



발병 3년 후 뇌졸중 환자에서 기능 저하 요인

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초 록

본 연구는 뇌졸중 발병 3년 시점의 환자 특성 중 발병 4년 시점의 기능 저하를 예측할 수 있는 인자를 파악하고자 하였다. 본 연구는 뇌졸중 환자의 재활에 있어 장기적인 기능 수준을 결정하는 요인에 대한 추적조사 연구(Korean Stroke Cohort for Functioning and Rehabilitation) 데이터를 분석한 결과이다. 기능 저하는 발병 4년 시점의 modified Rankin scale (mRS)이 발병 3년 시점에 비해 증가한 것으로 정의하였고, 대상자는 발병 3년 시점에 독립적 일상 활동 수행 환자군(mRS 0-1)과 비독립적 일상 활동 수행 환자군(mRS 2-4)으로 나누어 분석하였다. 전체 대상자 4,023명 중 독립적 일상 활동 수행 환자군은 3,028명, 비독립적 일상 활동 수행 환자군은 995명이었다. 독립적 일상 활동 수행 환자군 중 12.9%, 비독립적 일상 활동 수행 환자군 중 12.1%가 발병 4년 시점에 기능 저하를 보였다. 독립적 일상 활동 수행 환자군에서는 발병 3년 시점의 나이, 동반 질환 정도 및 이동 기능, 비독립적 일상 활동 수행 환자군에서는 발병 3년 시점의 나이와 인지 기능이 기능 저하의 예측 인자로 확인되었다. 본 연구 결과는 만성기 뇌졸중 환자의 기능 저하를 예방하기 위한 맞춤형 재활 전략 수립에 기여할 수 있을 것이다.

주요 검색어: 뇌졸중; 만성기; 기능 저하; 예측 인자; 코호트

서 론

뇌졸중은 전 세계적으로 주요한 사망 및 장애 원인 중 하나로, 생존자들의 장기적인 기능 상태와 삶의 질에 큰 영향을 미친다[1]. 급성기 치료 및 재활치료의 발달로 뇌졸중 환자의 생존율과 기대 여명이 증가함에 따라, 만성기 뇌졸중 환자의

장기적 관리가 중요한 의료 및 사회적 과제로 대두되었다[2]. 그러나 급성기 및 아급성기 기능 호전에 대한 연구에 비해 만성기 기능 변화에 대한 연구는 상대적으로 부족한 실정이다 [3].

만성기 뇌졸중 환자의 기능 변화는 복잡하고 다양한 인자가 영향을 미치는 과정이다. 일반적으로 만성기 환자는 시간

Received September 27, 2024 Revised October 11, 2024 Accepted October 11, 2024

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KDCA

Korea Disease Control and Prevention Agency

핵심요약

① 이전에 알려진 내용은?

급성기와 아급성기 뇌졸중 환자에게 집중 재활치료가 중요하다는 것은 잘 알려져 있지만, 만성기 환자의 기능 변화에 대한 정보는 부족했다.

② 새로이 알게 된 내용은?

발병 후 3-4년 사이 약 12-13%의 환자에서 기능 저하가 발생했으며, 독립적 일상 활동 수행 환자군에서는 나이, 동반 질환 정도, 이동 기능이, 비독립적 일상 활동 수행 환자군에서는 나이와 인지 기능이 주요 예측 인자로 확인되었다.

③ 시사점은?

환자의 기능 수준에 따른 맞춤형 관리 전략이 필요하며, 독립적 일상 활동 수행 환자군에서는 이동 기능 향상에, 비독립적 일상 활동 수행 환자군에서는 인지 기능 강화에 중점을 둔 재활 프로그램의 개발 및 적용이 필요하다.

이 지남에 따라 기능이 안정화되거나 점진적으로 저하될 수 있다[4]. 본 연구팀의 선행 연구에서는 뇌졸중 발병 3년에서 4년 사이에 통계적으로 유의한 일상생활 동작 수행 능력의 감소를 보고하였다[5,6]. 이러한 장기적 기능 수준 저하는 주목할 만한 현상으로, 환자의 의존성을 증가시켜 사회적 부담을 늘리고 장기적 생존율을 악화시킬 수 있다[7]. 따라서 이 시기의 기능 저하를 예측하고 예방하는 것이 중요하며, 이를 위해 발병 3년 시점의 환자 특성 중 발병 4년 시점의 기능 저하를 예측할 수 있는 인자를 파악하는 것이 필요하다. 이러한 예측 인자의 파악은 고위험군 환자를 조기에 식별하고, 맞춤형 중재를 제공하는 데 도움이 될 수 있다[8].

본 연구는 이러한 배경을 바탕으로, 뇌졸중 발병 3년 시점의 환자 특성 중 발병 4년 시점의 기능 저하를 예측할 수 있는 인자를 파악하고자 한다. 이를 통해 만성기 뇌졸중 환자의 기능 저하를 방지할 수 있는 효과적인 치료 전략 수립의 기초 자료를 제공하고, 궁극적으로 환자의 삶의 질 향상과 사회적 부담 감소에 기여하고자 한다.

방 법

1. 분석 대상자

본 논문은 질병관리청 정책 연구용역으로 진행 중인 뇌졸중 환자의 재활분야 장기추적조사, 한국뇌졸중재활코호트(Korean Stroke Cohort for Functioning and Rehabilitation, KOSCO) 연구의 1차 초발 뇌졸중 코호트 자료 분석을 통해 작성되었다. 1차 초발 뇌졸중 코호트는 2012년 8월부터 2015년 5월까지 전국 9개 병원에서 뇌졸중 발병 7일 이전에 입원한 모든 초발 급성 뇌졸중 환자 10,636명(뇌경색 8,210명, 뇌출혈 2,426명) 중 장기간 추적조사에 동의한 총 7,858명의 환자를 대상으로 구축되었다. KOSCO의 자세한 프로토콜은 이전 논문에 기술되어 있다[9]. 본 논문의 분석 대상자는 KOSCO 장기 추적 연구 참여에 동의한 7,858명 중 발병 3년 시점에 대면 기능 평가를 시행한 4,731명을 대상으로 하여 그 중 modified Rankin scale (mRS) [10]이 0-4로 무증상에서 중상증도의 장애를 보이는 뇌졸중 환자로 하였다. mRS 5의 경우, 더 이상의 장애 정도 악화를 평가할 수 없기 때문에 본 논문 분석에서는 제외하였다. 이에 발병 3년 시점에서 독립적 일상 활동 수행이 가능한 mRS 0-1인 3,266명을 독립적 일상 활동 수행 환자군(patients with independence), 독립적 일상 활동 수행이 불가능한 mRS 2-4인 1,165명을 비독립적 일상 활동 수행 환자군(patients with dependence)으로 정의하였다. 이 중 발병 4년 시점에 대면 기능 평가를 시행한 독립적 일상 활동 수행 환자군 3,028명, 비독립적 일상 활동 수행 환자군 995명, 총 4,023명을 대상으로 분석을 시행하였다(그림 1). 또한, 양 군에서 발병 3년 시점과 비교하여 발병 4년 시점에 기능 저하 발생으로 mRS가 증가한 경우를 기능 저하(functional deterioration)로, mRS 감소 혹은 유지한 경우를 기능 유지(no functional deterioration)로 정의하였다.

연령, 성별, 교육 수준, 가족 관계 등의 인구사회학적 특성 및 동반 질환, 뇌졸중 전 기능 수준 등은 의무기록을 통해 확

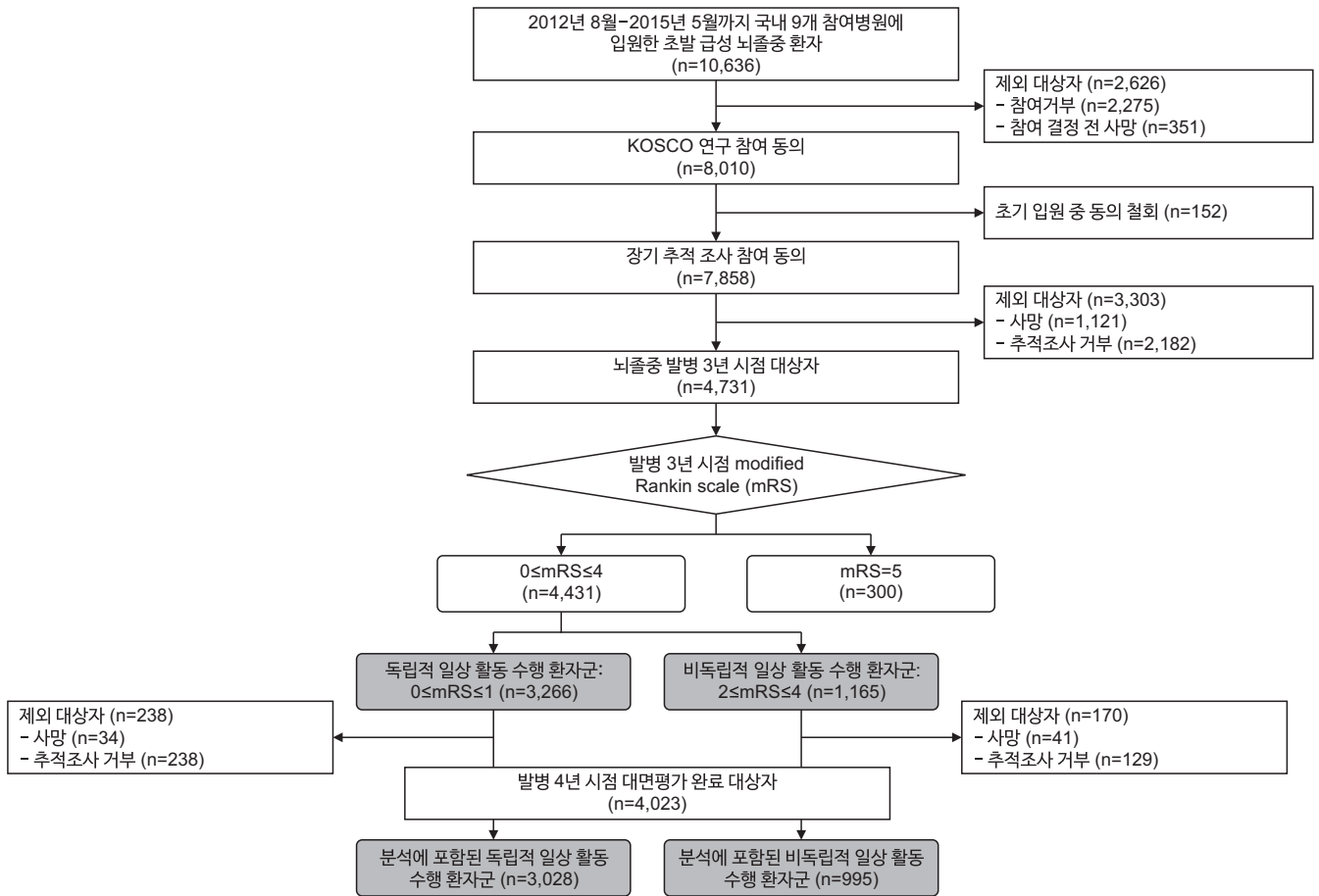


그림 1. 대상자 모집 흐름도

KOSCO=Korean Stroke Cohort for Functioning and Rehabilitation.

인하였으며, 동반 질환 정도는 Charlson comorbidity index의 combined condition- and age-related score (CCAS) [11]로 평가하였다. 뇌졸중 전 기능 수준은 mRS를 사용하여 평가하였다. 또한 뇌졸중 특성 및 발병 7일 뇌졸중 중증도 등을 조사하였다. 발병 3년 시점의 다면적 기능 평가는 인지 기능에 대한 Korean Mini-Mental State Examination (K-MMSE) [12], 운동기능에 대한 Fugl-Meyer Assessment [13], 이동 기능에 대한 Functional Ambulatory Category (FAC) [14], American Speech-Language-Hearing Association National Outcome Measurement System Swallowing Scale (ASHA-NOMS) [15]을 통한 삼킴기능 평가, Korean Version of the Frenchay Aphasia Screening Test (K-FAST) [16]를 통한 언어기능 평가를 1:1 대면 평가를 통해 시행하였다. Geriatric depression

scale-short form (GDS-SF) [17]을 활용한 설문조사를 시행하여 정서 수준을 평가하였다.

2. 분석방법

대상자의 인구통계학적 및 임상적 특성에 대한 정보는 기술 통계를 사용하였다. 독립적 일상 활동 수행 환자군과 비독립적 일상 활동 수행 환자군에서 각각 기능 저하 환자군과 기능 유지 환자군의 비교를 위해 연속형 변수는 independent t-test, 범주형 변수는 카이제곱 검정을 사용하였다. 연속형 변수의 결과는 평균(표준편차)으로, 범주형 변수의 결과는 빈도(백분율)로 기술하였다. 기능 저하 환자군과 기능 유지 환자군의 통계적 차이를 보이는 변수에 대해서는 종속변수를 기능 저하 환자군으로 설정 후 이분형 로지스틱 회귀분석(binary

logistic regression analysis)을 통해 기능 저하를 예측할 수 있는 독립적 변수를 검증하였다. p값이 0.05 미만을 통계적으로 유의미한 것으로 간주하였다. 모든 분석은 IBM SPSS 버전 24.0 (IBM Co.)를 사용하여 수행하였다.

결 과

전체 대상자 4,023명의 뇌졸중 발병 3년 시점의 평균 나이는 65.6 ± 12.4 세이며, 남성이 60.7%, 허혈성 뇌졸중이 79.5%였다. 전체 대상자의 뇌졸중 발병 3년 및 4년 시점의 평균 mRS는 각각 1.05 ± 1.17 , 1.10 ± 1.23 으로 통계적으로 유의한 감소를 보였다($p < 0.05$). 독립적 일상 활동 수행 환자군에서는 392명(12.9%), 비독립적 일상 활동 수행 환자군에서는 120명(12.1%)에서 발병 4년 시점에서 기능 저하가 발생하였으며, 양 군에서 기능 저하 발생률은 통계적 차이를 보이지 않았다(그림 2).

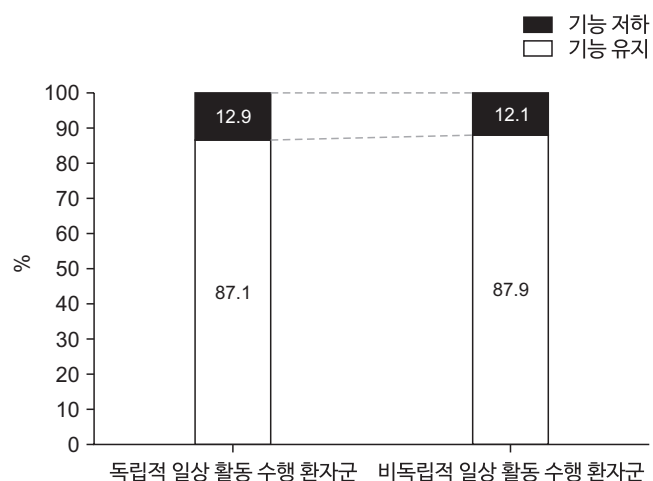


그림 2. 발병 3년 시점 독립 여부에 따른 발병 3년에서 4년 사이의 기능 저하 비율

두 그룹 간의 기능 저하 비율에 유의미한 차이가 없음.

1. 뇌졸중 발병 3년 시점 독립적 일상 활동 수행 환자군 분석

뇌졸중 발병 3년 시점에서 mRS 0-1로 장애를 보이지 않았던 3,028명에서 기능 저하 환자군 392명과 기능 유지 환자군 2,636명의 인구학적 및 임상적 특성은 표 1과 같다. 기능 저하 환자군이 기능 저하를 보이지 않은 환자군에 비해 나이가 많았으며, 배우자가 없는 비율이 높았다($p < 0.05$). 고혈압, 당뇨, 심방세동의 유병률이 통계적으로 높았으며($p < 0.05$), 이로 인해 동반 질환 정도가 통계적으로 유의하게 높았다($p < 0.05$). 또한 기능 저하 환자군에서 허혈성 뇌경색 비율이 통계적으로 보다 높았으나($p < 0.05$), 발병 전 기능 수준과 발병 7일 뇌졸중 중증도에서 양 군에서 유의한 차이를 보이지 않았다. 발병 4년 시점에 기능 저하를 보인 기능 저하 환자군에서 뇌졸중 발병 3년 시점의 인지, 운동, 이동, 삼킴, 언어 기능 및 정서에서 기능 유지 환자군에 비해 통계적으로 유의한 저하 소견을 보였다($p < 0.05$; 표 1).

기능 저하 환자군과 기능 유지 환자군에서 통계적 차이를 보인 인자를 통해 이분형 로지스틱 회귀분석을 시행하였을 때, 나이, 동반 질환 정도, 발병 3년 시점의 이동 기능이 독립적 예측 인자로 분석되었으며($p < 0.05$), 배우자 유무, 발병 3년 시점의 인지, 삼킴기능 및 정서 수준은 경향성을 보이는 예측 인자로 분석되었다(표 2).

2. 뇌졸중 발병 3년 시점 비독립적 일상 활동 수행 환자군 분석

뇌졸중 발병 3년 시점에서 mRS 2-4로 장애를 보인 995명에서 기능 저하 환자군 120명과 기능 유지 환자군 875명의 인구학적 및 임상적 특성은 표 3과 같다. 기능 저하 환자군에서 기능 저하를 보이지 않은 환자군에 비해 나이가 보다 많았으나($p < 0.05$), 교육 수준, 배우자 유무, 동반 질환 등에서는 통계적 차이를 보이지 않았다. 또한 뇌졸중 특성 및 발병 전 기능 수준, 발병 7일 뇌졸중 중증도에서 양 군은 유의한 차이

표 1. 독립적 일상 활동 수행 환자군의 발병 3년 시점 인구학적 및 기능적 특성

변수	기능 저하 환자군 (n=392)	기능 유지 환자군 (n=2,636)	p-value
인구학적 및 임상적 특성			
나이(세)	67.2±12.3*	63.6±11.9	<0.001
성별, 남성:여성	64.0:36.0	63.4:36.6	0.822
교육수준			
초등학교 졸업 이하	27.9	22.8	0.071
중, 고등학교 졸업	49.2	50.9	
대학교 졸업 이상	22.9	26.3	
배우자, 있음	80.7*	85.3	0.026
병력			
고혈압	55.2*	49.6	0.043
당뇨	24.8*	18.7	0.006
관상동맥질환	7.0	4.9	0.084
심방세동	8.1*	4.9	0.014
고지혈증	12.3	9.5	0.091
동반질환지수(CCAS)	2.6±1.7*	2.1±1.8	<0.001
병전 mRS(점수)	0.6±1.2	0.6±1.2	0.418
뇌졸중 특성, 허혈성:출혈성	84.7:15.3*	80.2:19.8	0.033
발병 7일 뇌졸중 중증도(NIHSS)	2.1±3.2	1.8±3.4	0.181
발병 3년 기능 수준			
인지 기능(K-MMSE)	27.1±3.6*	28.1±2.7	<0.001
운동기능(Fugl-Meyer Assessment)	97.9±7.0*	99.0±4.5	0.003
이동 기능(Functional Ambulatory Category)	4.9±0.4*	5.0±0.2	0.001
삼킴기능(AHSA-NOMS)	6.8±0.5*	6.9±0.3	0.001
언어기능(Short K-FAST)	17.3±3.4*	18.1±2.7	<0.001
우울정도(GDS-SF)	3.6±3.6*	2.9±3.2	0.001

단위는 평균±표준편차 혹은 %. CCAS=combined condition- and age-related score; mRS=modified Rankin scale; NIHSS=National Institutes of Health Stroke Scale; K-MMSE=Korean Mini-Mental State Examination; AHSA-NOMS=American Speech-Language-Hearing Association National Outcome Measurement System Swallowing Scale; Short K-FAST=Short Korean Version of the Frenchay Aphasia Screening Test; GDS-SF=Geriatric depression scale-short form. *p<0.05.

를 보이지 않았다. 발병 4년 시점에 기능 저하를 보인 기능 저하 환자군에서 뇌졸중 발병 3년 시점의 인지, 이동, 삼킴, 언어 기능에서 기능 유지 환자군에 비해 통계적으로 유의한 저하 소견을 보였다(p<0.05; 표 3).

기능 저하 환자군과 기능 유지 환자군에서 통계적 차이를 보인 인자를 통해 이분형 로지스틱 회귀분석을 시행하였을 때, 나이와 발병 3년 시점의 인지 기능이 독립적 예측 인자로 분석되었다(p<0.05; 표 2).

논 의

본 연구에서는 전체 대상자를 독립적 일상 활동 수행 환자군과 비독립적 일상 활동 수행 환자군으로 나누고, 각 군에서 뇌졸중 발병 3년 시점의 특성 중 발병 4년 시점의 기능 저하를 예측할 수 있는 인자를 확인하였다. 전체 대상자 4,023명 중 독립적 일상 활동 수행 환자군에서는 12.9%, 비독립적 일상 활동 수행 환자군에서는 12.1%가 4년 시점에 기능 저하를 보였다. 독립적 일상 활동 수행 환자군에서는 나이, 동반 질환

표 2. 발병 4년 시점의 기능 저하와 관련된 요소들을 확인하기 위한 발병 3년 시점의 이항 로지스틱 회귀 분석 결과

예측 변수	회귀계수	SE	Wald χ^2	p-value	Odds ratio (95% CI)
독립적 일상 활동 수행 환자군의 발병 3년 시점 관련요소					
나이	0.013*	0.006	4.801	0.028	1.013 (1.001-1.025)
배우자	-0.288	0.153	3.545	0.060	0.750 (0.555-1.012)
동반질환지수(CCAS)	0.094*	0.034	7.561	0.006	1.099 (1.028-1.175)
인지 기능(K-MMSE)	-0.041	0.022	3.674	0.055	0.960 (0.419-0.959)
이동 기능(Functional Ambulatory Category)	-0.456*	0.211	4.661	0.031	0.634 (0.419-0.959)
삼킴기능(AHSA-NOMS)	-0.301	0.175	2.953	0.086	0.740 (0.525-1.043)
우울정도(GDS-SF)	0.032	0.017	3.470	0.062	1.033 (0.998-1.068)
비독립적 일상 활동 수행 환자군의 발병 3년 시점 관련요소					
나이	0.030*	0.010	9.392	0.002	1.031 (1.011-1.050)
인지 기능(K-MMSE)	-0.026	0.014	3.463	0.063	0.974 (0.948-1.001)

SE=standard error; CI=confidence interval; CCAS=combined condition- and age-related score; K-MMSE=Korean Mini-Mental State Examination; AHSA-NOMS=American Speech-Language-Hearing Association National Outcome Measurement System Swallowing Scale; GDS-SF=Geriatric depression scale-short form. *p<0.05.

정도 및 이동 기능, 비독립적 일상 활동 수행 환자군에서는 나이와 인지 기능이 4년 시점의 기능 저하의 예측 인자로 확인되었다.

2021년 연간 국내 뇌졸중 발생 건수는 108,950건으로 보고되었다[18]. 본 연구 결과에 따르면 뇌졸중 발생 4년 시점에 약 12.1-12.9%의 기능 저하가 발생하므로, 매년 약 13,618명(12.5%로 계산)의 만성 뇌졸중 환자에서 기능 저하가 발생할 것으로 추정할 수 있다. 이러한 환자들에게 본 연구에서 확인된 예측 인자를 활용하여 기능 저하를 예측하고, 이를 예방하기 위한 맞춤형 재활치료를 제공하는 것이 개인의 삶의 질 향상뿐만 아니라 사회적 부담 감소에도 크게 기여할 수 있을 것이다.

두 군에서 기능 저하의 예측 인자는 서로 다른 양상을 보였으며, 이는 만성기 뇌졸중 환자의 기능 수준에 따라 차별화된 관리 전략이 필요함을 시사한다[19]. 뇌졸중 발병 3년 시점 독립적 일상 활동 수행 환자에서는 나이, 동반 질환 정도, 발병 3년 시점의 이동 기능이 통계적으로 유의한 독립적 기능 저하 예측 인자로 분석되었다. 이 중 이동 기능은 추가적인 재활치료로 변동이 가능한 유일한 조절 가능인자(modifiable

factor)이다[7]. 이동 기능 저하는 활동량을 줄이고, 이로 인해 탈조건화(deconditioning)가 유발되어 기능 저하가 나타났을 것으로 추정된다[20]. 따라서 독립적 일상 활동을 수행할 수 있는 만성기 뇌졸중 환자에서는 이동 기능을 유지 혹은 증가하기 위한 적절한 재활치료가 기능 저하를 방지할 수 있을 것으로 기대된다[20]. 특히 상대적으로 동반 질환이 많은 고령의 만성기 뇌졸중 환자에서는 기능 저하 발생률이 높기 때문에 이동 기능 증진을 위한 적절한 만성기 재활치료의 우선 대상자가 될 수 있을 것으로 생각한다[21].

반면, 뇌졸중 발병 3년 시점 비독립적 일상 활동 수행 환자에서는 나이와 발병 3년 시점의 인지 기능이 통계적으로 유의한 독립적 기능 저하 예측 인자로 분석되었다. 이는 상대적으로 낮은 이동 기능으로 인해 일상 활동 수행에 있어 인지 기능이 보다 중요한 역할을 하고 있었기 때문으로 추정된다[22]. 따라서 독립적 일상 활동을 수행하지 못하는 만성기 뇌졸중 환자에서는 인지 기능을 유지 혹은 증가하기 위한 적절한 재활치료가 기능 저하를 방지할 수 있을 것으로 기대된다[23]. 특히 상대적으로 고령의 만성기 뇌졸중 환자에서는 기능 저하 발생률이 높기 때문에 인지 기능 증진을 위한 적절한

표 3. 비독립적 일상 활동 수행 환자군의 발병 3년 시점 인구학적 및 임상적 특성

변수	기능 저하 환자군 (n=120)	기능 유지 환자군 (n=875)	p-value
인구학적 및 임상적 특성			
나이(세)	74.7±12.2*	69.6±12.2	<0.001
성별, 남성:여성	53.3:46.7	51.9:48.1	0.771
교육수준			
초등학교 졸업 이하	43.9	44.9	0.379
중, 고등학교 졸업	39.5	42.9	
대학교 졸업 이상	16.7	12.1	
배우자, 있음	70.2	72.9	0.576
병력			
고혈압	61.7	57.8	0.480
당뇨	27.4	26.3	0.824
관상동맥질환	7.6	6.0	0.540
심방세동	7.8	7.3	0.850
고지혈증	15.4	10.3	0.112
동반질환지수(CCAS)	2.6±2.2	2.6±1.9	0.764
병전 mRS(점수)	0.5±1.1	0.7±1.4	0.150
뇌졸중 특성, 허혈성:출혈성	80.8:19.2*	75.0:25.0	0.174
발병 7일 뇌졸중 중증도(NIHSS)	6.7±7.2	6.9±6.8	0.693
발병 3년 기능수준			
인지 기능(K-MMSE)	19.8±7.7*	21.9±7.1	0.007
운동기능(Fugl-Meyer Assessment)	73.9±28.5	73.8±27.5	0.972
이동 기능(Functional Ambulatory Category)	3.2±1.3*	3.5±1.4	0.017
삼킴기능(AHSA-NOMS)	6.4±1.0*	6.6±0.7	0.009
언어기능(Short K-FAST)	11.0±5.9*	12.6±5.6	0.006
우울정도(GDS-SF)	3.8±4.5	4.3±4.8	0.249

단위는 평균±표준편차 혹은 %. CCAS=combined condition- and age-related score; mRS=modified Rankin scale; NIHSS=National Institutes of Health Stroke Scale; K-MMSE=Korean Mini-Mental State Examination; AHSA-NOMS=American Speech-Language-Hearing Association National Outcome Measurement System Swallowing Scale; Short K-FAST=Short Korean Version of the Frenchay Aphasia Screening Test; GDS-SF=Geriatric depression scale-short form. *p<0.05.

만성기 재활치료의 우선 대상자가 될 수 있을 것으로 생각한다[24].

이러한 결과는 만성기 뇌졸중 환자의 기능 유지 및 개선을 위한 맞춤형 재활 전략의 중요성을 강조한다. 독립적 일상 활동 수행 환자군에서는 이동 기능 향상에 초점을 맞춘 프로그램이, 비독립적 일상 활동 수행 환자군에서는 인지 기능 강화에 중점을 둔 중재가 효과적일 수 있다[25,26]. 또한, 나이와 동반 질환 등 비가역적 요인들도 기능 저하의 중요한 예측 인자로 확인되었으므로, 이러한 고위험군 환자들에 대한 더욱

적극적이고 지속적인 관리가 필요할 것으로 보인다[2,27].

결론적으로, 본 연구는 만성기 뇌졸중 환자의 기능 저하 예측 인자를 규명함으로써, 개별화된 재활 전략 수립의 근거를 제시하였다. 향후 이러한 예측 인자들을 고려한 맞춤형 재활 프로그램의 개발 및 그 효과성 검증에 대한 추가 연구가 필요할 것으로 생각된다[27]. 또한, 본 연구의 결과를 바탕으로 만성기 뇌졸중 환자의 장기적 기능 유지 및 삶의 질 향상을 위한 정책 수립에도 기여할 수 있을 것으로 기대된다[2].

Declarations

Ethics Statement: This multicenter cohort study was approved by the Institutional Review Board of each participating hospital.

Funding Source: This study was supported by the Research Program funded by the Korea Disease Control and Prevention Agency (no. 3300-3334-300-260-00, 2013-E33017-00, 2013E-33017-01, 2013E-33017-02, 2016-E33003-00, 2016-E33003-01, 2016-E33003-02, 2019-E3202-00, 2019-E3202-01, 2019-E3202-02, 2022-11-006).

Acknowledgments: None.

Conflict of Interest: The authors have no conflicts of interest to declare.

Author Contributions: Conceptualization: YHL, YTK, YHK, and WHC. Data curation: DYK, JML, Min Kyun Sohn, YIS, YSL, Min-Keun Song, MCJ, SYL, DNC, GJO, JHA, JHH, YHK, and WHC. Formal analysis: DHK and WHC. Funding acquisition: YHK and WHC. Methodology: DHK, HSL, DYK, JML, Min Kyun Sohn, YIS, YSL, Min-Keun Song, MCJ, SYL, DNC, GJO, JHA, JHH, YHK, and WHC. Supervision: DYK, JML, Min Kyun Sohn, YIS, YSL, Min-Keun Song, MCJ, SYL, GJO, JHA, JHH, YHK, and WHC. Writing – original draft: DHK and HSL. Writing – review & editing: YHL, YTK, YHK, and WHC.

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Factors Associated with Functional Deterioration in Stroke Patients 3 Years after Onset: A KOSCO Study

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ABSTRACT

This study aimed to identify the factors predicting functional decline 4 years after stroke based on patient characteristics 3 years after stroke. We analyzed data from the Korean Stroke Cohort for Functioning and Rehabilitation study. Functional decline was defined as an increase in the modified Rankin scale (mRS) 4 years after stroke compared to that at 3 years after stroke. Participants were divided into two groups based on their mRS 3 years after stroke: independent (mRS 0–1) and dependent (mRS 2–4) activities of daily living groups. Of the 4,023 participants, 3,028 were in the independent group and 995 in the dependent group. Functional decline was observed in 12.9% and 12.1% of the independent and dependent groups, respectively, 4 years after stroke. In the independent group, age, degree of comorbidity, and mobility function 3 years after stroke were identified as predictors of functional decline. In the dependent group, age and cognitive function 3 years after stroke were predictive factors. These findings can contribute to the development of tailored rehabilitation strategies to prevent functional decline in patients with chronic stroke.

Key words: Stroke; Chronic phase; Functional deterioration; Predictive factors; Cohort

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Key messages

① What is known previously?

It is well known that intensive rehabilitation is crucial for patients with stroke in the acute and subacute phases. Still, information on functional changes in chronic stroke patients has been lacking.

② What new information is presented?

Between 3–4 years after stroke, approximately 12–13% of patients experience functional decline. Age, comorbidities, and mobility were key predictors in independent patients, while age and cognitive function were the main predictors in dependent patients.

③ What are implications?

Tailored treatment strategies based on patient functional levels are necessary. Improving mobility is essential for independent patients, while enhancing cognitive function in dependent patients should be the focus of rehabilitation programs.

Introduction

Stroke is a leading cause of death and disability worldwide; it significantly impacts the long-term functional status and quality of life of survivors [1]. Recent advances in treatment for stroke in the acute phase and in rehabilitation therapy have increased survival rate and life expectancy, but the long-term management of stroke in the chronic phase has become medically and socially challenging [2]. However, there are relatively few studies investigating changes in the functioning of patients in the chronic phase compared to studies investigating the improvement in functioning in the acute and subacute phases [3].

Functional changes in patients with stroke in the chronic phase are affected by various complex factors. In general, functional ability in the chronic phase may become stable or

deteriorate gradually [4]. In previous studies conducted by this study team, the ability of performing routine activities decreased statistically significantly between three years and four years after the stroke [5,6]. Remarkably decreased long-term functional ability can increase the patient’s dependency and present a sizeable societal burden, resulting in decreased long-term survival rate [7]. Accordingly, predicting and preventing a decrease in functional ability in these phases is critical. Therefore, it is necessary to identify factors within patient characteristics three years after the onset that can predict decreased functional ability four years after a stroke. Identifying predictive factors can help detect high-risk patients early and enable customized interventions [8].

This study determines factors that can predict a decline in functional ability four years after the onset from the patient characteristics investigated three years after a stroke. This will provide basic data to establish efficient therapeutic strategies that can prevent a decline in the functional ability of patients with stroke in the chronic phase and ultimately contribute to improved quality of life and reduced societal burden.

Methods

1. Study Population

This study analyzed data from first-ever stroke patients of the Korean Stroke Cohort for Functioning and Rehabilitation (KOSCO), designed as a consignment project and long-term follow-up of stroke patients conducted by the Korean Disease Control and Prevention Agency. The first-ever stroke cohort included 7,858 patients who consented to a long-term follow-up, among 10,636 first-ever acute stroke patients (8,210 with cerebral infarction and 2,426 with cerebral hemorrhage) who

were hospitalized seven days before the onset of stroke in nine hospitals nationwide between August 2012 and May 2015. The detailed protocol of the KOSCO is provided in the previous study [9]. Among the 7,858 participants who consented to the long-term follow-up of KOSCO, the functioning of 4,731 participants was evaluated face-to-face three years post onset. Of the 4,731 participants, this study analyzed data from stroke patients with the modified Rankin scale (mRS) [10] 0 to 4 (from no symptoms to moderate to severe symptoms). From those with mRS, five were excluded from this study because the level of disability could not be evaluated. Therefore, 3,266 participants with mRS 0 or 1, who were capable of independently performing routine activities, were defined as independent

patients. The 1,165 participants with mRS 2 to 4, who were incapable of independently performing routine activities, were defined as dependent patients. Among them, 4,023 participants, including 3,028 independent and 955 dependent patients, who were evaluated face-to-face for functioning four years post onset, were analyzed (Figure 1). Furthermore, an increase in the mRS score due to decreased functioning four years compared to three years post onset was defined as functional deterioration. A reduction or maintenance of mRS was defined as no functional deterioration in both groups.

Sociodemographic characteristics, such as age, sex, education level, family background, comorbidities, and pre-stroke functional level, were collected from medical records.

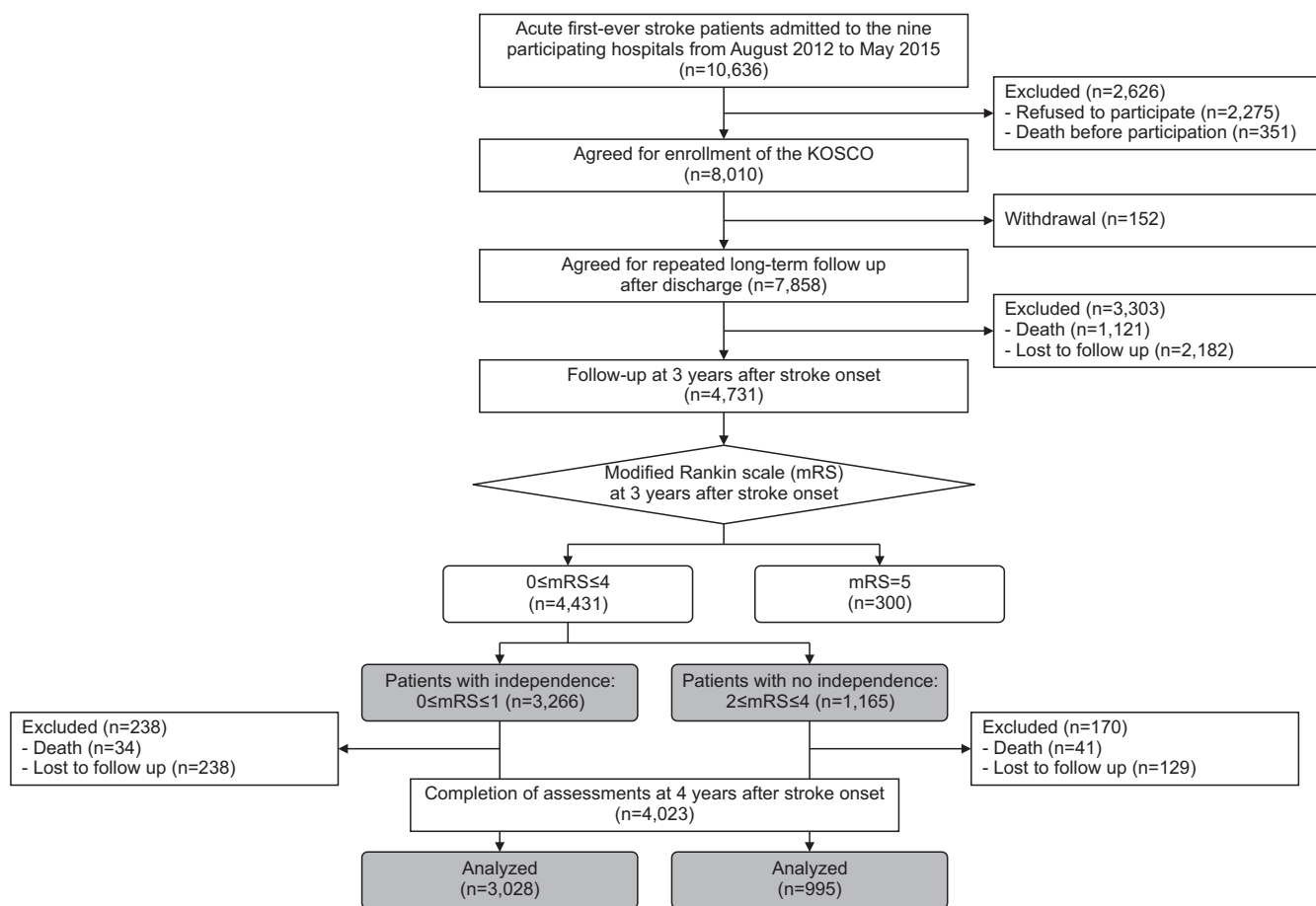


Figure 1. Flow chart of participants
KOSCO=Korean Stroke Cohort for Functioning and Rehabilitation.

The severity of comorbidity was evaluated with combined condition-and age-related score [11] of the Charlson comorbidity index. Pre-stroke functional level was evaluated using mRS. The features and severity of a stroke seven days post-onset were evaluated. Multifaceted assessment of functional outcomes three years post-onset was conducted by using the Korean Mini-Mental State Examination for cognitive function [12], Fugl-Meyer Assessment [13] for motor functioning, Functional Ambulatory Category for ambulation ability [14], American Speech-Language-Hearing Association National Outcome Measurement System Swallowing Scale [15] for swallowing ability, and the Korean Version of the Frenchay Aphasia Screening Test [16] for language. The evaluation was a one-on-one, face-to-face process. A questionnaire survey was conducted with the Geriatric Depression Scale-Short Form [17] to evaluate emotional level.

2. Analytical Methods

Descriptive statistics was used to describe the participants' demographic and clinical characteristics. To compare those with functional deterioration to those with no functional deterioration in every independent and dependent patient, an independent t-test and Chi-square test were used for continuous variables and categorical variables, respectively. The results of continuous variables were presented as mean (standard deviation), and the results of categorical variables were presented as frequency (percentage). For variables that showed statistical differences in the patients with functional deterioration and those with no functional deterioration, the dependent variables were set as the patients with functional deterioration. Independent variables that can predict functional decline were tested via binary logistic regression analysis. A p-value less than

0.05 was considered to be statistically significant. All data were analyzed using SPSS version 24.0 (IBM Co.).

Results

For the total 4,023 participants, the mean age 3 years post-onset was 65.6 ± 12.4 years, 60.7% were male participants, and 79.5% had experienced ischemic stroke. Among the total participants, the mean mRS at 3 years and 4 years post onset of stroke was 1.05 ± 1.17 and 1.10 ± 1.23 , respectively, showing a statistically significant reduction ($p < 0.05$). A functional decline 4 years post onset was reported in 392 (12.9%) patients with independence and 120 (12.1%) patients with dependence; no statistically significant difference in a decline in functioning was observed between the groups (Figure 2).

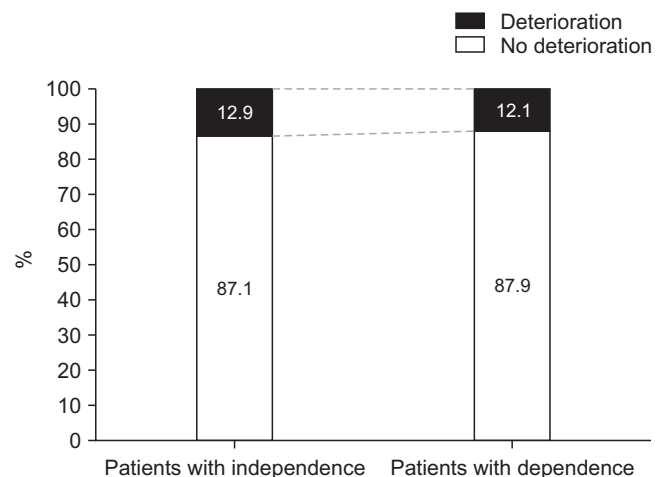


Figure 2. Rate of functional deterioration from 3 years to 4 years after stroke onset according to independence at 3 years after stroke

There was no significant difference in the rate of functional deterioration between the two groups.

1. Analysis of Independent Patients Three Years Post Onset of Stroke

For the 3,028 participants with mRS 0 or 1, who did not present disability 3 years post onset, Table 1 shows the demographic and clinical characteristics of 392 participants with functional deterioration and 2,636 participants with no functional deterioration. Compared to the latter, the former group was older with a higher rate of not having a spouse ($p<0.05$). The prevalence of hypertension, diabetes mellitus, and atrial

fibrillation was statistically higher ($p<0.05$), which caused a statistically significantly higher rate of comorbidity ($p<0.05$). A statistically higher rate of ischemic cerebral infarction was observed in the participants with functional deterioration ($p<0.05$), but no significant difference in pre-stroke functional level and the severity of stroke seven days post onset was observed between the two groups. Participants with functional deterioration four years post onset showed a statistically significant decline in cognitive function, motor functioning,

Table 1. General and functional characteristics of stroke patients with independence at 3 years after stroke

Variable	Functional deterioration (n=392)	No functional deterioration (n=2,636)	p-value
General and clinical characteristic			
Age (yr)	67.2±12.3*	63.6±11.9	<0.001
Sex, male:female	64.0:36.0	63.4:36.6	0.822
Education			
Elementary school degree or less	27.9	22.8	0.071
Middle school degree	49.2	50.9	
Bachelor's degree or more	22.9	26.3	
Spouse, yes	80.7*	85.3	0.026
Medical history			
Hypertension	55.2*	49.6	0.043
Diabetes mellitus	24.8*	18.7	0.006
Coronary heart disease	7.0	4.9	0.084
Atrial fibrillation	8.1*	4.9	0.014
Hyperlipidemia	12.3	9.5	0.091
CCAS	2.6±1.7*	2.1±1.8	<0.001
Premorbid mRS (score)	0.6±1.2	0.6±1.2	0.418
Stroke type, ischemic:hemorrhagic	84.7:15.3*	80.2:19.8	0.033
NIHSS at 7 days after stroke onset	2.1±3.2	1.8±3.4	0.181
Functional characteristics at 3 years after onset			
K-MMSE	27.1±3.6*	28.1±2.7	<0.001
Fugl-Meyer Assessment	97.9±7.0*	99.0±4.5	0.003
Functional Ambulatory Category	4.9±0.4*	5.0±0.2	0.001
AHSA-NOMS	6.8±0.5*	6.9±0.3	0.001
Short K-FAST	17.3±3.4*	18.1±2.7	<0.001
GDS-SF	3.6±3.6*	2.9±3.2	0.001

Data are presented as mean±standard deviation or %. CCAS=combined condition- and age-related score; mRS=modified Rankin scale; NIHSS=National Institutes of Health Stroke Scale; K-MMSE=Korean Mini-Mental State Examination; AHSA-NOMS=American Speech-Language-Hearing Association National Outcome Measurement System Swallowing Scale; Short K-FAST=Short Korean Version of the Frenchay Aphasia Screening Test; GDS-SF=Geriatric depression scale-short form. * $p<0.05$.

ambulation ability, swallowing ability, language skill, and emotional level three years post onset of stroke compared to those with no functional deterioration ($p < 0.05$, Table 1).

When factors with statistical differences between the participants with functional deterioration and those with no functional deterioration were verified using the binary logistic regression analysis, age, comorbidity severity, and ambulation ability three years post-onset were analyzed as independent predictive factors ($p < 0.05$). Presence of a spouse, cognitive function, swallowing ability, and emotional level three years post onset were analyzed as predictive factors with a tendency (Table 2).

2. Analysis of Dependent Patients Three Years Post Onset of Stroke

Among the 995 participants with mRS 2 to 4, who presented disability, Table 3 shows the demographic and clinical characteristics of 120 participants with functional deterioration

and 875 participants with no functional deterioration three years post onset. Compared to the participants with no functional deterioration, those with functional deterioration were older ($p < 0.05$), but no statistical difference in education level, presence of spouse, and comorbidities was observed. No significant difference in the features of a stroke, pre-stroke functional level, and the severity of stroke seven days post onset was observed between the two groups. Participants with functional deterioration four years post onset showed a statistically significant decline in cognitive function, ambulation ability, swallowing ability, and language skill three years post onset of stroke compared to those with no functional deterioration ($p < 0.05$, Table 3).

When factors with statistical differences between the participants with functional deterioration and those with no functional deterioration were verified using the binary logistic regression analysis, age and cognitive function three years post onset were analyzed as independent predictive factors ($p < 0.05$,

Table 2. Binary logistic regression analysis results to identify factors at 3 years after stroke associated with the functional deterioration at 4 years after stroke

Predictor	Regression coefficient	SE	Wald χ^2	p-value	Odds ratio (95% CI)
Stroke patients with independence at 3 years					
Age	0.013*	0.006	4.801	0.028	1.013 (1.001-1.025)
Spouse	-0.288	0.153	3.545	0.060	0.750 (0.555-1.012)
CCAS	0.094*	0.034	7.561	0.006	1.099 (1.028-1.175)
K-MMSE	-0.041	0.022	3.674	0.055	0.960 (0.419-0.959)
Functional Ambulatory Category	-0.456*	0.211	4.661	0.031	0.634 (0.419-0.959)
AHSA-NOMS	-0.301	0.175	2.953	0.086	0.740 (0.525-1.043)
GDS-SF	0.032	0.017	3.470	0.062	1.033 (0.998-1.068)
Stroke patients with dependence at 3 years					
Age	0.030*	0.010	9.392	0.002	1.031 (1.011-1.050)
K-MMSE	-0.026	0.014	3.463	0.063	0.974 (0.948-1.001)

SE=standard error; CI=confidence interval; CCAS=combined condition- and age-related score; K-MMSE=Korean Mini-Mental State Examination; AHSA-NOMS=American Speech-Language-Hearing Association National Outcome Measurement System Swallowing Scale; GDS-SF=Geriatric depression scale-short form. * $p < 0.05$.

Table 3. General and functional characteristics of stroke patients with dependence at 3 years after stroke

Variable	Functional deterioration (n=120)	No functional deterioration (n=875)	p-value
General and clinical characteristics			
Age (yr)	74.7±12.2*	69.6±12.2	<0.001
Sex, male:female	53.3:46.7	51.9:48.1	0.771
Education			
Elementary school degree or less	43.9	44.9	0.379
Middle school degree	39.5	42.9	
Bachelor's degree or more	16.7	12.1	
Spouse, yes	70.2	72.9	0.576
Medical history			
Hypertension	61.7	57.8	0.480
Diabetes mellitus	27.4	26.3	0.824
Coronary heart disease	7.6	6.0	0.540
Atrial fibrillation	7.8	7.3	0.850
Hyperlipidemia	15.4	10.3	0.112
CCAS	2.6±2.2	2.6±1.9	0.764
Premorbid mRS (score)	0.5±1.1	0.7±1.4	0.150
Stroke type, ischemic:hemorrhagic	80.8:19.2*	75.0:25.0	0.174
NIHSS at 7 days after stroke onset	6.7±7.2	6.9±6.8	0.693
Functional characteristics at 3 years after onset			
K-MMSE	19.8±7.7*	21.9±7.1	0.007
Fugl-Meyer Assessment	73.9±28.5	73.8±27.5	0.972
Functional Ambulatory Category	3.2±1.3*	3.5±1.4	0.017
AHSA-NOMS	6.4±1.0*	6.6±0.7	0.009
Short K-FAST	11.0±5.9*	12.6±5.6	0.006
GDS-SF	3.8±4.5	4.3±4.8	0.249

Data are presented as mean±standard deviation or %. CCAS=combined condition- and age-related score; mRS=modified Rankin scale; NIHSS=National Institutes of Health Stroke Scale; K-MMSE=Korean Mini-Mental State Examination; AHSA-NOMS=American Speech-Language-Hearing Association National Outcome Measurement System Swallowing Scale; Short K-FAST=Short Korean Version of the Frenchay Aphasia Screening Test; GDS-SF=Geriatric depression scale-short form. *p<0.05.

Table 2).

Discussion

This study divided the total participants into two groups, namely independent and dependent patients. Among the characteristics investigated three years post onset of stroke in each group, the factors that can predict a decline in functioning four years post onset were identified. Of the 4,023 participants,

12.9% independent patients and 12.1% dependent patients showed a functional decline four years post onset. The predictive factors for functional decline four years post onset were age, comorbidity severity, and ambulation ability in the independent patients and age and cognitive function in the dependent patients.

In 2021, the annual incidence of stroke was reported to be 108,950 cases in the Republic of Korea [18]. Since this study shows that approximately 12.1–12.9% of patients reported

functional decline 4 years post onset of stroke, an annual incidence of functional decline can be projected to be 13,618 patients (calculated as 12.5%) with chronic stroke. Predicting functional decline in those patients using the predictive factors identified in this study and providing customized rehabilitation therapy to prevent decline can significantly reduce societal burden and improve quality of life.

Predictive factors for functional decline were different between the two groups, which implies a need for management strategies that differ depending on the functional level of chronic phase stroke patients [19]. Among the independent patients three years post-onset of stroke, age, comorbidity severity, and ambulation ability were analyzed as predictive factors for a statistically significant decline in independent functioning. Among the factors, the ambulation ability is the sole modifiable factor that can fluctuate with additional rehabilitation therapies [7]. A decline in ambulation ability reduces activity level and causes deconditioning, which supposedly resulted in functional decline [20]. Accordingly, appropriate rehabilitation therapy to maintain or enhance ambulation ability for chronic phase stroke patients, who can perform daily routine activities independently, is expected to prevent functional decline [20]. The incidence of functional decline is higher especially among older adult stroke patients in the chronic phase since they are more likely to have comorbidities. They should be prioritized while administering appropriate rehabilitation therapy for chronic phase stroke to promote ambulation ability [21].

However, age and cognitive function three years post onset were analyzed as predictive factors for statistically significant decline in independent functioning among the dependent patients three years post onset of stroke. Owing to a relatively

low ambulation ability, cognitive function is assumed to play a more important role in performing daily routine activities [22]. Accordingly, appropriate rehabilitation therapy to maintain or enhance cognitive function for stroke patients in the chronic phase, who cannot perform routine activities independently, is expected to prevent functional decline [23]. Since the incidence of functional decline is higher especially among older chronic stroke patients, they should be prioritized while administering appropriate rehabilitation therapy in the chronic phase to promote cognitive function [24].

The results emphasize the importance of customized rehabilitation strategies to maintain and improve functioning for chronic stroke patients. A program focused on improved ambulation ability for independent patients and an intervention that emphasizes improved cognitive function for dependent patients can be effective [25,26]. Furthermore, since irreversible factors, such as age and comorbidity, were also identified as critical predictive factors, there is a need for more aggressive and persistent management for high-risk patients [2,27].

In conclusion, this study provides a basis for establishing customized rehabilitation strategies by investigating the predictive factors for functional decline in stroke patients in the chronic phase. Further research that develops a customized rehabilitation program in consideration of the predictive factors and verifies its effectiveness is needed [27]. Additionally, the results of this study are expected to contribute to the establishment of policy for maintaining long-term functioning and improving the quality of life of chronic phase stroke patients [2].

Declarations

Ethics Statement: This multicenter cohort study was

approved by the Institutional Review Board of each participating hospital.

Funding Source: This study was supported by the Research Program funded by the Korea Disease Control and Prevention Agency (no. 3300-3334-300-260-00, 2013-E33017-00, 2013E-33017-01, 2013E-33017-02, 2016-E33003-00, 2016-E33003-01, 2016-E33003-02, 2019-E3202-00, 2019-E3202-01, 2019-E3202-02, 2022-11-006).

Acknowledgments: None.

Conflict of Interest: The authors have no conflicts of interest to declare.

Author Contributions: Conceptualization: YHL, YTK, YHK, and WHC. Data curation: DYK, JML, Min Kyun Sohn, YIS, YSL, Min-Keun Song, MCJ, SYL, DNC, GJO, JHA, JHH, YHK, and WHC. Formal analysis: DHK and WHC. Funding acquisition: YHK and WHC. Methodology: DHK, HSL, DYK, JML, Min Kyun Sohn, YIS, YSL, Min-Keun Song, MCJ, SYL, DNC, GJO, JHA, JHH, YHK, and WHC. Supervision: DYK, JML, Min Kyun Sohn, YIS, YSL, Min-Keun Song, MCJ, SYL, GJO, JHA, JHH, YHK, and WHC. Writing – original draft: DHK and HSL. Writing – review & editing: YHL, YTK, YHK, and WHC.

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