Mapping the Relationship of Contributing Factors for Preclinical Alzheimer’s Disease

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While detecting and validating correlations among the contributing factors to the preclinical phase of Alzheimer’s disease (pAD) has been a focus, a potent meta-analysis method to integrate current findings is essential. The entity-relationship diagram with nodes as entities and edges as relationships is a graphical representation that summarizes the relationships among multiple factors in an intuitive manner. Based on this concept, a new meta-analysis approach with this type of diagram is proposed to summarize research about contributing factors of pAD and their interactions. To utilize the information for enriched visualization, width and color of the edges are encoded with reporting times, number of pAD subjects, correlation coefficient, and study design (cross-sectional or longitudinal). The proposed Probabilistic Entity-Relationship Diagram (PERD) demonstrated its effectiveness in this research for studying pAD. Another kind of diagram with occurrence order for some factors was also proposed to provide sequential information of the factors. In addition, PERD could potentially develop into an online application named PERD-online, which would help researchers to pool findings on the same relationships and guide further tests to validate uncertain relationships in PERD. PERD as a generic graphical meta-analysis tool can also be applied in studying other multifactorial diseases.

Alzheimer’s Disease (AD) is the most common form of dementia which usually presents in patients above 65 years of age¹. The disease starts with a preclinical phase, preclinical AD (pAD), in which AD neuropathology begins to accumulate but cognitive performance presents as normal². The early detection of pAD has become increasingly important because early intervention has the promise to slow down the progression towards AD. While extensive research has been directed towards improving existing imaging methods and understanding the underlying mechanism of the disease, a holistic understanding of contributing factors in pAD and their relationships is still lacking. Besides further research on potential biomarkers of pAD, an effective visualized meta-analysis approach for better understanding the existing findings is needed.

Diagrams with nodes representing factors and edges representing their relationships have been used in biological research on multifactorial progresses. For instance, a metabolic network enables visualization of large-scale structures in the organization of various organisms³. With a higher translational value, the cardiovascular network modeled through reviews with relevant progresses⁴ elucidates some higher-order interactions underlying the clinical traits in cardiovascular disease. This type of network analysis is also promising in the study of other multifactorial diseases⁵.

A new graphical meta-analysis method, namely the Probabilistic Entity-Relationship Diagram (PERD), is introduced in this paper. It is designed as a color map with nodes (biomarkers) and edges (correlations)

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showing the relationship of reported contributing factors resulting in pAD. This map will not only help researchers to find the biomarkers that are associated with pAD, but also provide inspirations to design trials for better understanding pAD pathology.

**Material and Methods**

**Keywords of the survey.** Preclinical AD; Imaging.

**Criteria.** The literature concerning the study of pAD in the past five years was surveyed and only the papers that involved imaging for test were used for meta-analysis. However, if the known biomarkers were not reported to be directly related with pAD in the past five years, the time span for surveying the literature would be expanded to ten years or even more to provide a reasonable appearance for the graphical meta-analysis. To make sure the included studies were about pAD rather than MCI or AD, we screened the papers based on the participants involved in the research. Namely, the subjects were either observed in conversion from normal control to MCI/AD in longitudinal studies, or grouped by well-established pAD biomarkers (e.g. Aβ42 (CSF/PET)) when they did not suffer cognitive impairment in cross-sectional studies. In addition, as familial (early-onset) AD cases differed from sporadic (late-onset) cases in pathophysiology (e.g. Aβ42 (CSF) increases early in sporadic AD, while it decreases early in familial AD), we excluded the studies that focused on familial pAD subjects. Finally, we only included the studies with significant findings to construct the PERD. The significance level for the p-value was defined as 0.1 rather than 0.05 to include more potential significant biomarkers that might be sacrificed by the small sample size of pAD subjects available, but their visual significance in PERD will be simultaneously controlled through graph generation.

**Database used.** PubMed was the only database used for data collection and analysis. According to the aforementioned keywords and criteria of literature survey, 24 studies related to imaging of pAD were included, and all the collected studies were used for graphical meta-analysis. In particular, 22 studies that reported findings of overall correlations between pAD biomarkers were utilized to generate the major diagram of PERD, while the detailed regional findings from these studies were further visualized in a complementary diagram. An extra diagram was proposed to present the occurrence order of the biomarkers with the findings from 3 aforementioned studies and 2 additional studies that were not used in the major diagram.

**Generation of the Probabilistic Entity-Relationship Diagram of preclinical AD.** The PERD of pAD was a colored diagram summarizing the imaging biomarkers of pAD and plotting their relationships. Well-established CSF pAD-predictors were also included. The nodes denoted the various contributors of pAD, while the edges stood for the corresponding relationship between the nodes. The width and color of the edge were designed to represent the strength of the relationship by integrating reporting times, number of subjects diagnosed with pAD, study design (longitudinal or cross-sectional), correlation coefficient and corresponding significance level (p-value) of the relationship. The colored map of relationships was generated with Microsoft Visio 2013, with the parameters specifying width and color of edges in Table 1. Although age is the most important predictor of AD, it was not included in visualization due to the inconsistency in statistical approaches for age. Instead, the age statistics reported in each literature would be expanded to ten years or even more to provide a reasonable appearance for the major diagram of PERD.

**Width of the Edge.** The width of edge showed the degree of consensus on a certain correlation. Among the factors describing the relationship of biomarkers, reporting times (T) and the number of pAD subjects (N) indicated the scale of work on the agreement of the relationship, which governed edge width (W). In addition, weighting was used to reflect the study design (cross-sectional or longitudinal) and the size of relationship significance (p-value). Compared to cross-sectional studies, longitudinal studies provide more convincing results due to observation of conversion of normal subjects to pAD onset. Therefore, a penalty coefficient α (α < 1) was proposed to adjust the significance of the results from cross-sectional studies. In order to make best of the existing studies, the surveyed literatures were weighted by a p-value penalty (β), which was designed to enlarge the impact of the findings with high significant level (Table 1).

\[ W = W_0 + \sum_{i=1}^{T} A \text{sign}(r_i)N_i\alpha_i\beta_i \]  \hspace{1cm} (1)

The equation (1) was applied to compute the width of the edge. \(W_0\) was the default width of edge for observed correlations (\(W_0 = 0.5pt\)). The weight \(A\) was empirically designed to adjust the appearance of the edges. The combined term on the right contained the results of various reports on the same relationship, and the parameter \(i\) referred to the result of a single report. Definitions of other parameters were further explained in Table 1.

**Color of the Edge.** Different colors represented the sign and strength of the correlation. The strength of correlation was illustrated with coded color from yellow to red for positive correlation and green to blue for negative correlation. Bearing in mind the difference of reports on the same relationship, we used...
weighted average correlation coefficient ($\overline{r}$) to designate the RGB value of the edge (a lookup table was provided in color, as was shown in the colorbar of Fig. 1 and Fig. 2). This coefficient was composed of the reported correlation coefficient ($r_i$), the number of pAD subjects, and the cross-sectional penalty ($\alpha_i$) (equation (2)). For those studies involving group comparisons or regression rather than correlation, $r_i$ was estimated empirically based on the p-value and the sign of the correlation, where $|r_i| = \min\left(\sqrt{0.001/p_i}, 1\right)$ (we defined 0.001 as a strict significance level).

$$r = \frac{\sum_{i=1}^{T} \alpha_i N_i r_i}{\sum_{i=1}^{T} \alpha_i N_i}$$ (2)

**Results**

Figures 1,2 below show the relationship among possible pAD contributing factors based on the literature findings (Table 2). In general, studies on the relationship of contributors of pAD focus on some specific regions of the brain. To include both global and regional findings of the listed biomarkers, while keeping the visualization neat and clear, Fig. 1 is taken as the main diagram of PERD (all the biomarkers listed in Table 2 are shown). The regional findings with no more than three different regions are specifically labeled. In detail, the labeled edges in Fig. 1 indicate the correlations are between regional imaging biomarkers and pAD or well-established pAD biomarkers. The edges without labels correspond to correlations that involve biomarkers with global findings or specific regional findings (with more than three different regions (e.g. atrophy) (Fig. 1)). For the biomarkers with more than three regional findings, they are visualized in a complementary diagram (Fig. 2).

The color bar on the right relates the correlation coefficients to the connections of the nodes. A correlation coefficient of +1 will be reported by red, and a correlation coefficient of −1 by blue. Besides coding color for the edges, we also color-code the major findings of biomarkers (Fig. 1), which are classified through imaging methods. For example, white matter integrity examined by DTI is set to blue (including Fractional Anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (axD)). Considering that Aβ42(CSF/PET) has been widely used to depict the status of pAD 8 and that the studies reporting the correlation of Aβ42(CSF/PET) and pAD has become increasingly scarce recently (Table 2), we include the studies that reported correlation of imaging biomarkers and pAD in addition to compute

**Table 1. Parameterization for the relationship of pAD biomarkers.**

| Factors                  | Description                                                                 |
|--------------------------|-----------------------------------------------------------------------------|
| Report times (T)         | The number of current studies regarding the same relationship.              |
| Number of pAD subjects (N) | The number of subjects clinical presented with pAD (longitudinal study) or related to a high risk factor for pAD (cross-sectional study) |
| Correlation coefficient (r) | This coefficient denotes the degree of correlation between two biomarkers. The sign of r shows the correlation is positive (sign(r) = +1) or negative (sign(r) = −1). |
| Cross-sectional penalty ($\alpha$) | If the study is cross-sectional, its result should bear a penalty, due to its restriction in observing the conversion in from NC (normal control) to real pAD patient. For cross-sectional study, $\alpha = 0.5$; for longitudinal study, $\alpha = 1$. The value of 0.5 in this penalty is determined empirically, and an alternative setting makes little difference with current findings in surveyed literatures. |
| Significance penalty ($\beta$) | This penalty is used to integrate the significance of a finding to width, where $\beta = (0.05/p)^{1/2}$ We use 0.05 as the reference significance level and introduce the square operation to avoid extreme edge appearance. |
| Scaling coefficient ($A$) | This coefficient is empirically set to adjust the width of edge for best appearance. ($A = 0.01$) |
| Major biomarkers | Related factors | Imaging modality | Cross-sectional / longitudinal | Number of CN : pAD | Age: mean(SD/range) (CN : pAD) | Correlation coefficient (r) | p-value | Published date | Authors |
|------------------|-----------------|-----------------|-------------------------------|-------------------|---------------------------------|----------------------------|---------|----------------|---------|
| Aβ42(PET)        | pAD             | PiB-PET         | longitudinal                  | 115:10            | 65.5(10.9):65.3(8.3)            | 0.141’                     | <0.05   | 2011–11        | Vlassenko AG et al. |
| Aβ42(PET)        | Aβ42(CSF)       | PiB-PET         | cross-sectional               | 160:29            | 64.7(10.4)                      | -0.512                     | <0.0001 | 2009–11        | Fagan AM et al.    |
| Aβ42(CSF)        | pAD             | NA              | longitudinal                  | 28:7              | 85                            | -0.583                     | 0.001   | 2003           | Skoog I et al. |
| CSF tau          | Aβ42(PET)       | PiB-PET         | cross-sectional               | 160:29            | 64.7(10.4)                      | 0.4508                     | <0.0001 | 2009–11        | Fagan AM et al. |
| CSF p-tau        | Aβ42(PET)       | PiB-PET         | cross-sectional               | 160:29            | 64.7(10.4)                      | 0.3856                     | <0.0001 | 2009–11        | Fagan AM et al. |
| CBF              | pAD             | sMRI, PET       | longitudinal                  | 99:22             | 72.2(6.5):74.1(7.5)             | 0.43                       | 0.04    | 2013–11        | Beason Held LL et al. |
| CBF(right superior medial frontal lobe) | tau | ASL | cross-sectional | 24:8             | 76.6(8.4) | -1’ | <0.001 | 2012–06 | Stomrud E et al. |
| CBF(right superior medial frontal lobe) | p-tau | ASL | cross-sectional | 24:8             | 76.6(8.4) | -0.5’ | <0.001 | 2012–06 | Stomrud E et al. |
| CBF(left frontal-temporal lobe) | p-tau | ASL | cross-sectional | 24:8             | 76.6(8.4) | 1’ | <0.001 | 2012–06 | Stomrud E et al. |
| DMN              | pAD             | rs-fMRI         | cross-sectional               | 132:46            | 66.4(9.8):74.5(7.5)             | -0.141’                    | <0.05   | 2004–10        | Brier MR et al. |
| DMN              | Aβ42(CSF)       | rs-fMRI         | cross-sectional               | 136:71            | 70.8(6.3)                      | 0.155                      | 0.026   | 2013–10        | Wang L et al. |
| DMN              | p-tau           | rs-fMRI         | cross-sectional               | 136:71            | 70.8(6.3)                      | -0.122                     | 0.081’  | 2013–10        | Wang L et al. |
| Occipital network | pAD            | rs-fMRI         | cross-sectional               | 132:46            | 66.4(9.8):74.5(7.5)             | -0.141’                    | <0.05   | 2004–10        | Brier MR et al. |
| Modularity (graph metrics) | pAD | rs-fMRI | cross-sectional | 132:46            | 66.4(9.8):74.5(7.5)             | -0.141’                    | <0.05   | 2004–10        | Brier MR et al. |
| FA(all the brain) | Aβ42(PET)       | PiB-PET, DTI    | longitudinal                  | 59:27             | 59.7(6.0):60.0(6.0)             | 0.141’                     | <0.05   | 2014–02        | Racine AM et al. |
| FA(left fornix)  | Aβ42(CSF)       | PiB-PET, DTI    | cross-sectional               | 11:9              | 76.2(5.8)                      | 0.63                       | 0.003   | 2014–05        | Gold BT et al. |
| MD(lateral frontal gray matter) | Aβ42(PET)   | PiB-PET, DTI    | longitudinal                  | 59:27             | 59.7(6.0):60.0(6.0)             | -0.392                     | 0.024   | 2014–02        | Racine AM et al. |
| DR(left fornix)  | Aβ42(CSF)       | PiB-PET, DTI    | cross-sectional               | 11:9              | 76.2(5.8)                      | -0.44                      | 0.09’   | 2014–05        | Gold BT et al. |
| axD              | Aβ42(CSF)       | PiB-PET, DTI    | cross-sectional               | 19:19             | 69.2(5.6):69.9(7.6)             | 0.57                       | 0.013   | 2014–06        | Molinuevo IL et al. |
| Glucose metabolism | pAD          | FDG-PET         | cross-sectional               | 36:21             | 76.1(5.9):77.7(5.5)             | -0.333’                    | 0.009   | 2014–09        | Kljajevic V et al. |
| Glucose metabolism | pAD          | FDG-PET         | longitudinal                  | 43:11             | 74.3(4.6):78.9(3.7)             | -0.5’                      | 0.004   | 2013–11        | Ewers M et al. |
| Glucose metabolism | pAD          | FDG-PET         | cross-sectional               | 90:57             | 76(74–80):80(76–82)             | -0.224’                    | 0.02    | 2013–08        | Knopman DS et al. |
| LMB              | Aβ42(PET)       | SWI, PiB-PET    | longitudinal                  | 68:29             | 74.2(7.3)                      | 0.141’                     | <0.05   | 2014–04        | Yates PA et al. |
| Atrophy(left amygdalo-hippocampal complex) | pAD | sMRI | longitudinal | 319:25            | 72.8(3.9):76.1(4.1)             | 1’ | <0.001 | 2014–03 | Bernard C et al. |
| Atrophy(MTL)     | pAD             | sMRI            | longitudinal                  | 90:57             | 76(74–80):80(76–82)             | 0.5’                       | 0.004   | 2013–08        | Knopman DS et al. |
| Atrophy(MTL)     | pAD             | sMRI            | cross-sectional               | 136:71            | 70.8(6.3)                      | 0.172                      | 0.026   | 2013–10        | Wang L et al. |

Continued
The width of edge between A/342 (CSF/PET) and pAD. In this way, the diagram appears more reasonable with available data.

As is shown from Fig. 1, brain atrophy and glucose metabolism are the most significant biomarkers for pAD in addition to A/342 (CSF/PET) in terms of edge width. The possibility that subjects suffer from pAD rises greatly if they have more severe brain atrophy or lower glucose metabolism. In addition, CSF tau and p-tau are relatively significant contributors to pAD because of their strong connections to A/342 (PET), a well-established biomarker for pAD. As for the color of the edge, regional cerebral blood flow (in right superior medial frontal lobe (R1) and left frontal-temporal lobe (R2)) and regional FA (in left fornix (R3)) are significantly related to known biomarkers of pAD (PiB-PET and CSF biomarkers). The widths and colors of other edges do not differ obviously, probably because the studies on these biomarkers are still lacking and that the number of participants with pAD that involve corresponding biomarkers is very small.

In Fig. 2, atrophy, which is reported with the most detailed anatomical information, is independently visualized with regional findings. In this diagram, the atrophy of left amygdala-hippocampal complex and medial temporal lobe in gray matter are significantly correlated with pAD directly in terms of edge width, and the atrophy of left amygdala-hippocampal complex also has significant prediction effect in terms of color. In addition, the atrophy of cerebral cortex is significantly associated with pAD indirectly visualized with regional findings. In this diagram, the atrophy of left amygdala-hippocampal complex is very small.

In addition, there are also studies that present evidence to the sequence of events for some biomarkers (Table 3). The major findings are described in Fig. 3, where the arrows indicate the sequence order. Fig. 3a reveals a macroscopic view regarding the occurrence order of several pAD-biomarkers, while the detailed order of regional changes in brain volume is presented in Fig. 3b.

### Table 2. Summary of the literatures surveyed.

| Major biomarker(s) | Related factors | Imaging modality | Cross-sectional / longitudinal | Number of CN : pAD | Age: mean(SD/range) (CN : pAD) | Correlation coefficient (r) | p-value | Published date | Authors |
|--------------------|-----------------|------------------|--------------------------------|---------------------|--------------------------------|---------------------------|---------|---------------|---------|
| Atrophy(MTL)       | pAD*            | sMRI             | longitudinal                    | 25:8                | 71.2(4.0):71.5(2.1)            | 0.141*                    | <0.05   | 2011–04       | Dickerson BC et al.24 |
| Atrophy(MTL)       | pAD*            | sMRI             | longitudinal                    | 40:8                | 76.1(5.7):77.1(5.2)            | 0.141*                    | <0.05   | 2012–04       | Tondelli M et al.20 |
| Atrophy(parietal lobe) | pAD*          | sMRI             | longitudinal                    | 35:9                | 69.1(7.7):73.8(4.3)            | 0.141*                    | <0.05   | 2011–03       | Jacobs HI et al.26 |
| Atrophy(superior frontal gyrus) | pAD*         | sMRI             | longitudinal                    | 25:8                | 71.2(4.0):71.5(2.1)            | 0.141*                    | <0.05   | 2011–04       | Dickerson BC et al.24 |
| Atrophy(temporal pole) | pAD*           | sMRI             | longitudinal                    | 25:8                | 71.2(4.0):71.5(2.1)            | 0.141*                    | <0.05   | 2011–04       | Dickerson BC et al.24 |
| Atrophy(basal ganglia) | pAD*          | sMRI             | longitudinal                    | 40:8                | 76.1(5.7):77.1(5.2)            | 0.141*                    | <0.05   | 2012–04       | Tondelli M et al.20 |
| Atrophy(basal forebrain) | A/342(PET) | sMRI, AV45-PET | cross-sectional                 | 36:21               | 76.2(6.0):77.6(5.6)            | 0.45                      | 0.04    | 2014–01       | Grothe MJ et al.27 |
| Atrophy(cerebral cortex) | A/342(CSF) | sMRI             | cross-sectional                 | 107:38              | 73.4(6.2)                      | 1*                        | <0.001  | 2014–08       | Fortea J et al.28 |
| Atrophy(cerebral cortex) | A/342(CSF) | sMRI             | cross-sectional                 | 18:15               | 68.3(6.4):72.7(7.9)            | NA(U-shaped)              | <0.05   | 2011–07       | Fortea J et al.28 |
| Atrophy(cerebral cortex) | p-tau         | sMRI             | cross-sectional                 | 107:38              | 73.4(6.2)                      | 1*                        | <0.001  | 2014–08       | Fortea J et al.28 |
| Atrophy(cerebral cortex) | A/342(CSF) & p-tau | sMRI       | cross-sectional                 | 107:38              | 73.4(6.2)                      | -1*                       | <0.001  | 2014–08       | Fortea J et al.28 |
| Atrophy(whole brain) | pAD*           | sMRI, PiB-PET    | cross-sectional                 | 148:75              | 78(75–83)                      | 0.141*                    | <0.05   | 2014–05       | Jack CR Jr et al.30 |
**Discussion**

The PERD offers a new methodology to study the mechanism of pAD by visualizing the relationship of the disease related factors through meta-analysis. It facilitates the detection of the primary causation of pAD and can be applied to the study of other diseases. Despite of the similarity of the proposed network with4 (in graph structure) and5 (in color coding the positive or negative correlation), PERD better utilizes color to illustrate the significance of correlation and width of edges to show the consistence in various trials on the same relationship. Due to inconsistence in study criteria for the correlation of pAD-biomarkers, edge-coding in PERD compromises to visualize the relationships. For example, the setting of the coefficients in the coding formula is empirically designed to reach an agreement with statistics concerning various studies. However, if researchers reach an agreement on imaging and correlation quantification methods, the evaluating potential of the proposed diagram will be highly improved. In addition, a map generated from PERD with time occurrences will also help to discover the areas where pathology of pAD is not well understood and to guide clinical studies to better understand the sequence of contributing factors.

A limitation of this work is that the current version of PERD only involves studies conducted within the preclinical phase of late-onset AD, the early onset AD or familial AD is not considered due to the difference in pathophysiology. In future work, the construction of PERD for familial pAD will help obtain a more comprehensive framework facilitating analysis of both types of pAD. While the current study mainly focuses on imaging biomarkers, other biomarkers of pAD could also be included. For example, episodic memory measurement was found to be sensitive to reflect subtle cognitive impairment (in...
amyloid-positive individuals), which presents in stage 3 of pAD\(^8\). Future converging evidence of neuropsychological variables for pAD staging could be included in \(\text{PERD} \) generation.

In addition, \(\text{PERD} \) could also become a platform to enable researchers who focus on pAD-biomarkers to communicate and update relevant findings through a website like \(\text{GenomeNet} \) (a Japanese network of database and computational services for genome research). With this type of platform, researchers may update relevant findings in a shared real time database of pAD-biomarkers. It would only be necessary to enter corresponding items as listed in the first row of Table 2. Embedded as a kennel tool in this website (\(\text{PERD-online} \)), \(\text{PERD} \) can be used to visualize synthesized results on corresponding correlations.

**Figure 2.** \(\text{PERD} \) of relationship between atrophy of different anatomical positions and pAD or its significant biomarkers. \(\text{GM} = \) gray matter.

**Table 3.** Literatures with findings on occurrence order of contributing factors of pAD.

| Inference of occurrence order of pAD-biomarkers | Published date | Authors |
|------------------------------------------------|----------------|---------|
| \(\text{A}\beta 42 \) metabolism and amyloid formation exceeds disruptions in CSF \(\beta\) tau metabolism. | 2009–11 | Fagan AM et al.\(^{10}\) |
| Early changes in CBF possibly present even earlier than amyloid-\(\beta\) accumulation. | 2014–08 | Wierenga CE et al.\(^{31}\) |
| Hypometabolism exceeds atrophy in preclinical AD: amyloid load may affect synaptic activity, leading to synaptic loss and subsequent neuronal loss. | 2014–09 | Kljaevic V et al.\(^{19}\) |
| Cortical thickening is associated with low CSF A\(\beta\), followed by atrophy once CSF p-tau becomes abnormal. | 2014–08 | Fortea J et al.\(^{28}\) |
| The atrophy change point in the ERC occurs first, indicating significant change 8–10 years prior to onset, followed by the hippocampus, 2–4 years prior to onset, followed by the amygdala, 3 years prior to onset. | 2014–04 | Younes L et al.\(^{32}\) |
Furthermore, authoritative pAD researchers on the leading edge would be also invited to regularly examine the operation of PERD-online, validate or exclude contributing factors as appropriate. Finally, joining efforts of researchers around the world concerning pAD will contribute to a constantly improving PERD-online, which enables better understanding of novel patterns from complex relationships as well as sufficient directions to channel further research efforts.

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Author Contributions
L.S. is responsible for the idea conceptualization, study design, and part of the literature survey, manuscript writing, and proofreading; L.Z. is responsible for part of the literature survey, manuscript writing and figure drawing; D.W. is responsible for the study design; A.W. and V.M. are responsible for providing the clinical advices and study design.

Additional Information
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