Peer Review File

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Reviewer A

Authors of this manuscript attempted to determine factors predicting cognitive decline after stroke. The topic is interesting, first part of the introduction well written and overall informative. Nonetheless there a few shortcomings which prevent me from recommending this work for publication.

1. I do not agree with authors' statement:
"Numerous studies have examined the risk factors of PSCI, but the clinical features of patients with cognitive impairment after cerebral ischemic stroke (CIS), especially the risk factors of cognitive impairment after CIS, have not been extensively investigated. "There are numerous studies on this subject. Moreover, authors cite many of them in their own discussion.
Response: Thanks very much for this suggestion. We changed it "Numerous studies have examined the risk factors of PSCI, but the clinical features of patients with cognitive impairment after cerebral ischemic stroke (CIS), especially the risk factors of cognitive impairment after CIS, have rarely been extensively investigated".

2. Pertaining to #1 it is not really clear to me what is novel about this work.
Response: Respected reviewer, this study conducted to better evaluate the characteristics of cognitive impairment after CIS and to explore risk factors and markers of PSCI progression through focusing on the clinical features of patients with cognitive impairment after CIS.

3. Although initially informative, the introduction becomes in its second part too wordy and repetitive.
Response: Respected reviewer, thank you for your valuable suggestion we have upgraded the second part of the introduction.

4. Statistics: it would be good to give more information about logistic regression models. How the final model was selected? Were all variables entered at once that would be probably not great approach give relatively small size of the group.
Response: Respected reviewer thanks for appreciation we modified it according to your valuable suggestion.

5. Figure 1 and 2 not very informative.
Response: Respected reviewer, thanks very much for this suggestion. We added more information for Figures 1 and 2 in the manuscript.

6. Table 1 does not have p values.
Response: Respected reviewer, p values have been provided in table 1 within their acceptable limits.

Group	Control group	Study group	χ^2/t	P

	(n=52)	(n=68)		
Age	58.95±4.23	65.93±5.34	7.746	<0.01
Gender (male/female)	16/36	50/18	21.768	<0.01
Education				
Junior high school and below	9 (17.31)	19 (27.94)	5.958	<0.01
High school	26 (50.00)	39 (57.35)		
College or above	17 (32.69)	10 (14.71)		
Stroke history	3 (5.77)	27 (39.71)	18.099	<0.01
History of hypertension	32 (61.54)	35 (51.74)	1.211	>0.05
History of diabetes mellitus	21 (40.38)	38 (55.88)	2.831	>0.05
History of atrial fibrillation	20 (38.46)	36 (52.94)	2.482	>0.05
Carotid intima thickness				
>1.2 mm	28 (53.85)	30 (44.12)	1.116	>0.05
≤1.2 mm	24 (46.15)	38 (55.88)		
Smoking history	29 (55.77)	34 (50.00)	0.393	>0.05
History of drinking	25 (48.08)	30 (44.12)	0.186	>0.05
Infarct area			4.422	<0.05
Large-area infarction	19 (36.54)	38 (55.88)		
Small- and medium-sized infarction	33 (63.46)	30 (44.12)		
Infarct site			15.334	<0.05
Temporal lobe	12 (23.08)	40 (58.82)		
Nontemporal lobe	40 (76.92)	28 (41.18)		

7. PSCI – how many cases had dementia and how many MCI? Did they differ?

Response: Respected reviewer, the probability of developing dementia after the first stroke is 10%, while that after recurrent stroke is more than one-third.

PSCI includes mild cognitive impairment and dementia. At present, there is no clear definition of PSCI, and it is only acknowledged that cognitive impairment that occurs or aggravates after stroke usually occurs in the acute phase. In addition, more than half of patients afflicted with stroke experience different forms of progressive cognitive decline (20). Early-onset cognitive impairment usually occurs 3–6 months after the stroke, and late-onset cognitive impairment takes months or even years (21). Cognitive impairment is 3 times more likely to occur in patients with acute complications than in those without complications. Common complications include urinary incontinence, dyskinesia, infection, seizures, pseudobulbar paralysis, delirium, and depression (22). The recurrence of stroke is usually accompanied by the enlargement of the infarction site or the deterioration of infarction degree. The risk of PSCI in patients with recurrent stroke is 2.7 times higher than that in patients with first stroke.

Minor:

Clarifications in the text are needed:

The term “Study group” is not very precise, the control group is also study group, I think authors meant cognitive impairment groups.

Response: Respected reviewer, yes, we meant the same, we replaced the study group with cognitive impairment group in the whole draft.

What does that mean: “In the study group, there was at least 1 case of cognitive impairment in the patients with CIS. “

Response: Respected reviewer, we have removed this text that was the typo error.

Serological data is not a great term - it mostly refers to antibody's studies.
Response: Respected reviewer, yes, we totally agreed with you actually we have also checked other than antibodies so we collectively used serological data term.

"Incidence of cognitive impairment after CIS" not a great wording as it rather refers to population.
Response: Respected reviewer, thank you for your valuable suggestion we replaced the term with population.

Reviewer B

The paper titled "Multivariate logistic regression analysis of clinical characteristics and risk factors of cognitive impairment after cerebral ischemic stroke: implications for clinical treatment" is interesting. Patients with cognitive impairment after CIS have imaging features of white matter degeneration, brain atrophy, and involvement of dominant hemispheres. The results of multivariate logistic regression analysis indicated that sex, age, education level, stroke history, infarct size, and infarct location were all risk factors of cognitive impairment after CIS. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) The abstract is not adequate and needs further revisions. The research background does not indicate the clinical needs of this research focus. The study results need to show the clinical characteristics of the two groups of patients.
   Response: Respected reviewer thank you very much for your valuable time and efforts to review our manuscript to improve its quality. We have revised the abstract part of the manuscript according to your suggestions.

2) This study only discusses the risk factors of cognitive impairment after CIS, and the content is relatively limited. It is recommended to increase the correlation study between peripheral immune markers and structural/functional neuroimaging examination results.
   Response: Respected reviewer, our group is consistently working on the risk factors involved in cognitive impairment after CIS. We will definitely include peripheral immune markers and structural/functional neuroimaging examination results in next studies.

3) What are the differences in the distribution characteristics of risk factors among high-risk stroke populations of different ages and genders? How to formulate precise intervention measures? It is recommended to add relevant content.
   Response: Respected reviewer, thanks very much for this suggestion. We added that "The study of Putaala (51) concluded that "The incidence of ischemic stroke in young adults has been increasing since the 1980s, which has occurred in parallel with

increasing prevalence of vascular risk factors and substance abuse among the younger population. Young adults have a considerably wider range of risk factors than older patients, including age-specific factors such as pregnancy/puerperium and oral contraceptive use. Behavioral risk factors such as low physical activity, excess alcohol consumption, and smoking are factors as well. More than 150 identified causes of early-onset ischemic stroke exist, including rare monogenic disorders. Several recent advances have been made in diagnosis and management of stroke in young adults, including molecular characterization of monogenic vasculitis due to deficiency of adenosine deaminase 2 and transcatheter closure of patent foramen ovale for secondary prevention.". They suggest that systematic identification of risk factors and causes for early onset ischemic stroke, as well as patients' motivation for long-term prevention and lifestyle changes, is critical to improving prognosis for early onset ischemic stroke (51).".

4) What are the differences in the relationship between inflammatory markers and cognitive impairment after different brain diseases? It is recommended to add relevant content.
Response: Respected reviewer, thanks very much for this suggestion. We added that "In the report of Anita et al, they found that cognitive impairment among people with type 2 diabetes mellitus was associated with systemic inflammation and lower brain derived neurotropic factor concentrations (52). These inflammatory characteristics support an increased inflammatory-vascular interaction associated with cognitive impairment in type 2 diabetes mellitus (52). For investigation of Custodero et al (53), they confirmed that IL-6 in cerebrospinal fluid was significantly higher in people with Vascular dementia compared to healthy subjects, and not compared to Alzheimer's disease patients, but due to limited evidence and high inconsistency across studies, we could not draw definite conclusion (53). Higher blood IL-6 levels might represent a useful biomarker able to differentiate people with Vascular dementia from those with Alzheimer's disease and might be correlated with higher risk of future Vascular dementia (53).".

5) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "Aberrant cerebral perfusion pattern in amnestic mild cognitive impairment and Parkinson's disease with mild cognitive impairment: a comparative arterial spin labeling study, Quant Imaging Med Surg, PMID: 34249637". It is recommended to quote this article.
Response: Respected reviewer, thanks very much for this suggestion. We cited this paper.

6) This study is a retrospective analysis, which is likely to cause some deviations in the results. It needs to be further confirmed by multi-center clinical trials.
Response: Respected reviewer, thanks very much for this suggestion. We confirmed it.

Reviewer C

1. Table 1

Please add the description to the table footnote that how the data are presented in table.

Age	58.95±4.23	65.93±5.34	7.746	<0.01
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Education				
Junior high school and below	9 (17.31)	19 (27.94)	5.958	<0.01
High school	26 (50.00)	39 (57.35)		
College or above	17 (32.69)	10 (14.71)		

Response: Thanks very much for your reminding. We added that "Age: Mean ± SD. The others: n (%).".

2. References/Citations

a) References are not in order. In the text, cite the references numerically (in round brackets) and consecutively in the order of appearance. Please update all the references and citations.

Response: Thanks very much for your reminding. We updated the order of all the references.

c) References 33-35 were not cited in the main text, please indicate. They should be cited between 32 and 36.

Response: Thanks very much for your reminding. We updated the order of all the references and cited References 33-35 in the manuscript.

d) Please double-check if more studies should be cited as you mentioned "studies".

In previous studies, VCI was the dominant concept in relation to PSCI.Camille de Montferrand et al. first put forward the concept of VCI in 1993 (32). It is generally

Response: Thanks very much for your reminding. We have changed it to "study".