INTRODUCTION

Cerebrovascular diseases (CVDs) have become severe diseases that endanger human health and are the main cause of death and disability in China. Among the CVDs, acute cerebral infarction (ACI) has a high incidence, disability, mortality, and recurrence rate, which brings us tremendous pain and burden.1 ACI is a common cerebrovascular disease caused by a sudden interruption in the supply of cerebrovascular blood flow. The causes of ACI in most patients with severe symptoms include embolic or thrombotic occlusion.2 Carotid

Evaluation of lipoprotein-associated phospholipase A2, serum amyloid A, and fibrinogen as diagnostic biomarkers for patients with acute cerebral infarction

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Funding information
Special Fund of Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Grant/Award Number: No:02.03.2018-130

Abstract

Objective: The aim of this study was to explore the clinical values of combined detection of lipoprotein-associated phospholipase A2 (Lp-PLA2), serum amyloid A (SAA), and plasma fibrinogen (FIB) in the diagnosis of acute cerebral infarction (ACI).

Methods: A case-control study including 100 hospitalized patients with ACI and 47 healthy controls was carried out. The level of Lp-PLA2, SAA, and FIB was detected, respectively, and their clinical values were analyzed. Carotid lesions and neurological impairment were also analyzed in each patient.

Results: The level of Lp-PLA2, SAA, and FIB in the ACI group was significantly higher than that of the controls, and the three biomarkers showed a significant positive correlation and were considered as risk factors for ACI. The area under the curve (AUC) for Lp-PLA2, SAA, and FIB was 0.858, 0.743, and 0.672, respectively. When three biomarkers were used in combination, the AUC was 0.879. Compared with the other groups, the levels of three biomarkers in bilateral carotid plaque ACI group were all significantly higher. In addition, the level of Lp-PLA2 and SAA in ACI patients with severe neurological impairment was also significantly higher than that of the mild-to-moderate group.

Conclusion: Lp-PLA2 combined with SAA and FIB had a high clinical value for rapid diagnosis and prediction of ACI. These biomarkers were also significantly associated with the formation of bilateral carotid atherosclerotic plaques and the severe neurological impairment in ACI patients.

KEYWORDS

acute cerebral infarction, atherosclerosis, fibrinogen, lipoprotein-associated phospholipase A2, serum amyloid A
lesions are the main cause of ACI, and atherosclerotic plaque formation is an early pathological feature of carotid lesions in ACI. Atherosclerotic plaques will gradually develop into vascular stenosis and even completely block the cerebral blood flow, leading to an ischemic stroke. Recent researches have confirmed that inflammatory response and various inflammatory factors play an important role in the development of ACI and it has become a research hot spot.

Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase, is mainly released from atherosclerotic plaque by macrophages and neutrophils. Multiple studies confirm that Lp-PLA2 plays an important role in the process of atherosclerosis and participates in the development of plaque. Lp-PLA2 can exert its enzymatic activity to hydrolyze oxidized phospholipids in low-density lipoproteins and then form lipid pro-inflammatory substances (such as oxidized free fatty acids and lysolecithin) to produce a variety of atherogenic effects (such as production of cytokines and adhesion factors, endothelial dysfunction, and endothelial cell death). Therefore, Lp-PLA2 is considered as a new vascular-specific inflammatory factor that can be used as an independent risk factor for cardiovascular and cerebrovascular events. The mass and activity of Lp-PLA2 in blood samples can be easily measured, and we can detect the level of Lp-PLA2 to predict the long-term risk of cerebral infarction. Serum amyloid A (SAA) is an acute-phase protein, and it exhibits several means that can render it atherogenic. Evidence has been provided that SAA can interact with cell surface receptors to initiate signaling pathways (MAPK and NF-kB), which promotes the production of pro-inflammatory cytokines and chemokines. In addition, SAA can interfere with the binding of apolipoprotein A1 to high-density lipoprotein (HDL), making HDL unable to efficiently transport cholesterol from surrounding tissues to the liver, leading to subendothelial lipid deposition, and promoting the development of atherosclerosis.

Furthermore, SAA induces the secretion of cytokines by macrophages, monocytes, vascular endothelial cells, and smooth muscle cells, which is a risk factor for the development of atherosclerosis. Fibrinogen (FIB) is a blood coagulation protein synthesized in the liver, also known as coagulation factor I. FIB promotes proliferation and contraction of smooth muscle and endothelial cells, promotes platelet aggregation and adhesion of red blood cells, increases peripheral vascular resistance and blood viscosity, and participates in the occurrence and development of atherosclerosis. Therefore, it may play crucial role in the pathogenesis of cardiovascular disease. According to the recent literature, elevated levels of plasma FIB indicate an increased risk of cerebral infarction, coronary heart disease, and peripheral vascular disease in individuals.

At present, the diagnosis of ACI is mainly based on imaging findings, such as computed tomography (CT) or magnetic resonance imaging (MRI) scans, but it is difficult to equip such expensive equipment in the emergency department of most medical institutions. Furthermore, many primary hospitals still lack such equipment. Therefore, the search for effective blood biomarkers for the rapid diagnosis of ACI is an urgent clinical need. However, unfortunately, there are still not much researches on this aspect. Our study was designed to detect Lp-PLA2, SAA, and plasma FIB levels in patients with ACI, and the diagnostic efficacy of three biomarkers for ACI was further evaluated, which could provide reference value for clinical applications. Furthermore, we also analyzed its relationship with ACI neurological dysfunction and carotid atherosclerotic plaque formation.

2 | SUBJECTS AND METHODS

2.1 | Subjects

In this case-control study, 100 patients (68 males/32 females, median age 60 years) with ACI from Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, between January 2018 and March 2019 were recruited. All patients were diagnosed with an ACI within 72 hours of symptom onset and confirmed by CT or MRI scans. The patients who had transient ischemic attack, subarachnoid hemorrhage, intracerebral hemorrhage, serious liver and renal dysfunction, infectious disease, coronary heart disease, myocardial infarction, surgery, cancer, or autoimmune system diseases were excluded in our study. The age- and gender-matched control group consisted of 47 healthy subjects (27 males/20 females, median age 58 years) who were recruited from the medical examination center in our hospital, without any evidence of cerebrovascular disease, carotid plaque, and inflammatory disease. All subjects were Chinese Han population from the same area in Middle China, and the study protocol was approved by the ethics committee at Tongji Medical College, Huazhong University of Science and Technology. Our study obtained informed consent of all experimental subjects.

2.2 | Collection of data

In our study, all patients were questioned to obtain demographic data, including age, gender, time from the onset of stroke to admission, past history, family history, and smoking and drinking habits. The clinical characteristic parameters such as length of hospital stay, diastolic blood pressure (DBP), systolic blood pressure (SBP), dyslipidemia, hypertension, diabetes, chest radiography, electrocardiogram, the imaging of head CT/MRI were collected carefully. Hypertension was defined as self-reported history of hypertension or diagnosed when a patient had resting SBP ≥140 mm Hg or resting DBP ≥90 mm Hg on repeated measurements. Diabetes mellitus was diagnosed if the patient was being treated with antidiabetic medications or insulin therapy or a fasting blood glucose level ≥7.0 mmol/L. In addition, we also collected other laboratory parameters at admission including cholesterol (TC), triglycerides (TGs), high-density lipoprotein (HDL), low-density lipoprotein (LDL), glycated hemoglobin (HbA1c), glucose (Glu), uric acid (UA), and homocysteine (HCY).
2.3 | Assessment of neurological impairment and carotid plaque

Stroke neurological severity was determined using the National Institutes of Health Stroke Scale (NIHSS) scores from admission, a 15-item neurological evaluation. The level of patient score was positively correlated with the degree of neurological impairment. According to the NIHSS score at admission, patients were divided into severe neurological injury group (NIHSS >15 points) and mild-to-moderate neurological injury group (NIHSS ≤15 points). In addition, according to the results of carotid color Doppler ultrasonography, ACI patients were divided into bilateral carotid plaque cerebral infarction group (46 cases), unilateral carotid plaque cerebral infarction group (37 cases), and non-carotid plaque cerebral infarction group (17 cases).

2.4 | Blood sampling and measurement of Lp-PLA2, SAA, and FIB

All blood samples of patients were collected within 72 hours after stroke onset. Blood samples of healthy controls were also collected. The blood samples were collected on the morning from the fasting subjects in all groups with the sodium citrate anticoagulant blue head tube (BD Corporation) for coagulation assay such as activated partial thromboplastin time (APTT), prothrombin time (PT), D-dimer (DD), and fibrinogen (FIB). The blood samples were collected with BD yellow tube and centrifuged at 1000 g for 10 minutes to separate serum. The upper layer of serum was used to detect Lp-PLA2 and SAA. Serum that was not detected in time was transferred to the Eppendorf (EP) tubes, labeled, and stored at −80˚C.

The serum Lp-PLA2 mass was measured with latex-enhanced scattering immunoturbidimetry analysis using NORMAN-2 scatter immunoturbidimeter apparatus (Nanjing Norman Biotechnology Co., Ltd.). Lp-PLA2 commercial kit was also provided by the NORMAN Company. The concentration of SAA was determined by latex-enhanced immunoturbidimetric method and was measured by AU5800 automatic biochemical analyzer (Beckman Coulter) with a commercial kit (Ningbo Purui Bo Biotechnology Co., Ltd.). The level of FIB was quantitatively determined in plasma with reagent from a complete set of coagulation of the STAGO Company; using STAR evolution automatic blood coagulation analyzer produced by France STAGO Company. The level of Lp-PLA2, SAA, and FIB was defined as a normal range 0–200 ng/mL, 0–10 μg/mL, and 2.0–4.0 g/L, respectively. The three biomarkers were detected according to the reagent instructions. Furthermore, strict calibration and quality control procedures were also performed.

2.5 | Statistical analysis

Data were analyzed by SPSS 19.0 software (IBM Co.). In our study, all quantitative data were non-normally distributed after normality testing. The non-normally distributed data were expressed as (median (P50), 25th percentile to 75th percentile [P25 ~ P75]), and Mann-Whitney U non-parametric test was used between the groups. The Spearman correlation was used to determine the relationship between two variables. Multivariate logistic regression analysis was performed to determine the risk factors for ACI. In addition, the diagnostic value of Lp-PLA2, SAA, and FIB for ACI was evaluated by calculating the areas under the ROC curves (AUC). P < .05 in a two-tailed test was considered statistically significant.

### TABLE 1

Demographic and clinical characteristics, P50 (P25 ~ P75)

| Variable                  | Control (n = 47) | ACI (n = 100) | P value |
|---------------------------|-----------------|---------------|---------|
| Sex (male/female)         | 27/20           | 68/32         | .21     |
| Age (years)               | 58 (48 ~ 66)    | 60 (54 ~ 70)  | .09     |
| Length of hospital stay (day) | 8 (6 ~ 11) |               |         |
| Family history (n[%])     | 0 (0)           | 30 (30)       | <.0001  |
| Dyslipidemia (n[%])       | 0 (0)           | 26 (26)       | <.0001  |
| Diabetes mellitus (n[%])  | 0 (0)           | 40 (40)       | <.0001  |
| Hypertension (n[%])       | 2 (4.26)        | 78 (78)       | <.0001  |
| Smoking (n[%])            | 16 (34.04)      | 40 (40)       | .488    |
| Drinking (n[%])           | 15 (31.91)      | 23 (23)       | .25     |
| Atrial fibrillation (n[%])| 0 (0)           | 32 (32)       | <.0001  |
| SBP/(mm Hg)               | 132 (122 ~ 140) | 145.5 (137 ~ 157) | .0001  |
| DBP/(mm Hg)               | 78 (70 ~ 84)    | 90 (80 ~ 98)  | .0001   |
| Glu/(mmol/L)              | 4.65 (4.4 ~ 4.93)| 6.03 (5.36 ~ 7.82) | <.0001 |
| HbA1c/(%)                 | 5.3 (5.2 ~ 5.5) | 6.4 (5.7 ~ 7.7) | <.0001  |
| TC/(mmol/L)               | 4.48 (4.15 ~ 5.02)| 3.79 (3.28 ~ 4.56) | <.0001 |
| TG/(mmol/L)               | 0.99 (0.75 ~ 1.25)| 1.42 (1.07 ~ 1.91) | <.0001  |
| HDL/(mmol/L)              | 1.38 (1.22 ~ 1.61)| 1.08 (0.93 ~ 1.29) | <.0001  |
| LDL/(mmol/L)              | 2.69 (2.42 ~ 3.04)| 2.56 (2.07 ~ 3.14) | .285    |
3 | RESULTS

3.1 | Demographic and clinical characteristics

The demographic and clinical characteristics of all participants are shown in Table 1. Compared with the control group, there was no significant difference in gender, age, smoking, drinking, and LDL between the two groups (P > .05). However, the following variables, including hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, SBP, DBP, TG, HbA1c, and Glu, were higher in the ACI group, while the levels of TC and HDL were lower than the controls. The difference was statistically significant (P < .05).

3.2 | Comparison of Lp-PLA2, SAA, and FIB levels between ACI and control group

The level of Lp-PLA2, HCY, SAA, UA, APTT, PT, DD, and FIB in the ACI group and healthy controls was detected, respectively. This result showed that the level of Lp-PLA2, SAA, and FIB in the ACI group was all significantly higher than that in healthy controls (P < .05). There were a small difference in HCY, UA, APTT, and DD between the two groups, but the difference was not statistically significant (P > .05) (Table 2).

3.3 | Correlation analysis between Lp-PLA2, SAA, FIB, and other indicators

The correlation between Lp-PLA2, SAA, FIB, and other indicators was analyzed. The level of Lp-PLA2 in patients with ACI was positively correlated with DBP, HCY, FIB, and SAA. Furthermore, the SAA level was also positively correlated with FIB. All these three indicators showed a significant positive correlation (P < .01). However, Lp-PLA2, SAA, FIB, and other indicators showed no significant correlation (P > .05) (Table 3).

3.4 | Logistic regression analyses

Multivariate logistic regression analysis was performed to seek the risk factors for ACI. The results suggested that SAA, FIB, and

| TABLE 2 | Comparison of Lp-PLA2, SAA, and FIB levels, P50 (P25 – P75) |
|---|---|---|---|
| Variable | Control (n = 47) | ACI (n = 100) | P value |
| Lp-PLA2 | 100 (100 – 110) | 243 (133 – 320) | <.0001 |
| HCY | 11.1 (9.25 – 12.65) | 10.7 (7.7 – 13.9) | .287 |
| SAA | 4.2 (2.05 – 5.60) | 79 (4.6 – 11.4) | <.0001 |
| UA | 316.2 (267.35 – 347.75) | 303.5 (240.9 – 375) | .209 |
| APTT | 34.8 (32.9 – 38.15) | 35.6 (33.7 – 38.1) | .528 |
| PT | 12.9 (12.5 – 13.2) | 13.15 (12.8 – 13.6) | .07 |
| FIB | 2.98 (2.60 – 3.18) | 3.4 (2.92 – 4.13) | .001 |
| DD | 0.29 (0.22 – 0.35) | 0.35 (0.27 – 0.54) | .08 |

3.5 | Diagnostic value of Lp-PLA2, SAA, and FIB for ACI

The diagnostic properties of three biomarkers were analyzed by using ROC curve. The area under the curve (AUC) for Lp-PLA2, SAA, and FIB was 0.858 (95% CI, 0.796–0.921), 0.743 (95% CI, 0.663–0.824), and 0.672 (95% CI, 0.582–0.762), respectively (Table 5). The results indicated that Lp-PLA2 had the highest diagnostic value than the others. When the three indicators were used together, the AUC was 0.879 (95% CI, 0.820–0.937). The ROC curves of Lp-PLA2, SAA, and FIB for discrimination between patients in the ACI group and non-ACI control group are shown in Figure 1.

3.6 | Comparison of Lp-PLA2, SAA, and FIB levels in ACI patients with carotid plaques

The level of Lp-PLA2, SAA, and FIB in bilateral carotid plaque ACI group was significantly higher than that in unilateral carotid plaque

| TABLE 3 | Correlation analysis between Lp-PLA2, SAA, FIB, and other indicators |
|---|---|---|---|
| Variable | Lp-PLA2 | SAA | FIB |
| | r | P value | r | P value | r | P value |
| Age | .138 | .189 | .147 | .173 | .041 | .699 |
| SBP | .048 | .655 | .047 | .669 | .055 | .614 |
| DBP | .247 | .020 | .023 | .836 | .174 | .106 |
| HCY | .11 | .03 | -.052 | .637 | -.106 | .334 |
| UA | .100 | .342 | .200 | .061 | .151 | .151 |
| TC | -.126 | .232 | .118 | .275 | .161 | .125 |
| TG | .024 | .819 | -.016 | .884 | .168 | .109 |
| HDL | -.151 | .150 | .061 | .570 | -.054 | .610 |
| LDL | -.104 | .323 | .078 | .468 | .139 | .187 |
| Glu | -.052 | .630 | .039 | .723 | .146 | .172 |
| FIB | .390 | < .001 | .470 | < .001 |
| SAA | .601 | < .001 |

Lp-PLA2 levels were significantly associated with ACI. The level of SAA, FIB, and Lp-PLA2 was associated with the risk of ACI with odds ratio (OR) of 1.56 (95% confidence interval (CI):1.13-2.15), 3.46 (95% CI: 1.05-11.42), and 1.04 (95% CI:1.02-1.07), respectively (Table 4).

| TABLE 4 | Logistic regression analysis of the risk factors for ACI |
|---|---|---|---|
| Variable | OR<sup>a</sup> | 95% CI | P values |
| SAA | 1.56 | 1.13-2.15 | .007 |
| FIB | 3.46 | 1.05-11.42 | .041 |
| Lp-PLA2 | 1.04 | 1.02-1.07 | .002 |

Abbreviations: CI, confidence interval; OR, odds ratio. |<sup>a</sup>Adjusting for age, gender, and lipid-lowering drug.
ACI group and non-carotid plaque ACI group (P < .05). However, there was no significant difference between the unilateral carotid plaque ACI group and non-carotid plaque ACI group (P > .05) (Table 6).

### 3.7 The relationship between Lp-PLA2, SAA, FIB, and the degree of neurological impairment in patients with ACI

According to NIHSS, patients with different degrees of neurological impairment were divided into mild-to-moderate group and severe group. The level of Lp-PLA2, SAA, and FIB was statistically analyzed. The level of Lp-PLA2 and SAA in the severe group was higher than that in the mild-to-moderate group, and the difference was statistically significant (P < .05). There was no significant difference in FIB level between the two groups (P > .05) (Table 7).

### 4 DISCUSSION

At present, the diagnosis of ACI mainly depends on imaging examination, and there is still a lack of a widely used, rapid, and sensitive blood biomarker. Specific biomarkers that can be detected in the blood during early stroke may facilitate accurate diagnosis in emergency situations, especially for small medical institutions that lack CT or MRI scanners. The ideal biomarkers for ACI should have the following characteristics, which are increased in the early stage of the event, rapidly released from the ischemic tissue to the blood circulation, have a certain half-life, and are specific to ischemic nerve tissue damage. At present, the role of atherosclerosis as an independent risk factor in ACI has been extensively studied. Inflammatory cells and inflammatory factors are also important in the development of atherosclerosis before an ischemic event. Similarly, abnormal levels of coagulation factors are also involved in the development and progression of ischemic events. Nowadays, many researchers are paying attention to the use of protein biomarkers in patients with ischemic cerebrovascular disease. Therefore, many biomarkers such as small dense low-density...
lipoprotein cholesterol, oxidized low-density lipoprotein, N-terminal pro-B-type natriuretic peptide, interleukin, matrix metalloprotease-9, and high-sensitivity C-reactive protein have been evaluated for the detection of ACI, but no globally recognized biomarkers. In addition, most researchers focus on the value of a single biomarker in ACI, and the combined effects on multiple biomarkers are still less studied.

Lp-PLA2 is a vascular-specific inflammatory mediator in the process of atherosclerosis. Previous studies showed that elevated Lp-PLA2 was strongly associated with acute ischemic stroke. In addition, the elevated Lp-PLA2 levels may contribute toward both stroke occurrence and recurrence. Furthermore, the results of the investigation of large clinical samples show that higher levels of Lp-PLA2 in the acute period are associated with increased short-term risk of recurrent vascular events. To our knowledge, atherosclerosis is a chronic inflammation associated with increased expression of the acute-phase isoforms of SAA. SAA is a plasma biomarker for future cardiovascular events. Similarly, many investigators have demonstrated that FIB is also a pro-inflammatory factor that plays an important role in the development of atherosclerosis. Some studies have shown that FIB is associated with cardiovascular disease. It may be an independent predictor of adverse cardiovascular outcomes such as coronary heart disease, myocardial infarction, heart failure, stroke, and atrial fibrillation.

In our study, we first compared the differences in the demographic and clinical characteristics of all participants between patients and the control group. We found that hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, SBP, DBP, Glu, HbA1c, and TG levels were higher in ACI patients than those in controls, while TC and HDL were lower than controls. These results were consistent with the currently identified high-risk factors for ACI. In view of the important role of atherosclerosis in ACI, we further analyzed the changes in inflammation and coagulation function between patients and controls, and found that the level of Lp-PLA2, SAA, and FIB in patients was significantly higher than the controls, while the HCY, UA, and DD indicators showed no significant difference between the two groups. In our research, we did not find that HCY and UA were significantly elevated in ACI. However, in some studies, these indicators were also considered as risk indicators in cerebrovascular disease. In addition, when the Spearman correlation analysis was performed on Lp-PLA2, SAA, and FIB, we found that there was a significant positive correlation among the three biomarkers. This result suggested that the change in Lp-PLA2, SAA, and FIB was in the same direction, and the combination of these three biomarkers had a certain value in the diagnosis of ACI. More important, multivariate logistic regression analysis suggested that Lp-PLA2, SAA, and FIB were all the independent risk factors for ACI. We further used the ROC curve to analyze the diagnostic characteristics of these three biomarkers for ACI, and found that Lp-PLA2 had the highest value if a single indicator was used to diagnose ACI. The AUC was 0.858 (95% CI, 0.796-0.921). When the three biomarkers were used in combination, the AUC was 0.879 (95% CI, 0.820-0.937). This indicated that the combined detection of Lp-PLA2, SAA, and FIB was more valuable than the detection of one indicator for ACI. In order to further analyze the relationship between the above three indicators and ACI, we subgrouped patients according to the result of carotid color Doppler ultrasonography. The level of Lp-PLA2, SAA, and FIB in the bilateral carotid plaque cerebral infarction group was significantly higher than the unilateral carotid plaque cerebral infarction group and non-carotid plaque cerebral infarction group. This result suggested that the level of Lp-PLA2, SAA, and FIB was closely related to the formation of bilateral plaques in ACI patients. The higher the level, the more severe the formation of carotid atherosclerotic plaque in patients. Furthermore, we divided patients with different degrees of neurological impairment according to NIHSS into a mild-to-moderate group and a severe group. The level of Lp-PLA2 and SAA in the severe group was significantly higher than that in the mild-to-moderate group, which indicated that the level of Lp-PLA2 and SAA might also be related to the degree of neurological damage in patients with ACI. The higher the level, the more severe the neurological damage.

In summary, Lp-PLA2, SAA, and FIB were significantly elevated in the patients with acute cerebral infarction. The combined detection of Lp-PLA2 and SAA and FIB had high clinical value in the diagnosis of ACI, which could provide reference value for clinical applications. The level of Lp-PLA2, SAA, and FIB was associated with bilateral atherosclerotic plaque formation and the degree of neurological impairment in patients with ACI.

ACKNOWLEDGMENTS

Our study was supported by the Special Fund of Union Hospital of Tongji Medical College, Huazhong University of Science and Technology (No: 02.03.2018-130). Tao Liang designed the study, conducted the statistical analysis, and wrote the draft of the article. Shichuan Wang collected the data and conducted literature searches. Detai Zhang and Lihua Hu designed the study, wrote the protocol, and contributed to the final article. In addition, we were also grateful to the anonymous reviewers for giving valuable advice and comments in the review.

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How to cite this article: Tao L, ShiChuan W, DeTai Z, Lihua H. Evaluation of lipoprotein-associated phospholipase A2, serum amyloid A, and fibrinogen as diagnostic biomarkers for patients with acute cerebral infarction. J Clin Lab Anal. 2020;34:e23084. https://doi.org/10.1002/jcla.23084