Original research

Pseudocoloboma-like maculopathy with biallelic \textit{RDH12} missense mutations

Che-Yuan Kuo,1,2 Ming-Yi Chung3,4, Shih-Jen Chen1,2

ABSTRACT

Background Hereditary maculopathy is a group of clinically and genetically heterogeneous disorders. With distinctive clinical features, subtypes of macular atrophy may correlate with their genetic defects.

Methods Seven patients from six families with adolescent/adult-onset maculopathy were examined in this clinical case series. A detailed medical history and eye examination were performed. Genomic DNA sequencing was performed using whole exome sequencing or direct sequencing of retinol dehydrogenase 12 (\textit{RDH12}) coding exons.

Results Seven patients, including one male and six female patients, with pseudocoloboma-like maculopathy had biallelic missense \textit{RDH12} mutations. The most common mutant allele found in six of the seven patients was p.Ala269Gly. The average disease onset was at age 19.3 years, and visual acuity ranged from count fingers to 1.0. Most of the patients had mild myopic refraction. Common findings on fundus examination and spectral-domain optical coherence tomography include discrete margins of pseudocoloboma-like macular lesions with variable degrees of chorioretinal atrophy, excavation of retinal tissue and pigmentary changes mainly in the macular area. The electroretinograms were relatively normal to subnormal in all participants.

Conclusions Progressive macular degeneration with a relatively normal peripheral retina and subsequent development of a pseudocoloboma-like appearance were the main clinical features in patients with compound heterozygous \textit{RDH12} missense mutations. Genetic testing may be crucial for early diagnosis and may play a key role in the development of future treatment strategies.

INTRODUCTION

Inherited retinal diseases (IRDs) are a group of retinal disorders caused by gene mutations and may lead to vision loss or even blindness. Before the advancement of gene identification, the classification of IRDs was primarily based on inheritance pattern, disease onset and clinical features. Through the increasing popularity of genetic diagnosis, it is clear that phenotypic variation exists among defects in a diseased gene. Among the IRD genes, mutations in the biallelic retinal dehydrogenase 12 (\textit{RDH12}) gene cause a wide range of clinical presentations from the early onset of Leber congenital amaurosis (LCA) with nystagmus to minimally impaired central macula accompanied by preserved electroretinogram (ERG).

\textbf{WHAT IS ALREADY KNOWN ON THIS TOPIC}

 Mutations in retinol dehydrogenase 12 (\textit{RDH12}) were identified for causing autosomal recessive Leber congenital amaurosis type 13 and retinitis pigmentosa type 53 as listed on OMIM.

\textbf{WHAT THIS STUDY ADDS}

 In this case series, we present a novel type of adolescent/adult-onset macular atrophy with pseudocoloboma-like feature resulting from compound heterozygous mutations in \textit{RDH12}.

\textbf{HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY}

 RDH12, a protein of 316 a.a., is suitable for the development of gene-augmented therapy. Early diagnosis of \textit{RDH12}-related retinopathy may benefit the patients.

\textit{RDH12}, a short-chain NADPH (nicotinamide adenine dinucleotide phosphate) -dependent retinal reductase expressed abundantly in the inner segments of the photoreceptors, is responsible for the reduction of all-trans-retinal to all-trans-retinol in the visual cycle to maintain the normal vision of human beings by preventing the accumulation of all-trans-retinal to all-trans-retinol. It is located on chromosome 14q24 with seven coding exons. Genetic defects that affect the enzymatic activity of \textit{RDH12} may result in the build-up of cytotoxic aldehydes, leading to death of photoreceptors and subsequent vision impairment.

It was postulated that different \textit{RDH12} missense mutations, in addition to numerous environmental factors, could explain these variable phenotypes. Among the different clinical presentations, the macular pseudocoloboma type with minimal intra- and periretinal pigment or peripheral pigmentary change was the most interesting and differed from the other presentations of IRD. Unlike other phenotypes of \textit{RDH12} such as night blindness, impairment of cone and rod responses, and severely impaired peripheral visual field (VF), pseudocoloboma-like lesions may present with asymmetrically decreased visual acuity and paracentral scotoma in early adulthood.\textsuperscript{3} The differential diagnosis of such a clinical manifestation as macular coloboma includes congenital macular coloboma, congenital toxoplasmosis, central areolar choroidal atrophy or North Carolina macular dystrophy (NCMD).

In this article, we present a novel type of adolescent/adult-onset pseudocoloboma-like maculopathy...
with minimal intraretinal or peripheral pigmentary change, relatively normal to subnormal ERG, and moderately impaired vision. Equally important is that its genetic defects are biallelic missense mutations in RDH12, which are apparently different from typical RDH12 phenotypes, that is, LCA13 and retinitis pigmentosa type (RP53).

METHODS
Clinical evaluation
Seven individuals diagnosed with pseudocoloboma-like maculopathy at Taipei Veterans General Hospital were enrolled in this study and underwent a complete ophthalmic examination, including best-corrected visual acuity (BCVA), intraocular pressure and measurements of refractive error using an automated refractor. Fundus colour photography, spectral-domain optical coherence tomography (SD-OCT) (Avanti RTVue XR, OptoVue, Fremont, California, USA), full-field ERG (UTAS Visual Diagnostic System with BigShot, LKC Technologies, USA), and a standard 24–4 program VF test (Model 750, Humphrey field analyser, Carl Zeiss Meditec, Dublin, California, USA), were performed on all participants. Full-field ERG was performed and recorded in accordance with the standards of the International Society for Clinical Electrophysiology of Vision. Informed consent was obtained from all the participants.

Sequence analysis
Genomic DNA was extracted from peripheral blood leukocytes, according to our laboratory protocols. Whole exome sequencing (WES) was performed in the first three cases. Briefly fragmented DNA was captured using the SureSelect Clinical Research Exome V2 kit (Agilent, Santa Clara, California, USA), followed by sequencing using Illumina HiSeq2500 (Illumina, San Diego, California, USA). Image analyses and base calling were performed using the Illumina pipeline with the default parameters. Reads were mapped to the human reference sequence (GRCh38) using the Burrows-Wheeler Aligner with maximal exact matches algorithm with duplicate reads removed using Picard tools. Variants were called using the Genome Analysis ToolKit pipeline (Broad Institute). The vcf files were imported into VarSeq (Golden Helix, Bozeman, Montana, USA) for further filtering and prioritisation. In addition to the artificial intelligence-assisted pipeline, determination of the possible pathogenicity of the variants was facilitated by the expression profile and segregation pattern in the family. CNVs were analysed using CNVkit with a reference depth prepared using 30 WES samples captured by the same kit. An integrated genome viewer was used to visualise the read alignment and variants. Direct DNA sequencing was performed using the deoxyribonucleotide chain termination method with the Sequenase V.2.0 DNA Sequencing Kit (ThermoFisher Scientific) to validate variants identified by WES and to screen for mutations in cases 4–7. PCR primers were designed to amplify exons 3–9 of RDH12, with at least 50 bp flanking the exon-intron junction. The PCR products were purified by exonuclease and shrimp alkaline phosphatase treatment and sequenced using one of the primers. Variants were called using the Phred-Phrap-Consed-polyPhred package and NCBI (National Center for Biotechnology Information) Reference Sequence NG_008321.1 Compound heterozygotes were validated using parental DNA samples or restriction fragment length polymorphism. Minor allele frequencies in East Asians were queried using gnomAD v3.1.3 (https://gnomad.broadinstitute.org).

RESULTS
A total of seven patients (six female and one male) with macular atrophy were examined. The mean age of onset was 19.3 years, ranging from 5 years to 47 years (table 1). The presenting symptoms included decreased BCVA, photophobia, nyctalopia and different degrees of VF scotomata. All patients had discrete boundaries of pseudocoloboma-like macular lesions in both eyes and additional features including chorioretinal atrophic change, macular scar and hyperpigmentation in the affected area (online supplemental figure 1). Visual acuity varied among the participants, ranging from count fingers to 1.0. Most of the patients had mild myopic refraction. Central, cecocentral and paracentral VF defects were observed depending on the severity and location of the involvement. The ERG was mostly normal in all participants.

Representative case descriptions
Case 1: A woman in her 30s presented with photophobia and nyctalopia that had persisted for 2 years. The patient’s family history was unremarkable. BCVA was 0.2 and 0.5 in the right and left eyes, respectively. Fundus examination revealed a well-demarcated large geographical macular atrophic change with variably scattered hyperpigmentation in both eyes. Fundus autofluorescence showed rims of hyperfluorescence along the temporal side of the central atrophic area whereas no hyperfluorescent rim was found at the nasal side. The visual acuity of this patient remained 0.2 and 0.5 after 7 years of follow-up (figure 1A and B). SD-OCT revealed coloboma-like choroid atrophy with an epiretinal membrane and thinning and disruption of the retinal structure (figure 1C and D). ERG levels were nearly normal (figure 1E). Nasal bilateral paracentral scotoma was detected using VF testing (figure 1F).

Case 7: A teenage girl presented to our clinic with decreased BCVA since the age of 11. On examination, BCVA was 0.1 in both eyes, and remained relatively stable after 4.5 years of follow-up. Fundus colour photography revealed variable degrees of pigmentation within the well-defined macular atrophy. SD-OCT showed atrophy of the outer nuclear layer and retinal pigment epithelium (RPE) at the baseline (figure 2A). Two years after the initial presentation, SD-OCT of the left eye demonstrated epiretinal membrane formation, progressive thinning of choroidal tissue, disruption of Bruch’s membrane and herniation of the overlying retinal tissue, mimicking a pseudocolobomatous lesion (figure 2C). VF testing showed a central scotoma in both eyes, and ERG showed bilateral subnormal cone signals.

RDH12 mutation
In this case series, the ophthalmoscopic findings in seven patients resembled those in NCMD; however, their age at onset ranged from adolescence to adulthood. In addition, with the exception of cases 3 and 4 who are siblings, all the others are the only affected members of their families, suggesting that these cases are not typical NCMD, and that the disease may be inherited in an autosomal recessive manner rather than an autosomal dominant manner. There are two loci for NCMD, MCDR1 and MCDR3, at 6q16.2 and 5p13.1–p15.33, respectively. MCDR1 is caused by a tandem duplication of PRDM1310 and the gene for MCDR3 has yet to be identified. WES was performed to detect single nucleotide variants (SNVs) and CNVs. CNV and SNV analyses using WES data did not detect any significant change in genome-wide copy number (online supplemental figure 2), nor small nucleotide variations in PRDM13 and genes at 5p13.1–p15.33. Unexpectedly, biallelic missense variants in RDH12

Genotype-phenotype correlations


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Table 1  Summary of clinical characteristics in examined participants with biallelic RDH12 mutations

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age at exam (decades)</th>
<th>Sex</th>
<th>Presenting symptoms</th>
<th>Age at onset (years)</th>
<th>Initial BCVA R/L</th>
<th>Follow-up period; latest BCVA R/L</th>
<th>Autorefraction</th>
<th>Fundus findings</th>
<th>VF</th>
<th>ERG</th>
<th>Additional findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>Fourth</td>
<td>F</td>
<td>Photophobia, nyctalopia</td>
<td>31</td>
<td>0.2/0.5</td>
<td>7.33 years; 0.2/0.5</td>
<td>► -0.25–2.25 ×174° ▶ -1.0–1.0 ×174°</td>
<td>Geographical macular atrophic scar with hyperpigmentation OU</td>
<td>Binasal scotoma OU</td>
<td>Normal</td>
<td>Family history unremarkable</td>
</tr>
<tr>
<td>Case 2</td>
<td>Third</td>
<td>F</td>
<td>Decreased BCVA</td>
<td>NA</td>
<td>0.8/0.8</td>
<td>9.5 years; 0.6/0.1</td>
<td>► -5.0–1.0 ×161° ▶ -5.0</td>
<td>Macular atrophy with small central island OU; peripheral RPE changes OU</td>
<td>Central scotoma OU</td>
<td>Normal</td>
<td>Family history unremarkable</td>
</tr>
<tr>
<td>Case 3</td>
<td>Fourth</td>
<td>F</td>
<td>Decreased BCVA</td>
<td>6</td>
<td>0.5/0.03</td>
<td>5 months; 0.4/0.08</td>
<td>► -1.5–2.0 ×162° ▶ -3.75–0.5 ×178°</td>
<td>Hyperpigmented chorioretinal atrophy with central island OU</td>
<td>Central scotoma with parapapillary island OU</td>
<td>Normal</td>
<td>Elder sister of case 4</td>
</tr>
<tr>
<td>Case 4</td>
<td>Fourth</td>
<td>M</td>
<td>Decreased BCVA</td>
<td>16</td>
<td>0.8/0.1</td>
<td>5 months; 0.8/0.1</td>
<td>► -3.0–0.5 ×165° ▶ -2.75–0.25 ×56°</td>
<td>Macular atrophy OU</td>
<td>Paracentral scotoma OU</td>
<td>Normal rod response; subnormal cone response</td>
<td>Younger brother of case 3</td>
</tr>
<tr>
<td>Case 5</td>
<td>Second</td>
<td>F</td>
<td>Decreased BCVA</td>
<td>5</td>
<td>0.2/0.3</td>
<td>1.25 years; 0.1/0.1</td>
<td>► -9.5–0.5 ×9° ▶ -8.5–0.25 ×179°</td>
<td>Central geographical macular atrophy with hyperpigmentation OU</td>
<td>Paracentral scotoma OD</td>
<td>Mild decreased rod and cone response</td>
<td>Family history unremarkable</td>
</tr>
<tr>
<td>Case 6</td>
<td>Sixth</td>
<td>F</td>
<td>Decreased BCVA</td>
<td>47</td>
<td>0.9/0.1</td>
<td>1 month; 0.9/0.1</td>
<td>► -4.75–0.25 ×2° ▶ -4.5–0.25 ×35°</td>
<td>Pigmented pseudocoloboma-like macular atrophy OU</td>
<td>Central scotoma OU</td>
<td>Subnormal rod and cone response</td>
<td>Family history unremarkable</td>
</tr>
<tr>
<td>Case 7</td>
<td>Second</td>
<td>F</td>
<td>Decreased BCVA, photophobia</td>
<td>11</td>
<td>0.1/0.1</td>
<td>4.5 years; 0.08/0.1</td>
<td>► -6.75–3.25 ×3° ▶ -6.25–4.5 ×162°</td>
<td>Variable degrees of pigmentation within the well-demarcated macular atrophy OU</td>
<td>Central scotoma OU</td>
<td>Subnormal cone response</td>
<td>Family history unremarkable</td>
</tr>
</tbody>
</table>

BCVA, best-corrected visual acuity; ERG, electroretinogram; F, female; L, left; M, male; NA, not available; OD, oculus dexter; OU, oculus uterque; R, right; RPE, retinal pigment epithelium; VF, visual field.
Genotype-phenotype correlations

were identified in the first three cases, and direct sequencing of the RDH12 exons was performed in all later cases as shown in figure 3A and summarised in table 2. All amino acid alterations corresponding to these non-synonymous SNVs were evolutionarily conserved (figure 3B), suggesting that they may be pathogenic or likely pathogenic.

DISCUSSION

RDH12 is one of the critical enzymes in the visual cycle.13 Mutations in RDH12 have been identified in LCA13,14 RP5315 16 and other retinal dystrophies.17 The clinical manifestations of patients diagnosed with RDH12 retinopathy usually comprise an early onset vision impairment after birth, or in early childhood, with progressive pigmentary retinopathy or maculopathy sparing the peripapillary area, atrophy of the RPE, yellowish deposits at the macula, and macular atrophy.5 18-20 Ultimately, the patient may have severely impaired vision or even blindness in adulthood.

Recently, Zou et al reported that in a cohort of 92 patients with cone-rod dystrophy, 2.2% (2/92) of the patients were associated with RDH12 mutations.5 However, the fundus manifestation of these two patients was different from that of other retinopathy associated with RDH12 mutations in terms of a confined lesion to the macula and relatively preserved peripheral retina. Accordingly, the ERG revealed mild to severely impaired cone and rod responses.5 The most consistent clinical features of RDH12 retinopathy include macular atrophy with or without retinal pigmentation. Based on the degree of retinal pigmentation, which ranges from mildly pigmented deposits to patchy pigment proliferation, the phenotypes of RDH12 retinopathy are further classified into four types: type 1, macular coloboma with mid-peripheral pigmentation; type 2, macular retinal pigmentary atrophy with widespread peripheral pigmentation; type 3, heavy pigmentation extending from the posterior pole to the mid-periphery; and type 4, macular atrophy and relatively normal peripheral retina.5 Aside from the pseudocoloboma-like pattern in the posterior pole, our cases mostly resemble category type 4, with the presentation of macular atrophy sparing most of the peripheral retina.21 22

Although the various clinical phenotypes of RDH12 retinopathy have been described in the literature, few reports have focused on the manifestation of pseudocoloboma-like maculopathy.5 18 23 In contrast to our study participants, most of the previous cases with pseudocolobomatous lesions exhibited concomitant dense
mid-peripheral retinal pigmentation, namely type 1 RDH12 retinopathy based on Zou's classification. As a result, more cases may be required to determine whether pseudocoloboma-like maculopathy sparing the peripheral retina is a developmental status within the spectrum between RDH12 retinopathy types 1 and 4 or a new distinctive category. Moreover, the mechanism underlying the sole manifestation of macular involvement in RDH12-mutated subjects remains unclear.

The macula is a small yellowish area at the centre of the retina and is essential for detail and focused colour vision. Higher metabolite demand at the macula may explain why retinal pigment epithelial cells are vulnerable to suboptimal RDH12 activity in photoreceptors. As RDH12 mutations primarily affect photoreceptor function and retinal pigmentation probably originates from proliferating retinal pigment epithelial cells, an interesting point regarding the formation of colobomatous lesions remains unclear. According to a longitudinal follow-up of three Japanese patients with RDH12-related LCA, all developed posterior staphylomata and atrophic macula over the years. Therefore, age may be a factor associated with the development of colobomatous lesions, as these lesions often present later in the disease course. This age-related hypothesis might be supported by our case 7, which demonstrated the development of a pseudocolobomatous lesion extending into the choroid in the left eye 2 years after the initial presentation. This pseudocoloboma-like lesion progressed from prior outer retinal atrophy (Figure 2).

Table 2 Compound heterozygous mutations in RDH12 identified in patients affected with pseudocoloboma-like maculopathy

<table>
<thead>
<tr>
<th>Case #</th>
<th>Nucleotide variants*</th>
<th>Amino acid change†</th>
<th>MAF‡</th>
<th>Clinical classification§</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>c.505C&gt;G, c.806C&gt;G</td>
<td>p.(Arg169Gly), p.(Ala269Gly)</td>
<td>0.000217, 0.003592</td>
<td>LP, VUS</td>
<td>36 37</td>
</tr>
<tr>
<td>Case 2</td>
<td>c.505C&gt;G, c.806C&gt;G</td>
<td>p.(Arg169Gly), p.(Ala269Gly)</td>
<td>0.000217, 0.003592</td>
<td>LP, VUS</td>
<td>36 37</td>
</tr>
<tr>
<td>Cases 3 and 4</td>
<td>c.437T&gt;A, c.806C&gt;G</td>
<td>p.(Val146Asp), p.(Ala269Gly)</td>
<td>0, 0.0003592</td>
<td>P, LP, VUS</td>
<td>37 38</td>
</tr>
<tr>
<td>Case 5</td>
<td>c.164C&gt;T, c.178G&gt;A</td>
<td>p.(Thr55Met), p.(Ala60Thr)</td>
<td>0.000019, 0.000019</td>
<td>LP, P</td>
<td>17 39</td>
</tr>
<tr>
<td>Case 6</td>
<td>c.505C&gt;G, c.806C&gt;G</td>
<td>p.(Arg169Gly), p.(Ala269Gly)</td>
<td>0.000217, 0.003592</td>
<td>LP, VUS</td>
<td>36 37</td>
</tr>
<tr>
<td>Case 7</td>
<td>c.505C&gt;G, c.806C&gt;G</td>
<td>p.(Arg169Gly), p.(Ala269Gly)</td>
<td>0.000217, 0.003592</td>
<td>LP, VUS</td>
<td>36 37</td>
</tr>
</tbody>
</table>

*“NC_000014.9(NM_152443.3);” omitted in all variant nomenclature.
†“NM_152443.3(NP_689656.2);” omitted in all variant nomenclature.
‡Minor allele frequency from East Asian, gnomAD v3.0.
§LOVD v3.0.
LOVD, Leiden Open Variation Database; LP, likely pathogenic; MAF, minor allele frequency; P, pathogenic; VUS, variant of unknown significance.
siblings, patients 3 and 4, being female and male, respectively. Such difference may suggest that biallelic RDH12 mutations presenting pseudocoloboma-like maculopathy had phenotypical variance that may be modified by additional environmental, physiological or other genetic factors. Analyses with larger patient cohorts may provide additional evidence.

Additionally, retinoic acid metabolism is essential for the normal morphogenesis of the eye, and disruption of this process may lead to various ocular defects including coloboma. For instance, aldehyde dehydrogenase family members are among the factors essential for eye development. In rodent models, knockout of Aldh1 family members causes congenital eye deformities such as uveal coloboma and optic fissure closure problems, while in humans, biallelic mutations in ALDH1A3 cause microphthalmia and anophthalmia. An animal model of ald7a1-knockdown zebrafish also showed that such genetic alteration can lead to the reduction of cell proliferation in the optic cup and disrupt the fusion process of the optic fissure. Nevertheless, a single genetic mutation in RDH12 may not sufficiently explain the formation of acquired pseudocoloboma-like lesions so far, and future studies are needed to elucidate the underlying mechanism.

In addition to RDH12, pseudocoloboma with early onset has been reported in patients with mutations in IDH3A (isocitrate dehydrogenase (NAD+) 3 catalytic subunit alpha, RP90), PAX6, or NMNAT1 (nicotinamide nucleotide adenlytransferase 1, LCA9). PAX6 is well known for its role in ocular development and defects are usually inherited in an autosomal dominant manner, while the other three are enzymes and mutations resulting in retinal diseases segregated in an autosomal recessive manner. Although located in different subcellular compartments, mitochondria for IDH3A, cytosol for RDH12 and nucleus for NMNAT1, all of these enzymes are involved in oxidation-reduction reactions. NMNAT1 catalyses the formation of NAD+ (nicotinamide adenine dinucleotide) from adenosine triphosphate and nicotinamide mononucleotide. IDH3A uses NAD+ as the electron acceptor for the oxidative decarboxylation of isocitrate to 2-oxoglutarate, and RDH12 catalyses the reduction of all-trans-retinal to all-trans-retinol using NADP+, the oxidized form of NADPH, as the electron acceptor, suggesting that inefficient metabolism of highly reactive oxidative molecules may lead to the development of a pseudocoloboma-like phenotype.

In our study, we identified seven frequently occurring mutations. The most frequent allele in the current report was p.Ala269Gly, followed by p.Arg169Gly, p.Val146Asp, p.Val60Thr and p.Ala60Thr. Notably, the p.Ala269Gly mutation has been rarely reported in the literature associated with retinopathy. The most common RDH12 mutation in another Chinese population was reported to be p.Val146Asp. In an Indian population, the most commonly found mutation was p.Cys201Arg; whereas the most frequent mutation was p.Ala269AlafsX1 in a group of British Caucasian participants.

Only one dominant mutation of RDH12 was identified in a large family affected with RPS3. This mutation, NC_000014.9(NM_152443.3): c.776del, is a single-nucleotide deletion at codon 259 resulting in a frameshift and premature termination after an extra 17 amino acids. The dominant inheritance of RPS3 suggests that there may be an important functional role in the last 57 amino acids of RDH12, and that the mutant RDH12 may interfere with the function of normal RDH12 in the cells of these patients, that is, in a dominant-negative manner, and resemble the loss of both alleles of RDH12.

In conclusion, we present seven cases from six families of RDH12-associated pseudocoloboma-like macular atrophy with variable disease onset, relatively normal ERG, and moderately impaired vision. All of these cases are compound heterozygotes for missense mutations in RDH12, in contrast to the nearly complete loss-of-function mutations in LCA and truncated RDH12 in adRP.

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Contributors Project design: S-JC, M-YC; Manuscript writing: S-JC, C-YK, M-YC; Patient recruitment and phenotyping: S-JC, C-YK; Genetic sequencing and interpretation: M-YC; Guarantor: S-JC.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Institutional Review Board of Taipei Veterans General Hospital (#2014-11-006B, #2021-02-021B) and conducted in accordance with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

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Competing interests

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