scale
HRQOL	health-related quality of life
IL-6	interleukin-6
LLA	large-artery atherosclerosis
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NO	nitric oxide
NRC	Narrative Review Checklist
PSD	post-stroke depression
SAFE	Stroke Alliance for Europe
SANRA	Scale for the Assessment of Narrative Review Articles
TNF-α	tumor necrosis factor-α
WHO	World Health Organization

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Figure 1a. Search stages and results from PubMed database (part 1).

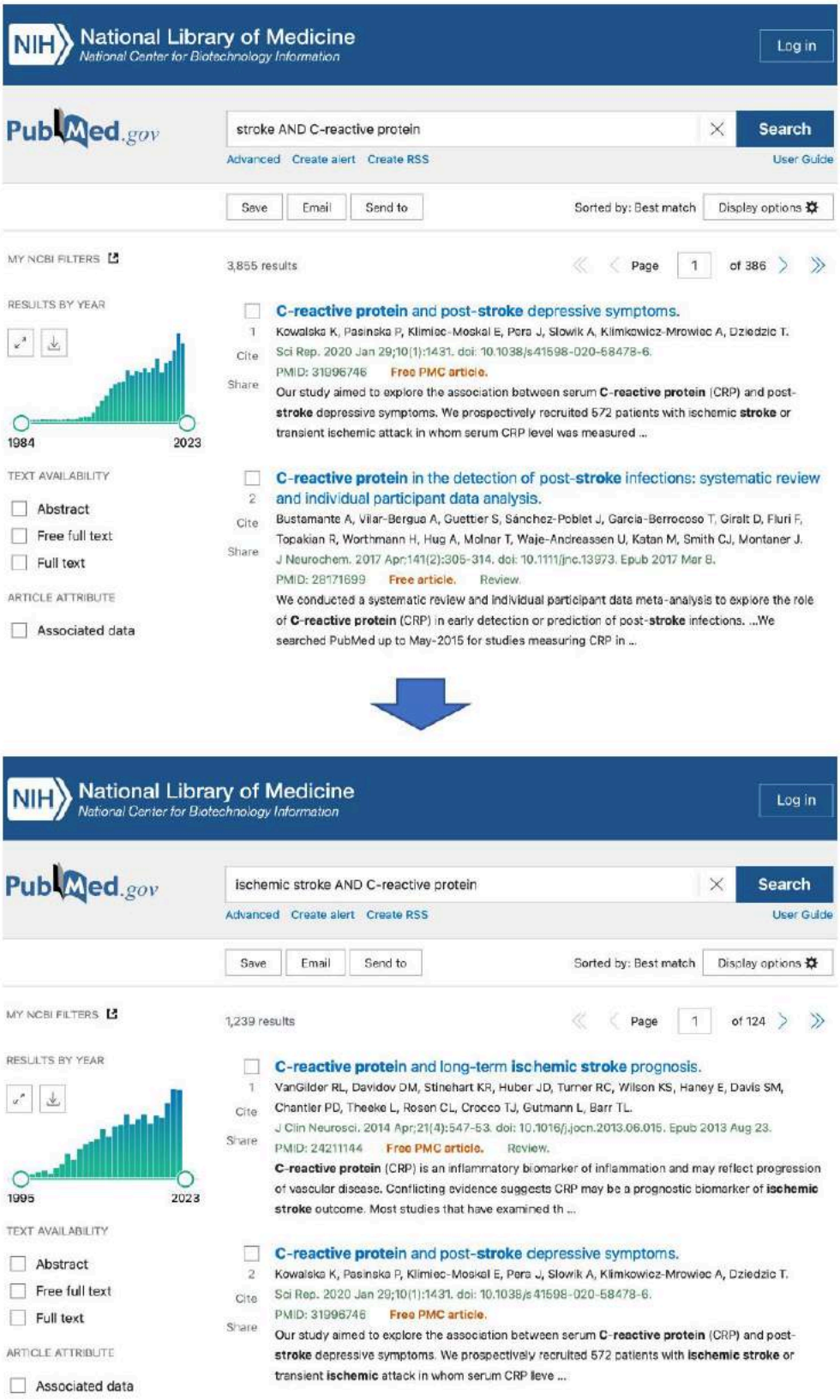

Figure 1b. Search stages and results from PubMed database (part 2).

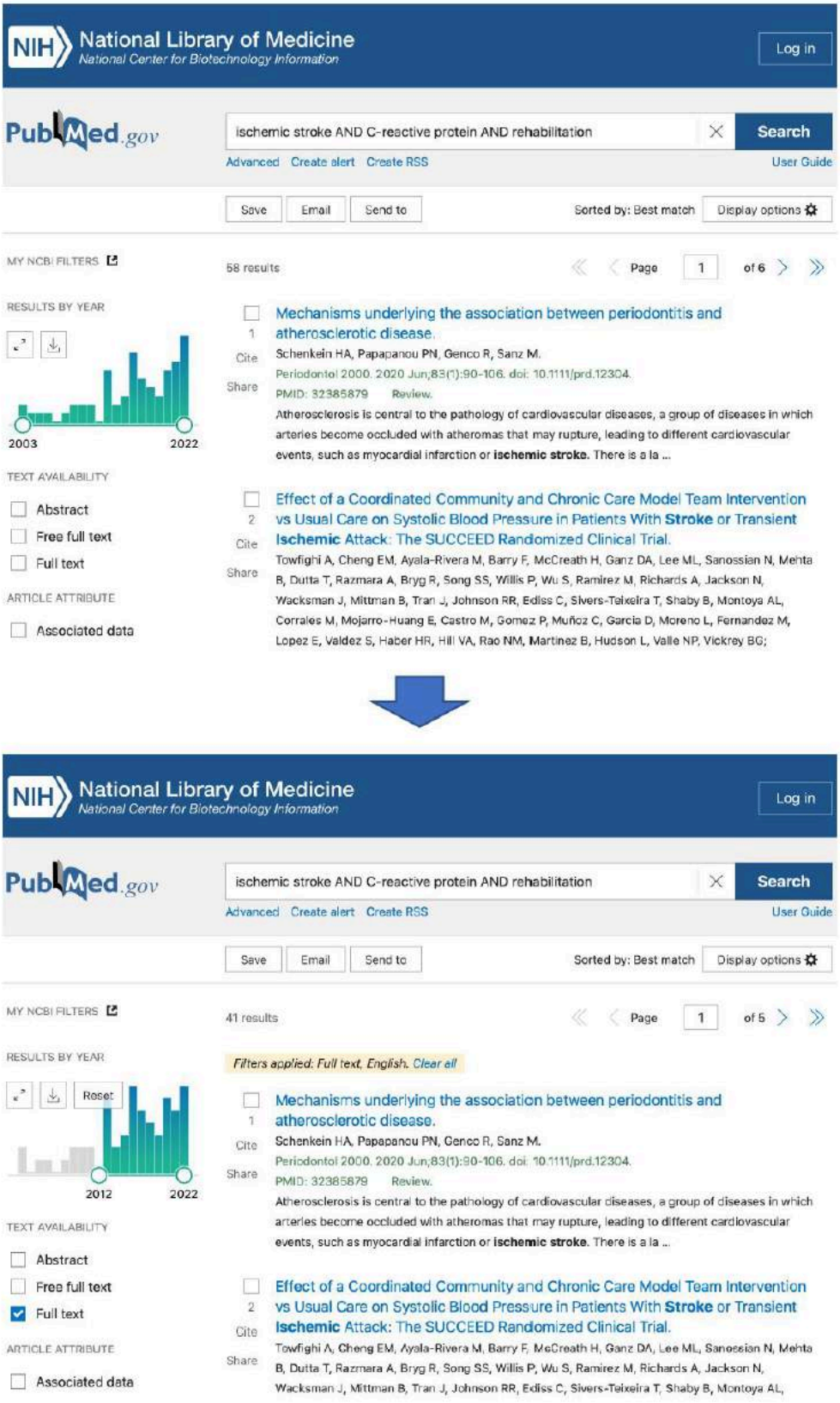

Figure 2a. Search stages and results from Scopus database (part 1).

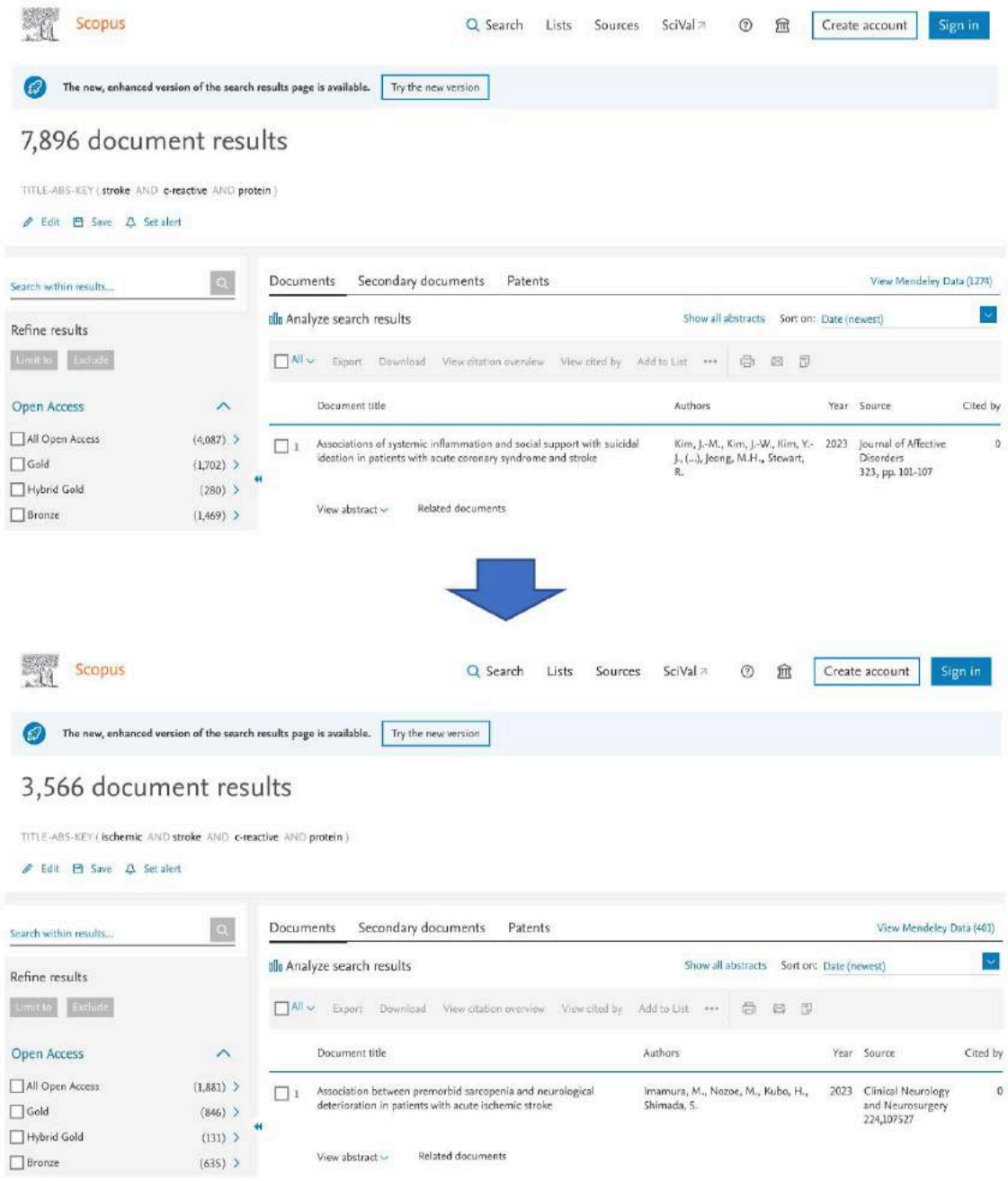

Figure 2b. Search stages and results from Scopus database (part 2).

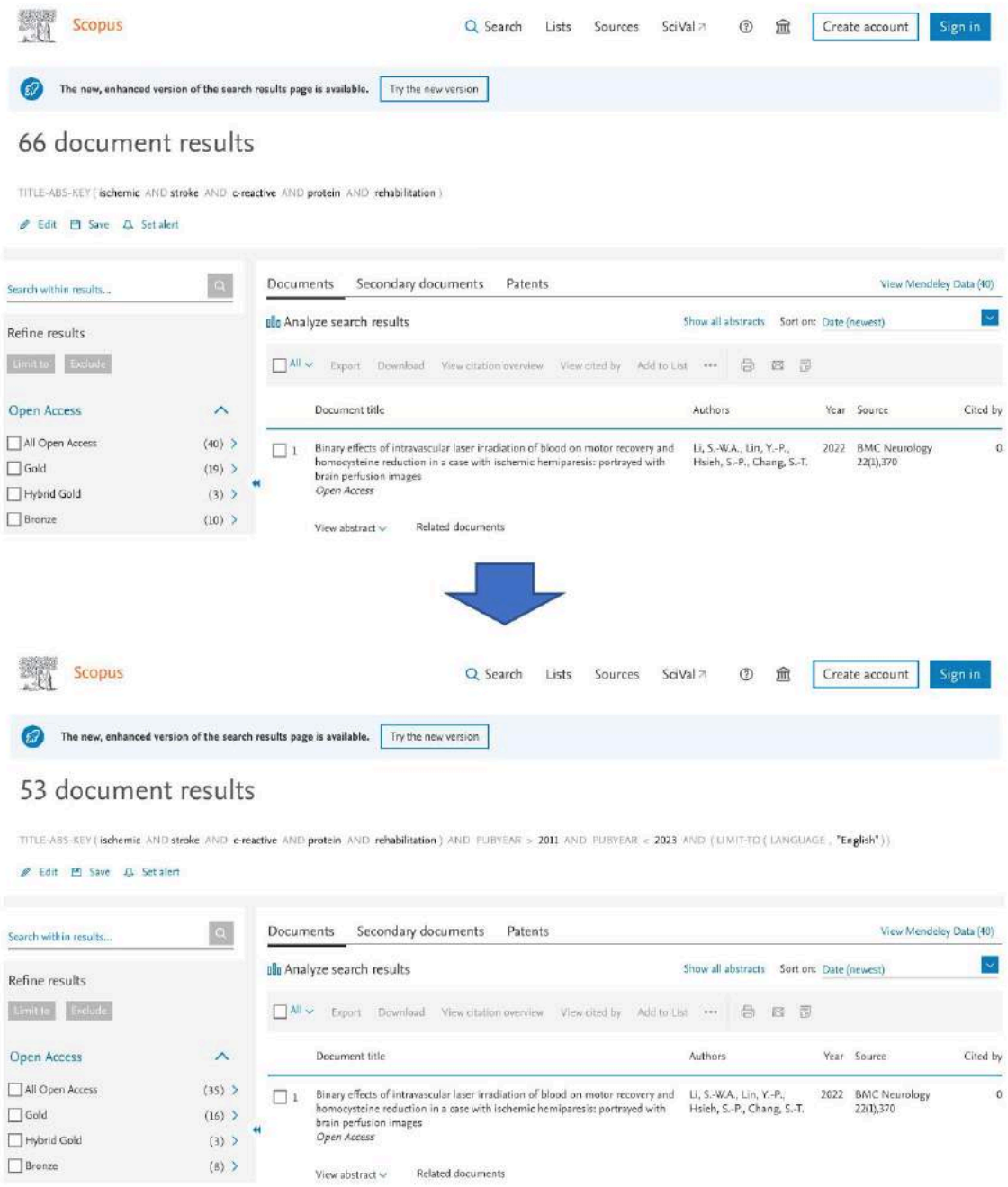

Figure 3. Search stages and results from PEDro database.

PEDro
Physiotherapy Evidence Database

PEDro is a free database of randomised controlled trials, systematic reviews and clinical practice guidelines in physiotherapy. You can search PEDro using this Advanced Search page. Those who are new to searching may like to begin with the Simple Search page. Patients and users of physiotherapy may prefer the Consumer Search page. For more information please visit the PEDro home page.

Home | New Search (Simple) | New Search (Advanced) | Search Help

Abstract & Title:	stroke AND C-reactive protein
Therapy:	
Problem:	
Body Part:	
Subdiscipline:	
Topic:	
Method:	
Author/Association:	
Title Only:	
Source:	
Published Since:	[YYYY]
New records added since:	[DD/MM/YYYY]
Score of at least:	[/10]
Return:	20 records at a time
When Searching:	Match all search terms (AND)

PEDro
Physiotherapy Evidence Database

Home | Display Selected Records | New Search (Simple) | Continue Searching (Advanced) | New Search (Advanced) | Search Help

Search Results

Click on a title to view details of that record. If your search has returned many records you may need to move to the next page (at the top or bottom of the list of records). To display a list of records from one or a series of searches, click on *Select* and then *Display Selected Records*

Found 9 records

Title	Method	Score (/10)	Select Record
The cardiac model of rehabilitation for reducing cardiovascular risk factors post transient ischaemic attack and stroke: a randomized controlled trial [with consumer summary]	clinical trial	8/10	Select
Secondary prevention of new vascular events with lifestyle intervention in patients with noncardioembolic mild ischemic stroke: a single-center randomized controlled trial	clinical trial	8/10	Select
(Effect of acupuncture on neurological function and high-sensitivity creactive protein in patients with acute cerebral infarction) [Chinese - simplified characters]	clinical trial	7/10	Select
Task-oriented circuit training as an alternative to ergometer-type aerobic exercise training after stroke	clinical trial	6/10	Select
Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea [with consumer summary]	clinical trial	6/10	Select
(Effect of acupuncture combined with rehabilitation on immune and neural functions in elderly patients with stroke) [Chinese - simplified characters]	clinical trial	5/10	Select
Randomization to treadmill training improves physical and metabolic health in association with declines in oxidative stress in stroke	clinical trial	4/10	Select
The effects of CPET-guided cardiac rehabilitation on the cardiopulmonary function, the exercise endurance, and the NT-proBNP and hscTnT levels in CHF patients	clinical trial	4/10	Select
Comparison of the effects between isokinetic and isotonic strength training in subacute stroke patients	clinical trial	3/10	Select

Załącznik 5. Pisemne oświadczenia współautorów publikacji.

Pierwsza praca z cyklu

Wrocław 27.02.2023

OŚWIADCZENIE

Oświadczam, że Pan **Lek. med. Wojciech BOROWICZ** wniósł znaczący wkład w powstanie publikacji oryginalnej: Wojciech Borowicz, Kuba Ptaszkowski, Eugenia Murawska-Ciałowicz, Joanna Rosińczuk. *Proprioceptive Neuromuscular Facilitation and Mirror Therapy Methods Are Comparable Methods of Rehabilitation after a First-Ever Ischemic Stroke: A Randomized Study*. Sustainability 2022, 14 (22): 15246; IF = 3,889 / MEiN = 100,00 pkt; który polegał na opracowaniu koncepcji i metodologii badania, przeprowadzeniu badania i zbieraniu danych, przygotowaniu bazy danych i udziale w wykonaniu analizy danych, sporządzaniu manuskryptu i nanoszeniu poprawek podczas recenzji, jak również zarządzaniu projektem badawczym oraz zaakceptowaniu ostatecznej wersji manuskryptu przed publikacją.

Dr Kuba PTASZKOWSKI, prof. UMW
Katedra Fizjoterapii, Wydział Nauk o Zdrowiu,
Uniwersytet Medyczny we Wrocławiu

Prof. dr hab. Eugenia MURAWSKA-CIAŁOWICZ
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i Sportu, Akademia Wychowania Fizycznego we Wrocławiu

Prof. dr hab. Joanna ROSIŃCZUK
Katedra Pielęgniarstwa i Położnictwa, Wydział Nauk o Zdrowiu,
Uniwersytet Medyczny we Wrocławiu

Druga praca z cyklu

Wrocław 27.02.2023

OŚWIADCZENIE

Oświadczam, że Pan **Lek. med. Wojciech BOROWICZ** wniósł znaczący wkład w powstanie publikacji oryginalnej: Wojciech Borowicz, Kuba Ptaszkowski, Lucyna Ptaszkowska, Eugenia Murawska-Ciałowicz, Joanna Rosińczuk. *Assessment of Changes in Serum C-Reactive Protein Levels in Patients after Ischemic Stroke Undergoing Rehabilitation—A Retrospective Observational Study.* Journal of Clinical Medicine 2023, 12 (3): 1029; IF = 4,964 / MEiN = 140,00 pkt; który polegał na opracowaniu koncepcji i metodologii badania, przeprowadzeniu badania i zbieraniu danych, przygotowaniu bazy danych i udziale w wykonaniu analizy danych, sporządzaniu manuskryptu i nanoszeniu poprawek podczas recenzji, jak również zarządzaniu projektem badawczym oraz zaakceptowaniu ostatecznej wersji manuskryptu przed publikacją

Dr Kuba PTASZKOWSKI, prof. UMW
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Prof. dr hab. Joanna ROSIŃCZUK
Katedra Pielęgniarstwa i Położnictwa, Wydział Nauk o Zdrowiu,
Uniwersytet Medyczny we Wrocławiu

Trzecia praca z cyklu

Wrocław 12.04.2023

OŚWIADCZENIE

Oświadczam, że Pan **Lek. med. Wojciech BOROWICZ** wniósł znaczący wkład w powstanie publikacji oryginalnej: Wojciech Borowicz, Kuba Ptaszkowski, Lucyna Ptaszkowska, Joanna Rosińczuk, Eugenia Murawska-Ciałowicz, *Relationship Between Serum Vitamin D Levels and Functional Outcomes in Patients After Ischemic Stroke Undergoing Rehabilitation – A Pilot Study*. Medical Science Monitor 2023, In Press, DOI: 10.12659/MSM.940115 [9 s.]; IF = 3.386 / MEiN = 140 pkt; który polegał na opracowaniu koncepcji i metodologii badania, przeprowadzeniu badania i zbieraniu danych, przygotowaniu bazy danych i udziale w wykonaniu analizy danych, sporządzaniu manuskryptu i nanoszeniu poprawek podczas recenzji, jak również zarządzaniu projektem badawczym oraz zaakceptowaniu ostatecznej wersji manuskryptu przed publikacją.

Dr Kuba PTASZKOWSKI, prof. UMW
Katedra Fizjoterapii, Wydział Nauk o Zdrowiu,
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i Sportu, Akademia Wychowania Fizycznego we Wrocławiu

Czwarta praca z cyklu

Wrocław 27.02.2023

OŚWIADCZENIE

Oświadczam, że Pan **Lek. med. Wojciech BOROWICZ** wniósł znaczący wkład w powstanie publikacji poglądowej: Wojciech Borowicz, Marta Szczepańska, Joanna Rosińczuk. *C-Reactive protein as a biomarker affecting neurorehabilitation outcomes in post-stroke patients: state of knowledge and global trends in research*. Journal of Education, Health and Sport 2023, 13 (4): 92-107; IF = 0 / MEiN = 40,00 pkt; który polegał na opracowaniu koncepcji pracy, przeszukaniu baz danych, krytycznym przeglądzie literatury, przygotowaniu wykazu prac oraz rycin, sporządzaniu manuskryptu i nanoszeniu poprawek podczas recenzji oraz zaakceptowaniu ostatecznej wersji manuskryptu przed publikacją.

Dr Marta SZCZEPAŃSKA
Centrum Neurorehabilitacji AFA-MED w Żarach

.....

Prof. dr hab. Joanna ROSIŃCZUK
Katedra Pielęgniarstwa i Położnictwa, Wydział Nauk o Zdrowiu,
Uniwersytet Medyczny we Wrocławiu

.....

Załącznik 6. Wykaz publikacji wchodzących w skład cyklu.

lek. Wojciech Borowicz

Wykaz publikacji stanowiących rozprawę doktorską

Lp	Opis bibliograficzny	IF	Punkty
1	**Borowicz Wojciech**, Ptaszkowski Kuba, Murawska-Ciałowicz Eugenia, Rosińczuk Joanna: Proprioceptive neuromuscular facilitation and mirror therapy methods are comparable methods of rehabilitation after a first-ever ischemic stroke: a randomized study, Sustainability, 2022, vol. 14, nr 22, art.15246 [11 s.], DOI:10.3390/su142215246	3,889*	100
2	**Borowicz Wojciech**, Ptaszkowski Kuba, Ptaszkowska Lucyna, Murawska-Ciałowicz Eugenia, Rosińczuk Joanna: Assessment of changes in serum C-reactive protein levels in patients after ischemic stroke undergoing rehabilitation - a retrospective observational study, Journal of Clinical Medicine, 2023, vol. 12, nr 3, art.1029 [11 s.], DOI:10.3390/jcm12031029	4,964*	140
3	**Wojciech Borowicz**, Kuba Ptaszkowski, Lucyna Ptaszkowska, Joanna Rosińczuk, Eugenia Murawska-Ciałowicz. Association Between Serum Vitamin D Levels and Physical Outcomes of Patients Who Underwent Rehabilitation Following Ischemic Stroke. Med Sci Monit 2023, In Press; DOI: 10.12659/MSM.940115	3,386*	140
4	**Borowicz Wojciech**, Szczepańska Marta, Rosińczuk Joanna: C-Reactive protein as a biomarker affecting neurorehabilitation outcomes in post-stroke patients: state of knowledge and global trends in research, Journal of Education, Health and Sport, 2023, vol. 13, nr 4, s. 92-107, DOI:10.12775/jehs.2023.13.04.010	—	40

**IF 2021*

Impact factor: **12,239**

Punktacja ministerialna: **420,0**

11-04-2023 Piotr Omanke

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Załącznik 7. Wykaz wszystkich publikacji.

lek. Wojciech Borowicz

Wykaz publikacji

1. Publikacje w czasopismach naukowych

1.1 Publikacje w czasopiśmie z IF

Lp	Opis bibliograficzny	IF	Punkty
1	Gieysztor Ewa, Pecuch Anna, Kowal Mateusz, **Borowicz Wojciech**, Paprocka-Borowicz Małgorzata: Pelvic symmetry is influenced by asymmetrical tonic neck reflex during young children's gait, International Journal of Environmental Research and Public Health, 2020, vol. 17, nr 13, art.4759 [12 s.], DOI:10.3390/ijerph17134759	3,39	140
2	Murawska-Ciałowicz Eugenia, Wiatr Mona, Ciałowicz Maria, de Assis Gilmara Gomes, **Borowicz Wojciech**, Rocha-Rodrigues Silvia, Paprocka-Borowicz Małgorzata, Marques Adilson: BDNF impact on biological markers of depression - role of physical exercise and training, International Journal of Environmental Research and Public Health, 2021, vol. 18, nr 14, art.7553 [21 s.], DOI:10.3390/ijerph18147553	4,614	140
3	Paprocka-Borowicz Małgorzata, Wiatr Mona, Ciałowicz Maria, **Borowicz Wojciech**, Kaczmarek Agnieszka, Marques Adilson, Murawska-Ciałowicz Eugenia: Influence of physical activity and socio-economic status on depression and anxiety symptoms in patients after stroke, International Journal of Environmental Research and Public Health, 2021, vol. 18, nr 15, art.8058 [14 s.], DOI:10.3390/ijerph18158058	4,614	140
4	Kowal Mateusz, Winiarski Sławomir, Gieysztor Ewa, Kołcz Anna, Walewicz Karolina, **Borowicz Wojciech**, Rutkowska-Kucharska Alicja, Paprocka-Borowicz Małgorzata: Symmetry function in gait pattern analysis in patients after unilateral transfemoral amputation using a mechanical or microprocessor prosthetic knee, Journal of NeuroEngineering and Rehabilitation, 2021, vol. 18, nr 1, art.9 [12 s.], DOI:10.1186/s12984-021-00810-w	5,208	140
5	Kowal Mateusz, Gieysztor Ewa, Kołcz Anna, Pecuch Anna, **Borowicz Wojciech**, Dymarek Robert, Paprocka-Borowicz Małgorzata: The acute influence of whole-body cryotherapy on electromyographic signals and jumping tasks, Applied Sciences-Basel, 2022, vol. 12, nr 10, art.5020 [8 s.], DOI:10.3390/app12105020	2,838*	100
6	Maciaszek Julian, Lenart-Bugla Marta, Szcześniak Dorota, Gawłowski Paweł, **Borowicz Wojciech**, Misiak Błażej, Rymaszewska Joanna: Does mental health affect the decision to vaccinate against SARS-CoV-2? A cross-sectional nationwide study before the vaccine campaign, Frontiers in Psychiatry, 2022, vol. 12, art.810529 [11 s.], DOI:10.3389/fpsyt.2022.810529	5,435*	100
7	**Borowicz Wojciech**, Ptaszkowski Kuba, Murawska-Ciałowicz Eugenia, Rosińczuk Joanna: Proprioceptive neuromuscular facilitation and mirror therapy methods are comparable methods of rehabilitation after a first-ever ischemic stroke: a randomized study, Sustainability, 2022, vol. 14, nr 22, art.15246 [11 s.], DOI:10.3390/su142215246	3,889*	100
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2. Monografie naukowe

2.1 Książka autorska -

2.2 Książka redagowana -

2.3 Rozdziały

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Załącznik 8. Zgoda Komisji Bioetycznej na przeprowadzenie badań.

KOMISJA BIOETYCZNA
przy
Uniwersytecie Medycznym
we Wrocławiu
ul. Pasteura 1; 50-367 WROCŁAW

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 813 /2020

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 133/XV R/2017 z dnia 21 grudnia 2017 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 28 z 1997 r. poz. 152 z późniejszymi zmianami) w składzie:

prof. dr hab. Jacek Daroszewski (choroby wewnętrzne, endokrynologia, diabetologia)
prof. dr hab. Krzysztof Grabowski (chirurgia)
dr Henryk Kaczkowski (chirurgia szczękowa, chirurgia stomatologiczna)
mgr Irena Knabel-Krzyszowska (farmacja)
prof. dr hab. Jerzy Liebhart (choroby wewnętrzne, alergologia)
ks. dr hab. Piotr Mrzygłód, prof. nadzw. (duchowny)
mgr prawa Luiza Műller (prawo)
dr hab. Sławomir Sidorowicz (psychiatria)
prof. dr hab. Leszek Szenborn, (pediatria, choroby zakaźne)
Danuta Tarkowska (pielęgniarstwo)
prof. dr hab. Anna Wiela-Hojeńska (farmakologia kliniczna)
dr hab. Andrzej Wojnar, prof. nadzw. (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)
dr hab. Jacek Zieliński (filozofia)

pod przewodnictwem
prof. dr hab. Jana Kornafela (ginekologia i położnictwo, onkologia)

Przestrzegając w działalności zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej, po zapoznaniu się z projektem badawczym pt.:

„Wpływ treningu usprawniającego pacjentów po udarze niedokrwiennym mózgu na poziom wybranych czynników wzrostu i plastyczności neuronalnej, mięśniowej i naczyniowej"

zgłoszonym przez **lek. Wojciecha Borowicza** uczestnika Szkoły Doktorskiej w Zakładzie Chorób Układu Nerwowego Katedry Pielęgniarstwa Klinicznego Uniwersytetu Medycznego we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła **wyrazić zgodę** na przeprowadzenie badania w Zamiejscowym Oddziale Rehabilitacji Neurologicznej Wojewódzkiego Szpitala Specjalistycznego we Wrocławiu pod nadzorem prof. dr hab. Joanny Rosińczuk **pod warunkiem zachowania anonimowości uzyskanych danych**.

Uwaga: Badanie to zostało objęte ubezpieczeniem odpowiedzialności cywilnej Uniwersytetu Medycznego we Wrocławiu z tytułu prowadzonej działalności.

Pouczenie: W ciągu 14 dni od otrzymania decyzji wnioskodawcy przysługuje prawo odwołania do Komisji Odwoławczej za pośrednictwem Komisji Bioetycznej UM we Wrocławiu.

Opinia powyższa dotyczy projektu badawczego będącego podstawą rozprawy doktorskiej.

Wrocław, dnia 14 grudnia 2020 r.

Uniwersytet Medyczny we Wrocławiu
KOMISJA BIOETYCZNA
przewodniczący
prof. dr hab. Jan Kornafel