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Differential effects of premorbid functional dependency on mortality in patients with anterior and posterior circulation stroke

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Background: This study investigated the impact of premorbid functional dependency on post-stroke mortality in patients with anterior circulation stroke (ACS) and posterior circulation stroke (PCS).

Methods: This study enrolled 9,698 patients who experienced ischemic stroke between January 2011 and December 2022. The patients were classified into the ACS and PCS groups. Premorbid functional dependency was defined as modified Rankin Scale of ≥ 3 . The risks of premorbid functional dependency and mortality at 3 months and 1-year post-stroke were assessed. A subgroup analysis was further performed to evaluate the risk of premorbid functional dependency in patients who underwent intravenous thrombolysis and endovascular treatment (EVT).

Results: Among 6,358 patients with ACS and 3,340 with PCS, those with premorbid dependency were older, predominantly female, and had a higher proportion of vascular risk factors and stroke severity. Premorbid functional dependency was associated with increased mortality at both 3 months and 1 year in the PCS (odds ratio [OR], 1.79; 95% confidence interval [CI], 1.00–3.13; $P=0.04$ and OR, 2.87; 95% CI, 1.86–4.38; $P<0.001$, respectively), but not in the ACS (OR, 1.08; 95% CI, 0.77–1.51; $P=0.639$ and OR, 1.22; 95% CI, 0.93–1.59; $P=0.140$, respectively) group. Among patients who underwent EVT, premorbid functional dependency increased the risk of mortality at 1 year in the ACS group (OR, 1.80; 95% CI, 1.04–3.08; $P=0.034$), but was not associated with the risk in the PCS group (OR, 2.56; 95% CI, 0.64–10.15; $P=0.176$).

Conclusion: Premorbid functional dependency increases the risk of mortality in patients with PCS.

Keywords: Ischemic stroke; Mortality; Stroke

INTRODUCTION

Stroke may be caused by occlusion of any cerebral vessel, while the neurological symptoms from the occluded vessels are present-

ed according to the territories in which the vessels are supplied. As such, neurological symptoms and stroke severity may present differently according to the location of the affected lesion. Stroke lesions are commonly categorized as anterior circulation stroke

(ACS) and posterior circulation stroke (PCS), with the latter associated with high post-stroke disability and mortality [1,2]. Furthermore, among patients with minor stroke, those with PCS were more likely to exhibit disability at 3 months after the index stroke compared with those who experience ACS [3]. This finding suggests the need to assess the differential effects of factors influencing post-stroke outcomes on ACS and PCS.

Premorbid functional status has been utilized as a strong predictor of post-stroke prognosis, while the premorbid modified Rankin Scale (mRS) has been associated with mortality in acute ischemic stroke patients [4]. Furthermore, as landmark clinical trials that proved the efficacy of endovascular treatment (EVT) only included premorbid-independent patients [5,6], any evidence of the efficacy of EVT in premorbidly dependent patients is not yet supported by clinical trials and has been decided based on clinicians' own decisions [7].

Therefore, as ACS and PCS have different outcomes, the individual impact of premorbid functional dependency on these two stroke types needs to be investigated. This study therefore aimed to evaluate whether premorbid functional dependency is associated with stroke-related mortality in patients with ACS and PCS.

METHODS

Study population

This was a retrospective cohort study from a single comprehensive stroke center that included patients admitted between January 2011 and December 2022. In total, 11,884 patients with ischemic stroke and transient ischemic attack were screened. Among the 10,346 patients with image-positive stroke, enrolled 9,698 with lesions solely in the anterior or posterior circulation, excluding those with concomitant lesions in both regions. ACS was defined as acute ischemic stroke lesions in the anterior cerebral artery, middle cerebral artery, or internal carotid artery (ICA) territories; whereas PCS was categorized as lesions in the posterior cerebral artery, basilar artery, vertebral artery, superior cerebellar artery, anterior inferior cerebellar artery, or posterior inferior cerebellar artery territories. All patients had information on premorbid mRS. A total of 6,358 and 3,340 patients with ACS and PCS were analyzed, respectively (Fig. 1).

Data collection

Clinical data were obtained from a retrospective review of the medical records. Information regarding age, sex, onset-to-arrival, and vascular risk factors, including hypertension, diabetes, hyperlipidemia, current smoking, history of stroke, history of coronary heart disease, premorbid mRS, initial systolic and diastolic blood

pressure (BP), initial glucose level, initial National Institute for Health Stroke Scale (NIHSS) score, symptomatic arterial steno-occlusion lesions, intravenous thrombolysis (IVT), and EVT, was evaluated. Onset to arrival time was categorized into ≤ 3 hours, > 3 hours and ≤ 6 hours, > 6 hours and ≤ 12 hours, > 12 hours and ≤ 24 hours, > 24 hours and ≤ 36 hours, > 36 hours and ≤ 48 hours, > 48 hours and ≤ 7 days, and > 7 days. Symptomatic arterial steno-occlusion was defined as the presence of any symptomatic stenosis of $\geq 50\%$, or occlusion.

Premorbid functional dependency was defined as a premorbid mRS of ≥ 3 , including mRS scores of: 3 (moderate disability, with patients requiring help, but able to walk without assistance), 4 (moderately severe disability, with patients unable to walk without assistance), 5 (severe disability, with patients being bedridden, incontinent, and requiring constant nursing care). The outcomes were all-cause mortality at 3 months and 1 year after the index event.

Statistical analysis

Baseline characteristics of each population (anterior and PCS) were described as the number (%), mean \pm standard deviation, or median (interquartile range [IQR]), as appropriate. The clinical characteristics of the patients according to premorbid functional dependency were also evaluated.

Multivariate models were established using binary logistic regression analysis. The covariates associated with post-stroke mortality were predetermined, including age, sex, initial NIHSS score, onset-to-hospital arrival time, hypertension, diabetes, hyperlipid-

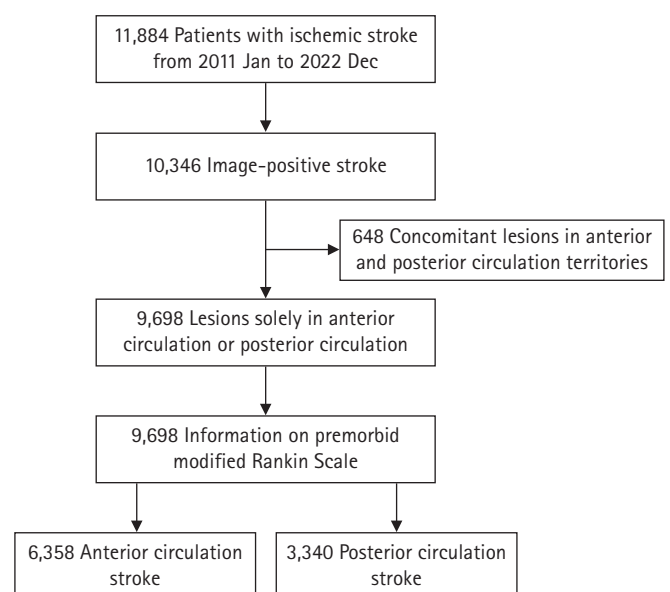


Fig. 1. Study flowchart.

emia, atrial fibrillation, history of coronary heart disease, current smoking, initial systolic BP, initial glucose level, symptomatic arterial steno-occlusion, IVT, and EVT. The odds ratios (ORs) and 95% confidence intervals (CIs) of premorbid dependency on the outcomes were also analyzed. Subgroup analyses were conducted for patients who underwent IVT and EVT in both the ACS and PCS groups. Statistical significance was set at $P < 0.05$. All statistical analyses were conducted using R 4.3.1 (2023-06-16; R Foundation for Statistical Computing).

RESULTS

Among the 6,358 patients with ACS and 3,340 patients with

PCS, the mean ages were 68.6 years (± 13.6) and 66.2 years (± 13.6), respectively, while both populations showed male predominance (59.7% and 63.5%, respectively) (Tables 1 and 2). The proportions of premorbid functionally dependent patients were 8.4% in the anterior circulation and 6.0% in the posterior circulation. The median premorbid mRS was 3 (IQR, 3–4) in both populations. Compared to patients with premorbid independence, those with premorbid functional dependence were older (mean age: 78.7 vs. 67.6 years in ACS and 78.4 vs. 65.4 years in PCS), and showed a female predominance (59.6% vs. 38.6% in ACS and 51.8% vs. 35.6% in PCS). Furthermore, the median NIHSS score and proportions of hypertension, atrial fibrillation, and history of coronary heart disease were higher in

Table 1. Baseline characteristics of anterior circulation stroke patients

Variable	Anterior circulation (n=6,358)	Premorbid functional independent (n=5,823)	Premorbid functional dependent (n=535)	P-value
Age (yr)	68.6 \pm 13.6	67.6 \pm 13.4	78.7 \pm 10.1	<0.001
Sex				<0.001
Female	2,565 (40.3)	2,246 (38.6)	319 (59.6)	
Male	3,793 (59.7)	3,577 (61.4)	216 (40.4)	
Onset to arrival time				0.935
≤ 3 hr	1,985 (31.2)	1,812 (31.1)	173 (32.3)	
>3 hr & ≤ 6 hr	749 (11.8)	680 (11.7)	69 (12.9)	
>6 hr & ≤ 12 hr	735 (11.6)	673 (11.6)	62 (11.6)	
>12 hr & ≤ 24 hr	657 (10.3)	608 (10.4)	49 (9.2)	
>24 hr & ≤ 36 hr	489 (7.7)	450 (7.7)	39 (7.3)	
>36 hr & ≤ 48 hr	223 (3.5)	202 (3.5)	21 (3.9)	
>48 hr & ≤ 7 day	1,098 (17.3)	1,011 (17.4)	87 (16.3)	
>7 day	422 (6.6)	387 (6.6)	35 (6.5)	
Vascular risk factor				
Hypertension	4,453 (70.0)	4,025 (69.1)	428 (80.0)	<0.001
Diabetes	2,040 (32.1)	1,829 (31.4)	211 (39.4)	<0.001
Hyperlipidemia	2,390 (37.6)	2,157 (37.0)	233 (43.6)	0.003
Atrial fibrillation	1,433 (22.5)	1,266 (21.7)	167 (31.2)	<0.001
Current smoking	1,424 (22.4)	1,395 (24.0)	29 (5.4)	<0.001
History of stroke	1,405 (22.1)	1,132 (19.4)	273 (51.0)	<0.001
History of coronary heart disease	674 (10.6)	592 (10.2)	82 (15.3)	<0.001
Premorbid mRS				<0.001
0	4,875 (76.7)	4,875 (83.7)	0	
1	605 (9.5)	605 (10.4)	0	
2	343 (5.4)	343 (5.9)	0	
3	339 (5.3)	0	339 (63.4)	
4	139 (2.2)	0	139 (26.0)	
5	57 (0.9)	0	57 (10.7)	
Stroke information				
Systolic BP (mmHg)	153.4 \pm 27.5	153.8 \pm 27.5	148.6 \pm 27.0	<0.001
Diastolic BP (mmHg)	82.9 \pm 17.4	83.4 \pm 17.4	77.5 \pm 16.5	<0.001
Initial glucose (mg/dL)	136.2 \pm 57.7	135.9 \pm 57.3	139.7 \pm 62.6	0.176
Initial NIHSS score	4 (1–9)	4 (1–8)	12 (6–20)	<0.001
Symptomatic steno-occlusive lesion	3,454 (54.3)	3,130 (53.8)	324 (60.6)	0.003
Emergent revascularization therapy				
Intravenous thrombolysis	762 (12.0)	710 (12.2)	52 (9.7)	0.106
Endovascular treatment	1,033 (16.2)	940 (16.1)	93 (17.4)	0.495

Values are presented as mean \pm standard deviation, number (%), or median (interquartile range). mRS, modified Rankin Scale; BP, blood pressure; NIHSS, National Institute for Health Stroke Scale.

Table 2. Baseline characteristics of posterior circulation stroke patients

Variable	Posterior circulation (n=3,340)	Premorbid functional independent (n=3,141)	Premorbid functional dependent (n=199)	P-value
Age (yr)	66.2±13.6	65.4±13.5	78.4±9.1	<0.001
Sex				<0.001
Female	1,220 (36.5)	1,117 (35.6)	103 (51.8)	
Male	2,120 (63.5)	2,024 (64.4)	96 (48.2)	
Onset to arrival time				0.149
≤3 hr	669 (20.0)	619 (19.7)	50 (25.1)	
>3 hr & ≤6 hr	339 (10.1)	322 (10.3)	17 (8.5)	
>6 hr & ≤12 hr	416 (12.5)	388 (12.4)	28 (14.1)	
>12 hr & ≤24 hr	427 (12.8)	394 (12.5)	33 (16.6)	
>24 hr & ≤36 hr	279 (8.4)	269 (8.6)	10 (5.0)	
>36 hr & ≤48 hr	128 (3.8)	122 (3.9)	6 (3.0)	
>48 hr & ≤7 day	769 (23.0)	730 (23.2)	39 (19.6)	
>7 day	313 (9.4)	297 (9.5)	16 (8.0)	
Vascular risk factor				
Hypertension	2,328 (69.7)	2,165 (68.9)	163 (81.9)	<0.001
Diabetes	1,165 (34.9)	1,078 (34.3)	87 (43.7)	0.009
Hyperlipidemia	1,252 (37.5)	1,165 (37.1)	87 (43.7)	0.072
Atrial fibrillation	471 (14.1)	418 (13.3)	53 (26.6)	<0.001
Current smoking	748 (22.4)	736 (23.4)	12 (6.0)	<0.001
History of stroke	635 (19.0)	536 (17.1)	99 (49.7)	<0.001
History of coronary heart disease	308 (9.2)	278 (8.9)	30 (15.1)	0.005
Premorbid mRS	0 (0–0)	0 (0–0)	3 (3–4)	<0.001
Premorbid mRS				<0.001
0	2,686 (80.4)	2,686 (85.5)	0	
1	306 (9.2)	306 (9.7)	0	
2	149 (4.5)	149 (4.7)	0	
3	142 (4.3)	0	142 (71.4)	
4	46 (1.4)	0	46 (23.1)	
5	11 (0.3)	0	11 (5.5)	
Stroke information				
Systolic BP (mmHg)	154.7±26.8	155.1±26.6	148.2±29.0	<0.001
Diastolic BP (mmHg)	83.9±16.3	84.3±16.2	77.1±16.8	<0.001
Initial glucose (mg/dL)	143.0±61.6	143.1±62.0	140.5±55.0	0.520
Initial NIHSS score	3 (1–5)	2 (1–5)	9 (4.5–15)	<0.001
Symptomatic steno-occlusive lesion	1,270 (38.0)	1181 (37.6)	89 (44.7)	0.053
Emergent revascularization therapy				
Intravenous thrombolysis	181 (5.4)	176 (5.6)	5 (2.5)	0.088
Endovascular treatment	163 (4.9)	146 (4.6)	17 (8.5)	0.021

Values are presented as mean±standard deviation, number (%), or median (interquartile range).

mRS, modified Rankin Scale; BP, blood pressure; NIHSS, National Institute for Health Stroke Scale.

premorbidly dependent patients than in independent patients. Inversely, the proportion of current smokers was lower (5.4% vs. 24.0% in ACS and 6.0% vs. 23.4% in PCS) and BP (mean systolic BP: 153.8 mmHg vs. 148.6 mmHg in ACS and 155.1 mmHg vs. 148.2 mmHg in PCS) were lower in premorbid dependent patients compared to independent patients.

The mortality rates at 3 months and 1 year were 5.3% and 10.2% for ACS and 3.2% and 6.4% for PCS, respectively (Fig. 2). The mortality of patients with premorbid dependence was higher in the ACS (3-month mortality, 14.0%; 1-year mortality, 27.8%)

and PCS (3-month mortality, 16.1%; 1-year mortality, 33.0%) groups than those with premorbid independence in ACS (3-month mortality, 4.5%; 1-year mortality, 8.6%) and PCS (3-month mortality, 2.4%; 1-year mortality, 4.7%).

While premorbid functional dependency increased the risk of 3-month mortality in the unadjusted analysis, it increased the risk in patients with PCS (OR, 1.79; 95% CI, 1.00–3.13; $P=0.044$), but not in those with ACS (OR, 1.08; 95% CI, 0.77–1.51; $P=0.639$) when adjusted for covariates (Table 3). For mortality at 1-year, a similar result was found, with the results indicating that

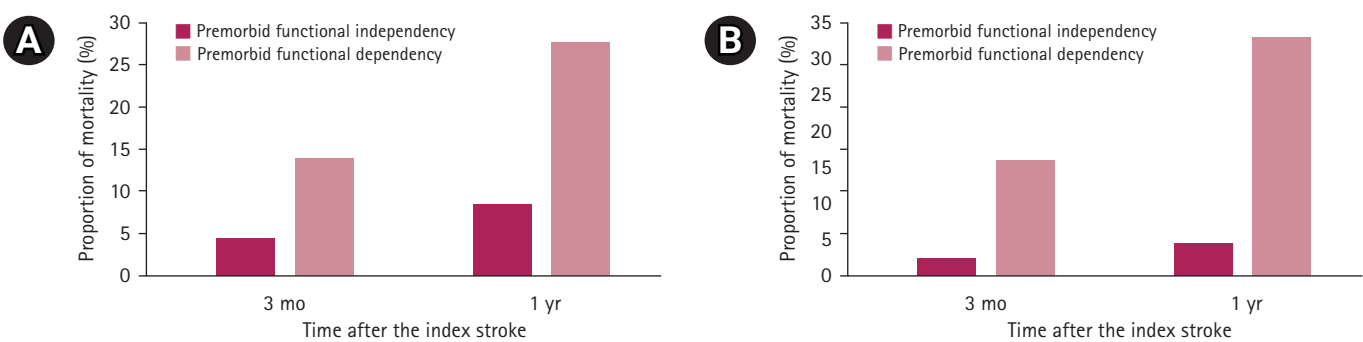


Fig. 2. Mortality rates with anterior circulation stroke (A) and posterior circulation stroke (B) at 3 months and 1 year in patients.

Table 3. Mortality rate according to premorbid functional dependency in patients with anterior and posterior circulation stroke

Variable	Unadjusted		Adjusted ^{a)}	
	HR (95% CI)	P-value	HR (95% CI)	P-value
3-Month mortality				
Anterior circulation stroke	3.42 (2.58–4.48)	<0.001***	1.08 (0.77–1.51)	0.639
Posterior circulation stroke	7.69 (4.89–11.86)	<0.001***	1.79 (1.00–3.13)	0.044*
1-Year mortality				
Anterior circulation stroke	4.07 (3.27–5.04)	<0.001***	1.22 (0.93–1.59)	0.140
Posterior circulation stroke	9.92 (6.98–14.01)	<0.001***	2.87 (1.86–4.38)	<0.001***

HR, hazard ratio; CI, confidence interval.

^{a)}Adjusted for age, sex, initial National Institutes of Health Stroke Scale score, onset-to-hospital arrival time, hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of coronary heart disease, current smoking, initial systolic blood pressure, initial glucose level, symptomatic arterial steno-occlusion, intravenous thrombolysis, and endovascular treatment.

P*<0.05, **P*<0.001.

premorbid functional dependency independently elevated the odds in PCS (OR, 2.87; 95% CI, 1.86–4.38; *P* < 0.001), but not in ACS (OR, 1.22; 95% CI, 0.93–1.59; *P* = 0.140) when adjusted.

In patients who underwent IVT, the risk of functional dependency for mortality at 3 months and 1 year in both the ACS and PCS groups was not significant after adjustment (Table 4). Among patients who underwent EVT, functional dependency was associated with the 1-year mortality rate in the ACS group (OR, 2.56; 95% CI, 1.04–3.08; *P* = 0.034), but in the PCS group (OR, 1.80; 95% CI, 0.64–10.15; *P* = 0.18) (Table 5).

DISCUSSION

In this retrospective observational study, we found that premorbid functional dependency was associated with stroke mortality at 3 months and 1 year in patients with PCS; however, it did not significantly increase mortality in patients with ACS. Among patients who underwent EVT, premorbid functional dependency increased the risk of 1-year mortality in ACS, but was not associated with the risk of 1-year mortality in PCS.

The causes of death after stroke can be multifactorial, and are not limited to index stroke events. Recent studies have indicated

infection, cardiovascular causes, cancers, and other factors as reasons for death after an index stroke [8,9]. Comorbidities can play a significant role in stroke mortality, and premorbid functional status, which reflects these comorbidities, may also affect mortality. Although categorized under the common heading of “ischemic stroke,” the presentations and clinical outcomes of ACS and PCS differ significantly. ACS cases typically present with motor function impairments and cortical symptoms, such as language dysfunction and neglect, whereas PCSs are more likely to involve vertigo, gaze palsy, ataxia, and severe bulbar symptoms, including airway issues and respiratory distress. Therefore, patients who are functionally dependent and have a PCS may be susceptible to life-threatening conditions. Additionally, in our data, the proportions of IVT and EVT for premorbidly dependent patients with PCS were lower at 2.5% and 8.5%, respectively, compared to 9.7% and 17.4% in patients with ACS. Therefore, while the mortality and prognosis of ACS may be more significantly influenced by hyperacute treatment, including IVT and EVT, more patients with PCS receive medical treatment, suggesting that the premorbid functional status could have a more significant impact on mortality.

The association between premorbid functional dependency

Table 4. Mortality according to premorbid functional dependency in patients with anterior and posterior circulation stroke who had undergone intravenous thrombolysis

Variable	Unadjusted		Adjusted ^{a)}	
	HR (95% CI)	P-value	HR (95% CI)	P-value
3-Month mortality				
Anterior circulation stroke	2.12 (0.89–4.52)	0.065	0.69 (0.25–1.70)	0.440
Posterior circulation stroke	6.04 (0.29–48.26)	0.129	4.80 (0.61–9,588.43)	0.094
1-Year mortality				
Anterior circulation stroke	3.36 (1.71–6.35)	<0.001***	1.27 (0.58–2.68)	0.536
Posterior circulation stroke	10.73 (1.30–72.38)	<0.001***	1.68 (0.72–539.31)	0.087

HR, hazard ratio; CI, confidence interval.

^{a)}Adjusted for age, sex, initial National Institute for Health Stroke Scale score, onset-to-hospital arrival time, hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of coronary heart disease, current smoking, initial systolic blood pressure, initial glucose level, symptomatic arterial steno-occlusion, and endovascular treatment.

*** $P < 0.001$.

Table 5. Mortality according to premorbid functional dependency in patients with anterior and posterior circulation stroke who had undergone endovascular treatment

Variable	Unadjusted		Adjusted ^{a)}	
	HR (95% CI)	P-value	HR (95% CI)	P-value
3-Month mortality				
Anterior circulation stroke	2.22 (1.20–3.90)	0.008**	1.18 (0.60–2.19)	0.622
Posterior circulation stroke	2.88 (0.74–9.49)	0.097	1.00 (0.14–5.72)	0.997
1-Year mortality				
Anterior circulation stroke	3.37 (2.08–5.40)	<0.001***	1.80 (1.04–3.08)	0.034*
Posterior circulation stroke	4.58 (1.48–13.84)	0.007**	2.56 (0.64–10.15)	0.176

HR, hazard ratio; CI, confidence interval.

^{a)}Adjusted for age, sex, initial National Institutes of Health Stroke Scale score, onset-to-hospital arrival time, hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of coronary heart disease, current smoking, initial systolic blood pressure, initial glucose level, symptomatic arterial steno-occlusion, and intravenous thrombolysis.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

and mortality in patients undergoing emergency reperfusion therapy differed from that in all patients with ischemic stroke. Premorbid functional dependency did not significantly increase the risk of mortality in patients receiving IVT. However, among ACS patients who underwent EVT, it elevated the risk of mortality at 1 year, but was not associated with mortality in PCS. According to a recent meta-analysis of EVT in patients with prestroke disability [7], premorbid disabled patients seem to benefit from EVT. Therefore, as EVT for patients with prestroke disability could be beneficial, cautious selection of EVT candidates is required to enhance stroke prognosis in patients with premorbid functional dependency. The lack of an association between premorbid functional dependency and mortality in patients with PCS could be partly explained by the smaller population of the EVT subgroup (161 patients [4.8%] who underwent EVT among the 3,340 patients with PCS). It has further been suggested that premorbid functionally dependent patients who undergo EVT are high-risk patients, and that a meticulous approach is crucial for these patients.

Interestingly, we found that one-third of premorbid functionally

dependent patients with PCS died within 1 year. This high mortality rate could be attributed to the characteristics of this patient group, which include a higher age, greater predominance of females, higher proportion of vascular risk factors, and more severe stroke (Table 2), all of which are comorbidities associated with post-stroke mortality. Additionally, 17.9% of premorbid functionally dependent patients with PCS died between 3 months and 1 year (Fig. 2), indicating that the management of post-stroke complications after 3 months needs to be more intensive. To address this, adjustments in the intervals between outpatient clinic visits could be considered, as well as periodic checkups and laboratory tests to monitor factors that could impact the general medical condition [10]. Furthermore, caregivers should be educated regarding the possibility of stroke recurrence and various complications that can occur in post-stroke patients [11].

This study had some limitations. First, this was a single-center retrospective cohort study, which weakens the generalizability of the results. However, it should be noted the center is a comprehensive stroke center capable of providing 24-hour, all-day EVT

and neurosurgery, allowing for the comprehensive investigation of patients who received appropriate care under feasible circumstances. Second, there is the potential for unmeasured confounding factors. Differences in treatment decisions for patients with premorbid function could arise based on prognostic expectations, or the preferences of patients and caregivers, which could not be adjusted for in the present study. Nevertheless, efforts have been made to include all available factors that could influence post-stroke mortality. Third, while the NIHSS score was used to assess stroke severity in both ACS and PCS, it has inherent limitations in fully reflecting stroke severity in PCS. Fourth, the study encompassed a wide time period from 2011 to 2022, during which the characteristics of patients receiving EVT may have varied significantly. For example, EVT would have been more limited to patients with more severe presentations in the early period; however, over time, the indications for EVT have expanded, leading to its application in a broader patient population. This temporal variability in patient profiles necessitates careful interpretation of the outcomes associated with EVT.

In conclusion, premorbid functional dependency was associated with mortality at 3 months and 1 year after an index stroke in patients with PCS. When premorbid functionally dependent patients present with PCS, more active endeavors to detect and manage post-stroke complications are needed, as a high mortality rate is expected.

ARTICLE INFORMATION

Ethics statement

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (No. B-2405-899-103). Informed consent was waived due to the retrospective study design.

Conflict of interest

Dong-Wan Kang is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Conceptualization: MSK, DYK, DWK, BKK, JHP, HJB. Methodology: all authors. Formal analysis: MSK, DYK. Data curation: MSK, DYK, JYK, JK, BJK, MKH, HJB. Visualization: MSK, DYK. Project administration: MSK, DYK, JYK, JK, BJK, MKH, HJB. Funding acquisition: MSK, DYK, JYK, JK, BJK, MKH, HJB. Writing—original draft: MSK, DYK, DWK, BKK, JHP, HSG, NK, SWC. Writing—review & editing: all authors.

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