Periodontitis as a risk indicator and predictor of poor outcome for lacunar infarct

Yago Leira[1,2]| Manuel Rodríguez-Yáñez[3]| Susana Arias[3]| Iria López-Dequidt|[3] Francisco Campos[3]| Tomás Sobrino[3]| Francesco D'Aiuto[2]| José Castillo[3]| Juan Blanco[1]

[1]Periodontology Unit, Faculty of Medicine and Odontology, Medical-Surgical Dentistry (OMEQUI) Research Group, Health Research Institute of Santiago de Compostela (IDIS), University of Santiago de Compostela, Santiago de Compostela, Spain

[2]Periodontology Unit, UCL Eastman Dental Institute and Hospital, University College London, London, UK

[3]Clinical Neurosciences Research Laboratory, Department of Neurology, Clinical University Hospital, Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain

Prof. José Castillo and Prof. Juan Blanco contributed equally as joint senior authors.

Correspondence

Yago Leira, Periodontology Unit, UCL Eastman Dental Institute and Hospital, University College London, London, UK. Email: y.leira@ucl.ac.uk

Funding information

This study was partially supported by grants from the Spanish Ministry of Economy and Competitiveness – Institute of Health Carlos III (PI13/02027 and PI15/01578), Spanish Research Network on Cerebrovascular Diseases RETICS-INVICTUS (RD12/0014), Xunta de Galicia (Consellería Educación GRC2014/027) and the European Union program FEDER. Y. Leira was supported by a fellowship from the Health Research Institute of Santiago de Compostela (IDIS). Currently, Y. Leira holds a Senior Clinical Research Fellowship supported by the UCL Biomedical Research Centre. Furthermore, F. Campos (CP14/00154) and T. Sobrino (CP12/03121-CPII17/00027) are recipients of a research contract from Miguel Servet Program of Institute of Health Carlos III. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Aim: To investigate the association between periodontitis (PD) and lacunar infarct (LI) as well as to analyse whether PD could be a predictor of poor functional prognosis in patients with LI. **Material and Methods**: Full-mouth periodontal examination was done in 120 cases (patients with LI) and 157 healthy controls. Demographic, clinical, medical and neurological information were collected from all of them. In addition, a measure of periodontal inflammation and disease activity, namely the periodontal inflamed surface area (PISA), was also calculated for each patient. Poor functional outcome was considered as a modified Rankin Scale >2 at 3 months. **Results**: PD was independently associated with the presence of LI (OR=3.3, $p < 0.001$). Poor outcome was observed in 31 patients with LI (25.8%), of which 90.3% had PD. A PISA value ≥727 mm^2 was an independent predictor of poor prognosis, after adjusting for clinical confounders (OR = 6.5, $p =$ 0.001). **Conclusions**: PD and LI were associated. Active moderate to severe PD predicted poor prognosis in patients with LI. Further evidence is warranted to confirm our re- sults and investigate potential mechanisms behind this association.

KEYWORDS

lacunar infarct, periodontal inflamed surface area, periodontitis, predictors, prognosis, stroke

Clinical Relevance

Scientific rationale for the study: Although PD has been associated with large vessel ischaemic stroke, little is known about the relationship between PD and LI as well as its prognosis.

Principal findings: PD is associated with the presence of LI and its poor functional outcome at 3 months.

Practical implications: Identifying conditions such as PD that could increase the risk of having LI as well as worsen- ing its prognosis may have significant therapeutic implica- tions in these patients.

1 | INTRODUCTION

Lacunar infarct (LI) is an ischaemic stroke within a small deep perforating artery that is attributable to a small infarct (<1.5 cm diameter) in the white matter, basal ganglia, pons or brainstem, and is consistent with a lacunar clinical syndrome (Wardlaw, Smith, & Dichgans, 2013). This type of cerebral small vessel disease (CSVD) is responsi- ble for almost 25% of the ischaemic strokes (Bamford, Sandercock, Jones, & Warlow, 1987). Although LI is considered to have a good prognosis (Petty et al., 2000), in one-third of the cases a certain grade of dependency could be seen as a result of a worse outcome (Blanco et al., 2006; Clavier, Hommel, Besson, Noèlle, & Perret, 1994; Samuelsson, Söderfeldt, & Olsson, 1996; Yokota, Minematsu, Hasegawa, & Yamaguchi, 2004). Hypertension, diabetes mellitus, age, silent infarcts (SIs) and leukoaraiosis (white matter hyperintensities) have been recognized as potential predictors for poor func- tional outcome (Blanco et al., 2006; De Jong, Kessels, & Lodder, 2002; Norrving, 2003; Samuelsson et al., 1996).

It has been shown that endothelial dysfunction is more conspicuous in LI patients compared to those with other manifestations of ischaemic stroke (Chen et al., 2006) and also compared to healthy controls and to subjects with similar vascular risk factors (Pretnar-Oblak, Sabovic, Pogacnik, Sebestjen, & Zaletel, 2006). In addition, there is an association between increased inflammatory response and early neurologic worsen in subjects with LI; thus, elevated serum levels of inflammatory mediators such as interleukin (IL)-6 or tumour necrosis factor (TNF)-α are related to poor functional prognosis (Blanco et al., 2006; Castellanos et al., 2002). Recently, evidence from a multicentre prospective study including 1,244 patients with LI showed that inflammatory markers for instance IL-6, C-reactive protein or TNF-α receptor 1 are associated with an increased risk of recurrent vascular events in these patients (Boehme et al., 2016; Elkind et al., 2014).

When periodontitis (PD) occurs, the inflamed and ulcerated subgingival pocket epithelium allows bacteria and their products (i.e., lipopolysaccharide [LPS]) to disseminate into the bloodstream (Geerts et al., 2002). These LPS along with bacterial antigens can trigger significant inflammatory processes. Based on this, white blood cells and acute phase reactants from hepatocytes or from endothelial cells may produce pro-inflammatory molecules. Furthermore, locally produced pro-inflammatory mediators (i.e., IL-6 or TNF-α) may spill into the systemic circulation and exert effects on distant organs such as brain

(Loos, 2005). Accordingly, PD could be regarded as a systemic inflammatory and endothelial vascular stressor.

Recently, a meta-analysis of observational studies showed that patients with PD had a 2.8-fold increased risk for developing large vessel ischaemic stroke (Leira et al., 2017). To date, however, little is known and with conflicting results about the relationship between PD and small vessel ischaemic stroke (i.e., LI) (Leira et al., 2016; Sen et al. 2018). On the other hand, ischaemic stroke patients with advanced PD had worse functional outcome at hospital discharge as well as greater neurological deficit compared to those without PD (Slowik et al., 2010).

Hence, the aim of the study was twofold. Firstly, to investigate the association between PD and its clinical parameters with the presence of LI. As a secondary objective, we sought to analyse whether PD could be a predictor of poor outcome in LI patients.

2 | MATERIALS AND METHODS

A case–control study was carried out by the Periodontology Unit of the University of Santiago de Compostela in collaboration with the Stroke Unit of the Clinical University Hospital of Santiago de Compostela by following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Von Elm et al., 2008). This research was performed in accordance with the Declaration of Helsinki of the World Medical Association (2008) and approved by the Ethics Committee of the Servizo Galego de Saúde (ID:2016/399). Informed consent was obtained from each patient or their relatives after full explanation of the procedures.

2.1 | Study population

Patients who had attended the Stroke Unit of the University Clinical Hospital of Santiago de Compostela between January 2014 and January 2015 were asked by telephone to participate in this study as cases. Cases were those with a diagnosis of LI based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (Adams et al., 1993) and they were included in the study if they fulfilled the following inclusion criteria: (a) >18 years of age; (b) at least 15 teeth (excluding third molars); and (c) written informed consent. Exclusion criteria were as follows: (a) patient who have received periodontal treatment in the previous 12 months; (b) history of neurovascular and/or neuroinflammatory disease; (c) systemic antibiotics, corticosteroids, and/or immunosuppressant therapy within 3 months

prior to periodontal assessment; and (d) chronic use of non-steroidal anti-inflammatory drugs.

Healthy control subjects, matched by age and gender, were selected from the hospital database. In order to include individuals without any neurological disorder, we reviewed 194 computed tomography/magnetic resonance imaging (CT/MRI) scans of subjects who were referred to the Department of Neurology with a suspicious diagnosis of non-confirmed neurological diseases such as non-specific headache, vestibular syndromes, brain tumours or altered level of consciousness between 2009 and 2013. Of these, 12 presented some subtype of asymptomatic CSVD (silent infarct [SI], $N = 4$; leukoaraiosis, $N = 8$) and, thus, were excluded from the study. Therefore, 182 subjects free from any neurological disease were contacted by telephone and asked to participate. Inclusion and exclusion criteria were the same as for the case group. Control individuals were clinically examined and interviewed in parallel with patient recruitment.

For both cases and controls, demographic and medical information were obtained by means of a questionnaire.

2.2 | Periodontal examination

The periodontal examination was performed by a single calibrated periodontist (YL). The calibration was completed before the start of the study in the Periodontology Unit of the Faculty of Odontology (University of Santiago de Compostela) using 10 non-study patients suffering from moderate or severe PD. Intra-examiner reliability was assessed by the intra-class correlation coefficients (for probing pocket depth [PPD], gingival recession [Rec] and clinical attachment level [CAL]), which were 0.79, 0.87 and 0.79, respectively, demonstrating a high degree of reliability in the measurements (Leira et al., 2016). In the present study, the following periodontal parameters were evaluated in all teeth (except 3o molars): (a) PPD, measured from the free gingival margin to the bottom of the sulcus or pocket; (b) CAL, measured from the cemento-enamel junction (CEJ) to the bottom of the sulcus or pocket; (c) Rec, measured as the distance from the free gingival margin to the exposed CEJ; (d) full-mouth plaque score (FMPS), defined as the number of sites with detectable supragingival dental plaque divided by the total number of sites per mouth, multiplied by 100 (O′Leary, Drake, & Naylor, 1972); (e) full- mouth bleeding score (FMBS), defined as the number of sites with gingival bleeding on probing (BoP) divided by

the total number of sites per mouth, multiplied by 100 (Ainamo & Bay, 1975); and (f) the number of missing teeth (excluding 3o molars).

All measurements were recorded at six sites per tooth (mesio-buccal, disto-buccal, mid-buccal, mesio-lingual, disto-lingual, and mid-lingual), except for FMPS (four sites/tooth) using a sterile mouth mirror and with a calibrated University of North Carolina periodontal probe (UNC 15; Hu-Friedy, Chicago, IL, USA).

The presence of PD was defined according to the Centers for Disease Control and Prevention (CDC)-American Academy of Periodontology (AAP) consensus for epidemiologic studies (Eke, Page, Wei, Thornton-Evans, & Genco, 2012; Holtfreter et al., 2015). Therefore, mild PD was defined as ≥2 interproximal sites with CAL ≥ 3 mm and ≥2 interproximal sites with PPD ≥ 4 mm (not on the same tooth) or 1 site with PPD ≥ 5 mm. Moderate PD was defined as ≥2 interproximal sites with CAL ≥ 4 mm (not on the same tooth) or ≥2 interproximal sites with PPD ≥ 5 mm, also not on the same tooth. Severe PD was defined as the presence of ≥2 interproximal sites with CAL ≥ 6 mm (not on the same tooth) and ≥1 interproximal site with PPD ≥ 5 mm. Total PD was the sum of mild, moderate, and severe PD.

In addition, a recently introduced measure of PD severity and activity, the periodontal inflamed surface area (PISA) was calculated (Nesse et al., 2008). PISA reflects the surface area of bleeding pocket epithelium in mm^2. PISA was calculated with a Microsoft Excel spreadsheet in the following steps: (a) Mean CAL and Rec for each particular tooth is calculated; (b) Linear mean CAL and Rec is translated into the periodontal epithelial surface area (PESA) for each specific tooth (Hujoel, White, García, & Listgarten, 2001). The PESA for a particular tooth consists of the root surface area of that tooth measured in mm^2, which is covered with pocket epithelium; (c) The PESA for a specific tooth is then multiplied by the proportion of sites around the tooth that was affected by BoP, resulting in the PISA for that particular tooth; and (d) The sum of all individual PISAs around individual tooth is calculated, rendering the full-mouth PISA value in mm^2 of each participant.

2.3 | Neurological examination

2.3.1 | Neuroimaging examination

A CT/MRI scan was carried out in all cases at admission. MRI images were obtained on a

1.5 T system (1.5 Magneton Symphony, Siemens, Erlangen, Germany), with echo planar capabilities of 25 mT/m gradients and 300–350 μs rise times. The MRI protocol included T_1-w (TR/TE: 370/7.7 ms), T_2-w (TR/TE: 6020/113 ms), DP-w (TR/TE: 6020/113 ms) and FLAIR (TR/TE: 9000/114 ms) (Rodríguez et al., 2010). One neuroradiologist who was blinded to the clinical data carried out the evaluation of CT/MRI. LI was diagnosed if the patient had one of the characteristic clinical lacunar syndromes, neurological deficit lasting >24 hr, no evidence of cerebral cortical dysfunction, and a CT/MRI that showed a deep focal infarction in an appropriate location with a diameter ≤15 mm. The presence of a LI in the baseline CT in which the topography does not correspond with the present clinical syndrome was considered a SI. For the purpose of this study, the thalamus was included, along with the caudate nucleus, putamen, and globus pallidus, as "basal ganglia." Leukoaraiosis was defined as ill-defined hyperintensities ≥5 mm on both T_2 and FLAIR MRI images without prominent hypointensities on T_1-w MRI scans and as ill-defined and moderately hypodense areas of ≥5 mm on CT. Leukoaraiosis was classified according to the Fazekas criteria (Fazekas et al., 1991, 1993) using the modified Fazekas scale (Pantoni et al., 2002). This method yields two separate scores for subcortical and deep white matter lesions and periventricular lesions. The four-point Fazekas scale of increasing severity was used to classify each score. For the purpose of the study, the presence of leukoaraiosis was categorized with 0 indicating a patient without leukoaraiosis and 1 with leukoaraiosis.

2.3.2 | Ultrasound examination

The same explorer (SA), blinded to clinical data, performed the ultrasonographic study using high-resolution B-mode ultrasound (Aplio 50 [Toshiba aplio 50, MCM1754TSA, Rome, Italy] Toshiba SSA-700 [Toshiba Medical Systems Corporation, Otawara-SHI, Japan]) with a 7.5 MHz, linear-array transducer (Linear array transducer PLT- 704AT, Toshiba, Tochigi, Japan; Phased array transducer PST-20CT, Toshiba, Tochigi, Japan) (Rodríguez et al., 2010). In brief, the image was focused on the posterior (far) wall of the left carotid artery. A minimum of four measurements of the common carotid far wall was taken 10 mm proximal to the bifurcation, to derive the mean carotid intima-media thickness (IMT) (Raitakari et al., 2003). The presence of an atheroma plaque was evaluated in the common and internal carotid extracraneal arteries as well as the bifurcations according to standardized scanning and reading protocols (Touboul et al., 2007). Plaque was defined as a

focal structure that encroaches into the arterial lumen at least 0.5 mm or 50% of the surrounding IMT value, or demonstrates a thickness >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface. For the purpose of the study, the presence of carotid atheromatosis was categorized with 0 indicating a patient without carotid atheromatosis and 1 with it.

2.3.3 | Outcome evaluation

Functional outcome was evaluated at 3 months using the modified Rankin scale (mRS) (UK-TIA Study Group, 1988; Van Swieten, Koudstaal, Visser, Schouten, & van Gijn, 1988), and a poor outcome was defined as a mRS score >2.

2.4 | Statistical analysis

The sample size calculation was performed using the Macro !NSize for PASW Statistics (http://www.metodo.uab.cat/macros.htm.). Based on a pilot study carried out by our group, to detect an expected odds ratio (OR) of 4.20 in the association between PD and LI (Leira et al., 2016), assuming α-risk = 0.05 and β-risk = 0.10, a sample of 240 subjects was calculated (120 cases and 120 controls, 1:1 case:control).

All data analyses were performed with IBM SPSS Statistics 20.0 software for Mac (SPSS Inc., Chicago, IL, USA). Continuous normally distributed variables analysed with Kolmogorov–Smirnov test were reported as mean ± standard deviation, whereas categorical variables were expressed as percentages. Differences between two groups were assessed by independent *t* test (continuous normally distributed variables) and χ^2 test (categorical variables). Non- normally distributed variables were showed as median (interquartile range) and compared using Mann–Whitney *U* test.

Conditional logistic regression models were performed to test potential associations between PD and its clinical parameters and LI presence. Binary logistic regression analysis was done to investigate the relationship between periodontal parameters and poor prognosis. The model selection procedure selected was stepwise regression with bidirectional elimination that is a combination of forward selection and backward elimination. The criterion chosen for selection was the Akaike information criterion (AIC), so the model with the lower AIC was selected as the best in order to avoid collinearity effects (Leira et al., 2016). The selection procedure was replicated using the Bayesian information criterion and the covariates selected with the AIC.

To identify the best discriminant cut-off point of the mean PISA to identify poor outcome in patients with LI, a receiver operating characteristic (ROC) analysis was carried out.

All tests were performed at a significance level of $\alpha = 0.05$.

3 | RESULTS

A total of 321 adults were asked to participate in this study. This population included 139 patients diagnosed with LI and 182 healthy controls. Of these, 19 cases and 25 controls were excluded leading to a final study sample of 120 cases and 157 controls.

3.1 | Study groups—baseline characteristics

The number of patients with a history of hypertension, diabetes mellitus, hypercholesterolaemia, ischaemic heart disease, and peripheral arterial disease was significantly higher in cases than controls. As expected, patients with LI were taking significantly more medication than healthy controls (i.e., statins, antiaggregants, and antihypertensives (Table 1).

3.2 | Study groups—PD

LI cases and controls differed significantly in all periodontal parameters examined, including both cumulative measures of past PD (i.e., CAL), as well as measures of current periodontal inflammatory activity (i.e., FMBS, PPD, and PISA) (Table 1). According to this, PD was present in 85 of 120 patients with LI (70.8%) and in 51 of 157 control subjects (30.8%) (Figure 1a). Regarding PD severity, almost half of the periodontal patients with LI had severe PD compared to 7.8% in the control group (Figure 1b). No differences were found between groups with regard to dental variables (Table 1).

Patients with LI who had PD showed significantly higher prevalence of leukoaraiosis and carotid atheromatosis than those without PD. Poor functional outcome at 3 months was found in 32.9% of LI patients with PD in comparison to 8.6% without PD ($p = 0.006$) (Table 2).

3.3 | Association between PD and its clinical parameters and the presence of LI

After adjusting for age, gender, hypertension, diabetes mellitus, hypercholesterolaemia, ischaemic heart disease, smoking, and statins consumption in multiple logistic regression, among patients with PD, the odds for having LI was 3.3 (95% CI: 1.7–6.4) compared to those without PD. Likewise, severe PD was strongly associated with the presence of LI (OR = 9.8, 95% CI: 2.4–38.9; $p < 0.001$), independently of the same confounding factors.

After adjusting for the most relevant clinical periodontal parameters, only PISA was mildly associated with LI (OR = 1.1, 95% CI: 1.0–1.1; $p < 0.001$).

3.4 | Study groups based on prognosis—baseline characteristics

Within the 120 LI patients studied, 31 (25.8%) had a poor outcome at 3 months. Patients with poor outcome were significantly older and more likely to have a history of hypertension and diabetes mellitus. Accordingly, significantly more individuals in the poor outcome group were under hypertensive medication. Leukoaraiosis was present in 19 of 89 good outcome patients (21.3%) and in 16 of 31 patients with poor outcome (51.6%) ($p = 0.001$). Furthermore, SIs were detected in more than half of the poor outcome subjects (54.8%) compared to 33.7% in the good outcome group ($p = 0.038$). No differences were observed between poor and good prognosis groups in relation to both demographic and vascular risk variables as well as LI location (Table 2).

3.5 | Study groups based on prognosis—PD

The prevalence of PD in poor outcome subjects was significantly higher than those from the good outcome (90.3% versus 64.0%, $p = 0.006$) (Figure 2a). There was an about 1.7-fold increase in the percentage of patients with poor outcome who suffered from severe PD compared with good outcome individuals (64.3% versus 38.6, $p = 0.039$) (Figure 2b).

Clinical periodontal parameters of current disease activity (i.e., FMBS, PPD, and PISA) were significantly elevated in patients with poor prognosis in comparison to good prognosis patients, whereas the main indicator of prolonged exposure to PD (i.e., CAL) did not differ between groups (Table 3).

3.6 | Association between periodontal clinical parameters and poor outcome in patients with LI

After adjusting for age, gender, hypertension, leukoaraiosis, SIs, FMBS, and mean PPD, PISA (OR = 1.1, 95% CI: 1.0–1.1, $p = 0.016$) and diabetes mellitus (OR = 2.8, 95% CI: 1.0–7.9, $p = 0.049$) were the only predictors significantly associated with poor outcome in patients with LI.

ROC analysis showed an area under the curve of 0.7 (95% CI: 0.6–0.8, $p < 0.001$), which suggests that a value ≥ 727 mm^2 predicted PISA association with poor outcome, with a sensitivity of 71% and a specificity of 70%. Therefore, after categorizing PISA (<727 mm^2 and ≥ 727 mm^2), this indicator of current PD activity (OR = 6.5, 95% CI: 2.0–20.7, $p =$

0.001) along with a previous history of diabetes (OR = 3.4, 95% CI: 1.1–10.3, $p = 0.029$) still reached statistical significance independently of aforementioned clinical variables.

4 | DISCUSSION

In our study, we found that PD was very common and was present in almost three-quarters of our patients with LI. Furthermore, we showed that periodontal inflammation measured by the PISA method was associated with poor prognosis in patients diagnosed with LI. Indeed, a PISA value ≥727 mm^2 (moderate to severe periodontal cases) (Leira, Martín-Lancharro, & Blanco, 2018) was an independent powerful predictor of poor outcome at 3 months.

The prevalence of PD in our LI group (70.8%) was more than double compared to our control group without any neurological disorder (30.8%) (Leira et al., 2016) and, accordingly was almost two times what is common in the Spanish employed population (38.4%) (Carasol, 2016). In the present study, we found a positive association between PD and the LI, independent of other well-known vascular risk factors. Similarly to previous data, history of hypertension and diabetes mellitus was more common in LI patients than controls (Bezerra, 2012). Our results are in contrast with recent findings, where PD was associated with both incident atherothrombotic and cardioembolic stroke but not with LI (Sen, 2018). There are several possible factors attributable to this difference such as PD case definition, lack of medication adjustment in regression models as well as the limited number of incident cases of LI ($n = 61$).

Because PISA reflects the amount of periodontal inflamed tissue, it is believed to be an accurate method to assess both infectious and inflammatory burden posed by PD (Leira et al., 2018; Nesse et al., 2008). In fact, in our LI patients, the mean estimated surface area of the periodontal ulcerated epithelium was 10.4 cm^2 compared to 1.9 cm^2 corresponding to the control group. Such a wound surface must be regarded as significant. It is speculated that the inflamed and ulcerated subgingival pocket epithelium forms an easy port of entry for periodontal bacteria either producing bacteremias or endotoxemias (Loos, 2005). In accordance, our analysis provided evidence of a positive association between PISA and LI. A previous study demonstrated that PPD was increased in LI, but failed to demonstrate a relationship between clinical periodontal parameters and the presence of LI (Taguchi et al. 2013). Similarly, although our patients with LI showed worse periodontal conditions in

terms of past (i.e., CAL) and current PD (i.e., FMBS and PPD), none of them were significantly associated with a higher risk of LI.

In general, LIs have a good prognosis, as mortality is low and functional recovery is usually good (Fisher, 1982; Petty et al., 2000). Nevertheless, in one-third of patients suffering from LIs a certain grade of dependency could be seen as a result of a worse outcome (Blanco et al., 2006; Clavier et al., 1994; Samuelsson et al., 1996; Yokota et al., 2004). Similarly to previous reports, in the present study, 31 out of 120 patients with LI (25.8%) had a poor functional outcome at 3 months (Blanco et al., 2006; Clavier et al., 1994; Petty et al., 2000; Roquer, Campello, & Gomis, 2004; Samuelsson et al., 1996; Yokota et al., 2004). Ageing, diabetes mellitus, hypertension, leukoaraiosis, and SIs on CT at admission have been recognized as potential predictors for poor prognosis (Blanco et al., 2006; De Jong et al., 2002; Norrving, 2003; Samuelsson et al., 1996). In our sample, we found that patients with poor outcome were older and more likely to have a previous history of hypertension and diabetes mellitus. The prevalence of leukoaraiosis and SIs was also significantly higher in the poor outcome group compared to the good outcome group.

PD was more frequent in LI patients with poor prognosis than the subjects of the good outcome group. While clinical periodontal parameters of current disease activity (i.e., FMBS, PPD, and PISA) were significantly elevated in poor outcome patients, the main indicator of prolonged exposure to PD (i.e., CAL) did not show statistical differences between the two groups. Importantly, our findings show that periodontal inflammation measured by the PISA method was significantly associated with poor outcome at 3 months. When PISA was categorized, a value $\geq$727 mm^2 (moderate to severe periodontal cases) (Leira et al., 2018) showed to be an independent powerful predictor of poor outcome. Nevertheless, history of diabetes mellitus also seems to predict poor functional prognosis in our LI patients. A previous study that included 169 ischaemic stroke patients showed that patients with advanced PD had greater neurological deficit on admission as well as poor functional outcome at 3 months compared to those without PD (Slowik et al., 2010). In PD, it appears that the host overreacts to infectious stimuli by releasing increased amount of inflammatory molecules (i.e., IL-6 and TNF-α) that may be disseminate to systemic circulation (Loos, 2000; Loos, 2005), which may contribute to pathogenesis of cerebral ischaemia by accelerating brain atheroma plaques progression as well as promoting

endothelial dysfunction (Leira, Blanco, Blanco, & Castillo, 2015). Furthermore, it is suggested that systemic inflammation may be involved in early neurological deterioration in LI patients (Blanco et al., 2006; Castellanos et al., 2002).

We have to be cautious when interpreting the results of the present study due to the low number of patients with poor functional outcome (n = 31). Nevertheless, previous reports (Blanco et al., 2006; Clavier et al., 1994; Petty et al., 2000; Roquer et al., 2004; Samuelsson et al., 1996; Yokota et al., 2004) showed that between 18%–42% of LI patients presented poor functional outcome at 3 months. Accordingly, we observed worse prognosis in 25.8% of these patients, which was between the ranges proposed in the literature. It is worth mentioning that diabetes was also a predictor of poor outcome in our analysis. Due to diabetes is linked with both PD and LI, we cannot rule out the possible synergistic effect of diabetes and PD or vice versa that could lead to a hyperinflammatory state increasing the risk for poor prognosis in LI. On the other hand, the PISA method has several limitations. The formulas that transform CAL and Rec into surface area are based on mean values of both root surface area and root lengths, therefore, leading to bias when PISA is calculated (Nesse et al., 2008).

Patients with gingival overgrowth due to antihypertensives may also influence PISA calculation, resulting in an underestimation of true PESA and thereby underestimate true PISA because the gingival margin is located above the CEJ (Nesse et al., 2008). The use of either antiaggregants or statins may also influence PISA values because of either increased or reduced gingival bleeding, respectively. Smoking produces vasoconstriction leading to reduction in BoP and PISA values. In our study, however, we recorded the use of all these medications and were included in our analysis to avoid bias. Despite all these shortcomings, PISA is considered to be a useful tool in periodontal medicine research because reflects the amount of periodontal inflamed tissue and, thus, can accurately measure the infectious and inflammatory burden posed by PD (Leira et al., 2018). Another important limitation of the present study is the lack of inclusion in our analysis of some potentially relevant confounders such as socioeconomic status (i.e., monthly or annually income, employment status or marital status), medical and dental compliance. Nevertheless, in our study education level that is considered as part of the socioeconomic status of the participants did not differ between cases and controls. Furthermore, the last dental visit of

each participant could be considered as a surrogate marker of dental compliance. In the present analysis, 40.8% of patients with stroke went less than once a year compared to 32.5% of controls, but this difference was not significant.

In conclusion, PD was positively and independently associated with the presence of LI. Moderate to severe active PD (i.e., PISA $\geq$ 727 mm^2) was an independent predictor of poor functional outcome at 3 months in patients with LI. However, further data from studies with a large sample size are warranted to explore if this association is causal as well as potential biological mechanisms underlying this relationship. Studies with a high number of LI patients with poor outcome are needed to confirm our results. In addition, future interventional trials might address the question of whether periodontal therapy could have any prognostic implications in these patients.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

REFERENCES

Adams, H. P. Jr, Bendixen, B. H., Kappelle, L. J., Biller, J., Love, B. B., Gordon, D. L., & Marsh, E. E. 3rd (1993). Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*, *24*, 35–41. https://doi.org/10.1161/01.STR.24.1.35

Ainamo, J., & Bay, I. (1975). Problems and proposals for recording gingivitis and plaque. *International Dental Journal*, *25*, 229–235.

Bamford, J., Sandercock, P., Jones, L., & Warlow, C. (1987). The natural history of lacunar infarction: The Oxfordshire Community Stroke Project. *Stroke*, *18*, 545–551. https://doi.org/10.1161/ STR.18.3.545

Bezerra, D. C., Sharrett, A. R., Matsushita, K., Gottesman, R. F., Shibata, D., Mosley, T. H. Jr, Coresh, J., Szklo, M., Carvarlho, M. S., & Selvin, E. (2012). Risk factors for lacune subtypes in the Atherosclerosis Risk in Communities (ARIC) Study. *Neurology*, *78*, 102–108. https://doi. org/10.1212/WNL.0b013e31823efc42.

Blanco, M., Castellanos, M., Rodríguez-Yáñez, M., Sobrino, T., Leira, R., Vivancos, J., ... Castillo, J. (2006). High blood pressure and inflammation are associated with poor prognosis in lacunar infarctions. *Cerebrovascular Diseases*, *22*, 123–129. https://doi. org/10.1159/000093240

Boehme, A. K., McClure, L. A., Zhang, Y., Luna, J. M., Del Brutto, O. H., Benavente, O. R., & Elkind, M. S. (2016). Inflammatory markers and outcomes after lacunar stroke: Levels of inflammatory markers in treatment of stroke. *Stroke*, *47*, 659–667. https://doi.org/10.1161/ STROKEAHA.115.012166

Carasol, M., Llodra, J. C., Fernández-Meseguer, A., Bravo, M., García- Margallo, M. T., Calvo-Bonacho, E., Sanz, M., & Herrera, D. (2016). Periodontal conditions among employed adults in Spain. *Journal of Clinical Periodontology*, *43*, 448–556. https://doi.org/10.1111/ jcpe.12558.

Castellanos, M., Castillo, J., García, M. M., Leira, R., Serena, J., Chamorro, A., & Dávalos, A. (2002). Inflammation-mediated damage in progressing lacunar infarctions: A potential therapeutic target. *Stroke*, *33*, 982–987. https://doi.org/10.1161/hs0402.105339

Chen, P. L., Wang, P. Y., Sheu, W. H., Chen, Y. T., Ho, Y. P., Hu, H. H., & Hsu, H. Y. (2006). Changes of brachial flow-mediated vasodilation in different ischemic stroke

subtypes. *Neurology*, *67*, 1056–1058. https://doi.org/10.1212/01.wnl.0000237526.32692.67

Clavier, I., Hommel, M., Besson, G., Noèlle, B., & Perret, J. E. (1994). Long-term prognosis of symptomatic lacunar infarcts. A hospital- based study. *Stroke*, *25*, 2005–2009. https://doi.org/10.1161/01. STR.25.10.2005

De Jong, G., Kessels, F., & Lodder, J. (2002). Two types of lacunar infarcts: Further arguments from a study on prognosis. *Stroke*, *33*, 2072–2076. https://doi.org/10.1161/01.STR.0000022807.06923.A3

Eke, P. I., Page, R. C., Wei, L., Thornton-Evans, G., & Genco, R. J. (2012). Update of the case definitions for population-based surveillance of periodontitis. *Journal of Periodontology*, *83*, 1449–1454. https://doi. org/10.1902/jop.2012.110664

Elkind, M. S., Luna, J. M., Mc Clure, L. A., Zhang, Y., Coffey, C. S., Roldan, A., ... LIMITS Investigators (2014). C-reactive protein as a prognostic marker after lacunar stroke: Levels of inflammatory markers in the treatment of stroke study. *Stroke*, *45*, 707–716. https://doi.org/10.11 617STROKEAHA.113.004562

Fazekas, F., Kleinert, R., Offenbacher, H., Payer, F., Schmidt, R., Kleinert, G., ... Lechner, H. (1991). The morphologic correlate of incidental punctate white matter hyperintensities on MR images. *American Journal of Neuroradiology*, *12*, 915–921.

Fazekas, F., Kleinert, R., Offenbacher, H., Schmidt, R., Kleinert, G., Payer, F., ... Lechner, H. (1993). Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology*, *43*, 1683–1689. https:// doi.org/10.1212/WNL.43.9.1683

Fisher, C. M. (1982). Lacunar strokes and infarcts: A review. *Neurology*, *32*, 871–876. https://doi.org/10.1212/WNL.32.8.871

Geerts, S. O., Nys, M., De, M. P., Charpentier, J., Albert, A., Legrand, V., & Rompen, E. H. (2002). Systemic release of endotoxins induced by gentle mastication: Association with periodontitis severity. *Journal of Periodontology*, *73*, 73–78. https://doi.org/10.1902/jop.2002.73.1.73

Holtfreter, B., Albandar, J. M., Dietrich, T., Dye, B. A., Eaton, K. A., Eke, P. I., ... Joint EU/USA Periodontal Epidemiology Working Group. (2015). Standards for reporting chronic periodontitis prevalence and severity in epidemiologic studies: Proposed standards from de Joint EU/ USA Periodontal Epidemiology Working Group. *Journal of Clinical Periodontology*, *42*, 407–412. https://doi.org/10.1111/jcpe.12392

Hujoel, P. P., White, B. A., García, R. I., & Listgarten, M. A. (2001). The dentogingival epithelial surface area revisited. *Journal of Periodontal Research*, *36*, 48–55. https://doi. org/10.1034/j.1600-0765.2001.00011.x

Leira, Y., Blanco, M., Blanco, J., & Castillo, J. (2015). Association between periodontal disease and cerebrovascular disease. A review of the lit- erature. *Revista de Neurología*, *61*, 29–38.

Leira, Y., López-Dequidt, I., Arias, S., Rodríguez-Yáñez, M., Leira, R., Sobrino, T., ... Castillo, J. (2016). Chronic periodontitis is associated with lacunar infarct: A case-control study. *European Journal of Neurology*, *23*, 1572–1579. https://doi.org/10.1111/ene.13080

Leira, Y., Martín-Lancharro, P., & Blanco, J. (2018). Periodontal inflamed surface area and periodontal case definition classification. *Acta Odontologica Scandinavica*, *76*, 195–198. https://doi.org/10.1080/00 016357.2017.1401659

Leira, Y., Seoane, J., Blanco, M., Rodríguez-Yáñez, M., Takkouche, B., Blanco, J., & Castillo, J. (2017). Association between periodontitis and ischemic stroke: A systematic review and meta-analysis. *European Journal of Epidemiology*, *32*, 43–53. https://doi.org/10.1007/ s10654-016-0170-6

Loos, B. G. (2005). Systemic markers of inflammation in periodontitis. *Journal of Periodontology*, *76*(11 Suppl), 2106S–2115S. https://doi. org/10.1902/jop.2005.76.11-S.2016

Loos, B. G., Craandijk, J., Hoek, F. J., Wertheim-van Dillen, P. M., & van der Velden, U. (2000). Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. *Journal of Periodontology*, *71*, 1528–1534. https://doi.org/10.1902/ jop.2000.71.10.1528.

Nesse, W., Abbas, F., van der Ploeg, I., Spijkervet, F. K., Dijkstra, P. U., & Vissink, A. (2008). Periodontal inflamed surface area: Quantifying inflammatory burden. *Journal of Clinical Periodontology*, *35*, 668–673. https://doi.org/10.1111/j.1600-051X.2008.01249.x

Norrving, B. (2003). Long-term prognosis after lacunar infarction. *The Lancet Neurology*, *2*, 238–245. https://doi.org/10.1016/ S1474-4422(03)00352-1

O′Leary, T. J., Drake, R. B., & Naylor, J. E. (1972). The plaque control record. *Journal of Periodontology*, *43*, 38. https://doi.org/10.1902/ jop.1972.43.1.38

Pantoni, L., Simoni, M., Pracucci, G., Schmidt, R., Barkhof, F., Inzitari, D., & for the

European Task Force on Age-Related White Matter Changes. (2002). Visual rating scales for age-related white matter changes (leukoaraiosis): Can heterogeneity be reduced? *Stroke*, *33*, 2827–2833. doi:10.1161.STR.0000038424.70926.5E. https://doi. org/10.1161/01.STR.0000038424.70926.5E

Petty, G. W., Brown, R. D. Jr, Whisnant, J. P., Sicks, J. D., O'Fallon, W. M., & Wiebers, D. O. (2000). Ischemic stroke subtypes: A population-based study of functional outcome, survival, and recurrence. *Stroke*, *31*, 1062–1068. https://doi.org/10.1161/01. STR.31.5.1062

Pretnar-Oblak, J., Sabovic, M., Pogacnik, T., Sebestjen, M., & Zaletel, M. (2006). Flow-mediated dilatation and intima-media thickness in patients with lacunar infarctions. *Acta Neurologica Scandinavica*, *113*, 273–277. https://doi.org/10.1111/j.1600-0404.2006.00578.x

Raitakari, O. T., Juonala, M., Kähönen, M., Taittonen, L., Laitinen, T., Mäki-Torkko, N., ... Viikari, J. S. (2003). Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: The Cardiovascular Risk in Young Finns Study. *Journal of the American Medical Association*, *290*, 2277–2283. https://doi.org/10.1001/ jama.290.17.2277

Rodríguez, I., Lema, I., Blanco, M., Rodríguez-Yáñez, M., Leira, R., & Castillo, J. (2010). Vascular retinal, neuroimaging and ultrasonographic markers of lacunar infarcts. *International Journal of Stroke*, *5*, 360–366. https://doi.org/10.1111/j.1747-4949.2010.00462.x

Roquer, J., Campello, A. R., & Gomis, M. (2004). Association of lacunar infarcts with small artery and large artery disease: A comparative study. *Acta Neurologica Scandinavica*, *110*, 350–354. https://doi. org/10.1111/j.1600-0404.2004.00336.x

Samuelsson, M., Söderfeldt, B., & Olsson, G. B. (1996). Functional outcome in patients with lacunar infarction. *Stroke*, *27*, 842–846. https:// doi.org/10.1161/01.STR.27.5.842

Sen, S., Giamberardino, L. D., Moss, K., Morelli, T., Rosamond, W. D., Gottesman, R. F., Beck, J., & Offenbacher, S. (2018). Periodontal disease, regular dental care use, and incident ischemic stroke. *Stroke*, *49*, 355–362. https://doi.org/10.1161/STROKEAHA.117.018990.

Slowik, J., Wnuk, M. A., Grzech, K., Golenia, A., Turaj, W., Ferens, A., ... Slowik, A. (2010). Periodontitis affects neurological deficit in acute stroke. *Journal of the*

Neurological Sciences, *297*, 82–84. https://doi. org/10.1016/j.jns.2010.07.012

Taguchi, A., Miki, M., Muto, A., Kubokawa, K., Migita, K., Higashi, Y., & Yoshinara, N. (2013). Association between oral health and the risk of lacunar infarction in Japanese adults. *Gerodontology*, *59*, 499–506. https://doi.org/10.1159/000353707.

Touboul, P. J., Hennerici, M. G., Meairs, S., Adams, H., Amarenco, P., Bornstein, N., ... Zureik, M. (2007). Mannheim carotid intima-media thickness consensus (2004–2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovascular Diseases*, *23*, 75–80. https://doi.org/10.1159/00007034

UK-TIA Study Group. (1988). United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: Interim results. *British Medical Journal (Clinical Research Edition)*, *296*, 316–320.

Van Swieten, J. C., Koudstaal, P. J., Visser, M. C., Schouten, H. K., & van Gijn, J. (1988). Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*, *19*, 604–607. https://doi. org/10.1161/01.STR.19.5.604

Von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., Vandenbroucke, J. P., & STROBE Initiative (2008). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Journal of Clinical Epidemiology*, *61*, 344–349. https://doi.org/10.1016/j. jclinepi.2007.11.008

Wardlaw, J. M., Smith, C., & Dichgans, M. (2013). Mechanisms of sporadic cerebral small vessel disease: Insights from neuroimaging. *The Lancet Neurology*, *12*, 483–497. https://doi.org/10.1016/ S1474-4422(13)70060-7

Yokota, C., Minematsu, K., Hasegawa, Y., & Yamaguchi, T. (2004). Long- term prognosis, by stroke subtypes, after a first-ever stroke: A hospital-based study over 20-year period. *Cerebrovascular Diseases*, *18*, 111–116. https://doi.org/10.1159/000079258

Table 1. Baseline characteristics.

VARIABLES	Cases (n=120)	Controls (n=157)	*P*-value
Age (years)	66.4±9.9	65.4±9.9	0.391
Males, n (%)	82 (68.3)	108 (68.8)	0.935
BMI	26.9±3.4	26.7±4.7	0.726
Hypertension, n (%)	74 (61.7)	44 (28.0)	<0.001
Diabetes mellitus, n (%)	33 (27.5)	13 (8.3)	<0.001
Hypercholesterolemia, n (%)	55 (45.8)	28 (17.8)	<0.001
Ischemic heart disease, n (%)	22 (18.3)	4 (2.5)	<0.001
Peripheral arterial disease, n (%)	5 (4.2)	0 (0.0)	0.010
Smoking habit			0.075
-Never smoker, n (%)	82 (68.3)	126 (80.3)	
-Former smoker, n (%)	16 (13.3)	13 (8.3)	
-Current smoker, n (%)	22 (18.3)	18 (11.5)	
Alcohol consumption, n (%)	21 (17.5)	17 (10.9)	0.172
Medication			
-Statins, n (%)	56 (46.7)	28 (17.8)	<0.001
-Antiaggregants, n (%)	46 (38.3)	4 (2.5)	<0.001
-Antihypertensives, n (%)	70 (58.3)	44 (28.0)	<0.001
Education level			0.869
-High, n (%)	30 (25.0)	36 (22.9)	
-Medium, n (%)	52 (43.3)	67 (42.7)	
-Low, n (%)	38 (31.7)	54 (34.4)	
FMPS (%)	54.8±17.5	27.0±12.0	<0.001
FMBS (%)	59.4±18.2	28.3±13.6	<0.001
PPD measures			
-Mean PPD (mm)	3.6±1.0	2.6±0.6	<0.001
-Number of sites/mouth PPD ≥4 mm	75.8±51.2	17.8±32.2	
-Number of sites/mouth PPD ≥6 mm	18.1±25.3	1.8±9.4	<0.001
Rec (mm)	0.6±0.4	0.3±0.3	<0.001
CAL measures			
-Mean CAL (mm)	4.3±1.4	2.9±0.9	<0.001
-Number of sites/mouth CAL ≥3 mm	116.3±39.4	109.6±40.0	0.169
-Number of sites/mouth CAL ≥5 mm	63.7±50.1	17.7±30.8	<0.001
Number of present teeth	20.0±3.7	24.6±2.6	<0.001
PISA (mm^2)	1040.4±1145.8	193.2±357.1	<0.001
Last dental visit			0.152
-Within the last 12 months, n (%)	71 (59.2)	106 (67.5)	
-Less often, n (%)	49 (40.8)	51 (32.5)	
Tooth brush frequency			0.370
-<2 times/day	44 (36.7)	49 (31.2)	
-≥2 times7day	76 (63.3)	108 (68.8)	
Use of interdental care devices, n (%)	9 (7.5)	17 (10.8)	0.409

BMI: body mass index; FMPS: full-mouth plaque score; FMBS: full-mouth bleeding score; PPD: probing pocket depth; Rec: gingival recession; CAL: clinical attachment level; PISA: periodontal inflamed surface area.

Table 2. Characteristics of LI patients according to periodontal status.

VARIABLES	PD (n=85)	No PD (n=35)	*P*-value
Age (years)	67.5±10.0	63.8±9.5	0.061
Males, n (%)	60 (70.6)	22 (62.9)	0.408
BMI	26.9±3.7	27.1±2.3	0.734
Hypertension, n (%)	53 (62.4)	21 (60.0)	0.810
Diabetes mellitus, n (%)	24 (28.2)	9 (25.7)	0.779
Hypercholesterolemia, n (%)	36 (42.4)	19 (54.3)	0.233
Ischemic heart disease, n (%)	16 (18.8)	6 (17.1)	0.829
Peripheral arterial disease, n (%)	4 (4.7)	1 (2.9)	0.645
Smoking habit			0.900
-Never smoker, n (%)	58 (68.2)	24 (68.6)	
-Former smoker, n (%)	12 (14.1)	4 (11.4)	
-Current smoker, n (%)	15 (17.6)	7 (20.0)	
Alcohol consumption, n (%)	18 (21.1)	3 (8.6)	0.201
Medication			
-Statins, n (%)	36 (42.4)	20 (57.1)	0.140
-Antiaggregants, n (%)	30 (35.3)	16 (45.7)	0.286
-Antihypertensives, n (%)	49 (57.6)	21 (60.0)	0.812
Education level			0.894
-High, n (%)	21 (24.7)	9 (25.7)	
-Medium, n (%)	36 (42.4)	16 (45.7)	
-Low, n (%)	28 (32.9)	10 (28.6)	
Leukoaraiosis, n (%)	32 (37.6)	3 (8.6)	0.001
Carotid atheromatosis, n (%)	42 (49.4)	10 (28.6)	0.036
SIs, n (%)	36 (42.4)	11 (31.4)	0.265
mRS at admission	0.5±0.6	0.8±1.0	0.132
mRS at 3 months	1.6±1.2	1.0±0.9	0.007
Poor prognosis (mRS > 2), n (%)	28 (32.9)	3 (8.6)	0.006
LI location			0.799
-Hemispheric, n (%)	31 (36.5)	14 (40.0)	
-Basal ganglia, n (%)	43 (50.6)	18 (51.4)	
-Brainstem, n (%)	9 (10.6)	3 (8.6)	
-Other locations, n (%)	2 (2.4)	0 (0.0)	

PD: periodontitis; BMI: body mass index; SI: silent infarct; mRS: modified Rankin Scale; LI: lacunar infarct.

Table 3. Baseline characteristics of LI patients according to functional outcome at 3 months.

VARIABLES	Good outcome (n=89)	Poor outcome (n=31)	*p*-value
Age (years)	65.5±10.6	69.1±7.3	0.043
Males, n (%)	65 (73.0)	17 (54.8)	0.061
BMI	27.4 [24.9-29.4]	27.0 [24.4-29.4]	0.854
Hypertension, n (%)	49 (55.1)	25 (80.6)	0.012
Diabetes mellitus, n (%)	19 (21.3)	14 (45.2)	0.011
Hypercholesterolemia, n (%)	38 (42.7)	17 (54.8)	0.243
Ischemic heart disease, n (%)	18 (20.2)	4 (12.9)	0.364
Peripheral arterial disease, n (%)	5 (5.6)	0 (0.0)	0.178
Smoking habit			0.641
-Never smoker, n (%)	59 (66.3)	23 (74.2)	
-Former smoker, n (%)	12 (13.5)	4 (12.9)	
-Current smoker, n (%)	18 (20.2)	4 (12.9)	
Alcohol consumption, n (%)	18 (20.2)	3 (9.7)	0.396
Medication			
-Statins, n (%)	38 (42.7)	18 (58.1)	0.140
-Antiaggregants, n (%)	33 (37.1)	13 (41.9)	0.632
-Antihypertensives, n (%)	46 (51.7)	24 (77.4)	0.012
Education level			0.477
-High, n (%)	20 (22.5)	10 (32.3)	
-Medium, n (%)	41 (46.1)	11 (35.5)	
-Low, n (%)	28 (31.5)	10 (32.3)	
Leukoaraiosis, n (%)	19 (21.3)	16 (51.6)	0.001
Carotid atheromatosis, n (%)	39 (43.8)	13 (41.9)	0.855
SIs, n (%)	30 (33.7)	17 (54.8)	0.038
LI location			0.878
-Hemispheric, n (%)	33 (37.1)	12 (38.7)	
-Basal ganglia, n (%)	46 (51.7)	15 (48.4)	
-Brainstem, n (%)	9 (10.1)	3 (9.7)	
-Other locations, n (%)	1 (1.1)	1 (3.2)	
FMPS (%)	54.7±17.0	54.9±19.3	0.951
FMBS (%)	57.5±19.0	65.1±14.7	0.026
PPD measures			
-Mean PPD (mm)	3.5±1.0	3.9±1.0	0.046
-Number of sites/mouth PPD ≥4 mm	69.6±49.1	93.7±53.6	0.023
-Number of sites/mouth PPD ≥6 mm	15.6±24.6	25.2±26.3	0.069
Rec (mm)	0.6±0.5	0.6±0.4	0.542
CAL measures			
-Mean CAL (mm)	4.2±1.4	4.5±1.4	0.251
-Number of sites/mouth CAL ≥3 mm	114.5±39.3	121.3±39.9	0.414
-Number of sites/mouth CAL ≥5 mm	58.6±48.3	78.4±52.9	0.058
Number of present teeth	19.9±3.6	20.2±4.3	0.712
PISA (mm^2)	813.8±1041.5	1690.9±1198.6	0.001
Last dental visit			0.885
-Within the last 12 months, n (%)	53 (59.6)	18 (58.1)	
-Less often, n (%)	36 (40.4)	13 (41.9)	
Tooth brush frequency			0.480

VARIABLES	Good outcome (n=89)	Poor outcome (n=31)	*p*-value
-<2 times/day	31 (34.8)	13 (41.9)	
-≥2 times7day	58 (65.2)	18 (58.1)	
Use of interdental care devices, n (%)	5 (5.6)	4 (12.9)	0.185

BMI: body mass index; SI: silent infarct; LI: lacunar infarct; FMPS: full-mouth plaque score; FMBS: full-mouth bleeding score; PPD: probing pocket depth; Rec: gingival recession; CAL: clinical attachment level; PISA: periodontal inflamed surface area.

Figure 1. a) Prevalence of PD in subjects with and without LI. **b)** Percentage of patients according to PD severity in subjects with and without LI.

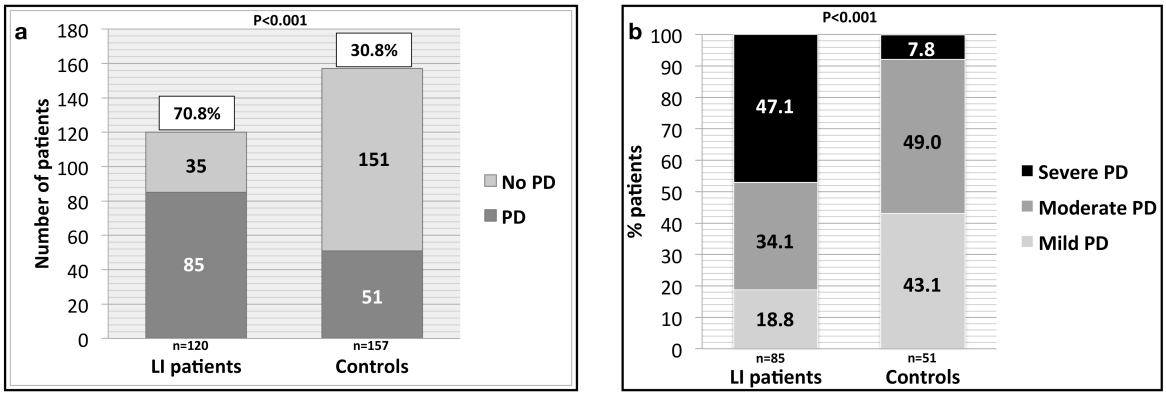

Figure 2. a) Prevalence of PD within LI patients according to functional outcome at 3 months. **b)** Severity of PD within LI patients according to functional outcome at 3 months.