Prediction of the response to photodynamic therapy in patients with chronic central serous chorioretinopathy based on optical coherence tomography using deep learning

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ABSTRACT

Purpose: To assess the prediction of the response to photodynamic therapy (PDT) in chronic central serous chorioretinopathy (CSCR) based on spectral-domain optical coherence tomography (SD-OCT) images using deep learning (DL).

Methods: Retrospective study including 216 eyes of 175 patients with CSCR and persistent subretinal fluid (SRF) who underwent half-fluence PDT. SD-OCT macular examination was performed before (baseline) and 3 months after treatment. Patients were classified into groups by experts based on the response to PDT: Group 1, complete SRF resorption (n=100); Group 2, partial SRF resorption (n=66); and Group 3, absence of any SRF resorption (n=50). This work proposes different computational approaches: 1st approach compares all groups; 2nd compares groups 1 vs. 2 and 3 together; 3rd compares groups 2 vs. 3.

Results: The mean age was 55.6 ±10.9 years and 70.3% were males. In the first approach, the algorithm showed a precision of up to 57% to detect the response to treatment in group 1 based on the initial scan, with a mean average accuracy of 0.529 ±0.035. In the second model, the mean accuracy was higher (0.670 ±0.046). In the third approach, the algorithm showed a precision of 0.74 ± 0.12 to detect the response to treatment in group 2 (partial SRF resolution) and 0.69 ± 0.15 in group 3 (absence of SRF resolution).

Conclusion: Despite the high clinical variability in the response of chronic CSCR to PDT, this DL algorithm offers an objective and promising tool to predict the response to PDT treatment in clinical practice.

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Short Title: Response to PDT in chronic CSCR by OCT using deep learning.

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INTRODUCTION

Central serous chorioretinopathy (CSCR) is a chorioretinal disease that causes subretinal fluid (SRF) and retinal pigment epithelium (RPE) detachment in the posterior pole, associated with leakage areas from the choroid through defects in the RPE outer blood-retina barrier.[1,2] The chronic presence of this SRF can ultimately damage the RPE and result in the decreased visual acuity (VA) of patients.[2] The pathogenesis of CSCR remains poorly understood, although choroidal thickening, hyperpermeability and increased hydrostatic pressure have been postulated to play a role. Recently, it has been hypothesized that the vascular resistance and congestion of choroidal outflow in the vortex veins might be regulated by the thickness and rigidity of the sclera and it has been demonstrated that the anterior scleral thickness (AST) is increased in CSCR patients.[3]

Multimodal imaging is essential in order to accurately diagnose CSCR. The combined use of optical coherence tomography (OCT), indocyanine green angiography (ICGA) and fundus autofluorescence allows to distinguish between CSCR and similar conditions with overlapping clinical features.[1] Using OCT, the presence of SRF can be both assessed and quantified. This is generally considered useful for estimating the episode duration and for determining the subsequent treatment strategy.[4] The thickness and integrity of the retinal layers visualized on OCT might also be of interest to predict visual outcome.[5,6]

Photodynamic therapy (PDT) is often a successful treatment in non-resolving or chronic CSCR, accelerating the resolution of SRF with a favorable safety profile. The PLACE trial, the first large prospective randomized controlled trial for chronic CSCR, demonstrated that half-dose PDT is superior to high-density subthreshold micropulse laser (SML) and the former is thus considered the gold standard treatment.[7] PDT offers high efficacy for SRF resorption and VA stabilization or improvement in patients with CSCR.[2,6]

Nevertheless, response to PDT in clinical practice is variable and it is unknown which patients are going to have a good treatment response with complete resorption of SRF. SRF resolution with half-fluence PDT ranges from 67 to 97%, according to different series.[7–10] Moreover, different authors have described that certain clinical factors have been associated with a worse response to PDT such as advanced age, low baseline VA or the degree of RPE damage involvement.[2] However, there are few studies to objectively quantify the predictive value of these characteristics. Furthermore, although there are some known associated factors, which anatomical basal characteristics of patient, particularly in the OCT, can determine a good or bad response to PDT remain unknown.

The main artificial intelligence (AI) applications in ophthalmology aim at optimizing images and predicting clinical results.[11–13] However, to date, few studies have investigated their utility in the analysis of CSCR, although deep learning (DL) has proved good precision to detect CSCR using fundus images, as well as, to differentiate between acute and chronic form with imaging analysis.[14,15] Recently Xu et al. have published an AI-based work that has demonstrated that their DL and machine learning-based algorithms can predict within very small error VA and post-therapeutic OCT images in patients with CSCR.[16] Although they pointed out retinal integrity (retinal neuroepithelial layer) as the most important factor for predicting long-term VA, more OCT variables are probably involved and are still to be identified.

Therefore, the aim of this study is to assess the prediction of PDT response in chronic CSCR using OCT images pre and post treatment based on a DL algorithm.

METHODS

In this retrospective study, data from chronic CSCR patients treated with half-fluence PDT between January 2017 and December 2020 were analyzed. This study protocol was approved by the Ethics Committee of the Hospital Clínico San Carlos, in Madrid (HCSC). A total of 216 eyes of 175 patients were included, analyzing the pre- and post-PDT images of each affected eye.

Patients with another retinal pathology were excluded from the study, as well as those with OCT images with suboptimal quality. A comprehensive examination was performed based on clinical and biomicroscopy, funduscopy, OCT, FA and ICGA features of the disease. Inclusion criteria were patients over 18 years old who had been diagnosed with chronic CSCR and scheduled for half-fluence PDT in that time interval.

Photodynamic therapy

PDT was performed according to standard dosing protocol with an intravenous infusion of Verteporfin (Visudyne; Novartis AG, Michigan, USA) at 6 mg/m^2 in a 10-minute infusion. Laser administration was carried out 15 minutes after the start of the infusion with 693-nm wavelength (VitraPDT; Quantel Medical, Cournon-d'Auvergne, France) centered on the fovea. Half-fluence (25 J/cm^2) of light energy was delivered to the area of irradiation over 83 seconds, guided by OCT and also encompassing the hyperfluorescent areas in the middle to late phases of ICGA.

OCT explorations

Spectral domain optical coherence tomography (SD-OCT) images (Spectralis, Heidelberg Engineering, Heidelberg, Germany) were collected before PDT treatment and 3 months later. Macular cube images were extracted from the OCT images, which represent a macular area of 6 mm x 6 mm. Furthermore, 7 slabs from each patient were used. In this sense, central slices with the presence of pathological fluid were used, avoiding peripheral slices where no significant differences between patients are perceived and, therefore, decreasing the degrees of freedom of the analyzed problem. Consequently, a total of 1512 slices were used.

Patient Classifications

Patients were classified by experts (JIFV and VGC) according to the SRF resolution after PDT. Measurement and comparison of the SRF pre- and post-treatment were performed using the OCT software's own tools and the sample was divided into (Fig 1):

- Group 1: those who presented a complete resolution of the SRF (Fig 1A).
- Group 2: those with partial resolution of the SRF defined as a decrease of at least 15% of the baseline SRF height (Fig 1B).
- Group 3: those with no SRF resorption, defined as a decrease of less than 15% of the baseline SRF height (Fig 1C)**.**

Deep Learning Methodology

The proposed system receives an OCT image as input. As illustrated in Fig 2, we used a DL strategy based on a densely connected convolutional network to perform the prediction of the response to PDT in patients with CSCR and SRF. In order to perform a more comprehensive analysis, 3 fully automatic computational approaches were designed for the prediction tasks, considering the 3 groups of clinical relevance defined above: Group 1, 2 and 3. Finally, the proposed system presents, as output, useful information for a more precise analysis of the response to treatment.

Computational approaches for the prediction of the response to PDT

Different computational approaches were done to perform a comprehensive analysis of the prediction of the response to PDT in OCT images, considering 3 different clinical scenarios that are relevant in this context. Each of these approaches is explained below:

- 1st Approach: Predictive analytics of (Group 1) vs (Group 2) vs (Group 3). In this first approach, it was analyzed 3 possible cases of prediction of the response to PDT in CSCR eyes and persistent SRF: complete resorption; partial resorption; and absence of any resorption. In this way, a complete

analysis of the separability between all the clinical scenarios under consideration was performed in this work.

- 2nd Approach: Predictive analytics of (Group 1) vs (Group 2 + Group 3). In this second scenario, it was designed a predictive approach to analyze the degree of separability between positive and negative responses to PDT. For this purpose, the responses partial resorption and any resorption were grouped in the same class.

- 3rd Approach: Predictive analytics of (Group 2) vs (Group 3). Finally, it was designed a computational approach to determine the degree of class separability, considering only cases in which the prediction of response to PDT is negative (partial resorption and any resorption).

In addition, to provide a visual interpretation of the proposed approaches the Gradient Class Activation Map (Grad-CAM)[17] algorithm was used to generate the class activation maps of the predictive models, showing what the neural network sees. Complementarily, a color bar to indicate the degree of confidence using a scale with values between 0 and 1 was incorporated, allowing a better interpretation of the importance of each region in the prediction process. Figure 3 is a representative example of the activation map that was generated from the predictions, illustrating parts of the OCT images that were strongly activated.

Network architecture and training details

This work uses a Dense Convolutional Network Architecture (DenseNet) that was introduced by Huang et al.[18] Due to its excellent performance and implementation flexibility, DenseNet is one of the most popular and widely used artificial neural networks in medical image analysis. This architecture was originally proposed as a network that, due to its skip connections between the encoder and decoder, is able to return a prediction with a limited number of samples. The main principle of this architecture is to reuse image features in the network through densely connected blocks, thereby lifting the utilization rate of image features and optimizing neural network parameters. This way, the layers close to the original data can be updated more efficiently than in a conventional convolutional neural network. In addition, a transfer learning-based strategy has been used, which attempts to mitigate the data scarcity problem, which is very frequent in several domains of medical image analysis. To this end, we adapted a version of the DenseNet-121 architecture that was pre-trained with the ImageNet dataset.[9] Specifically, its final layer was replaced by a fully connected two-class/three-class layer and trained with available OCT data. A schematic representation of this architecture can be found in Fig 4.

For each computational approach, the OCT dataset was divided into mutually exclusive subsets, being 80% and 20% for training and testing, respectively. In addition, the weights from a model pretrained on the ImageNet dataset was used for the network initialization to mitigate the problem of data scarcity. In addition, this model was trained using cross-entropy as a loss function. The network weights optimization was performed using the algorithm of Stochastic Gradient Descent (SGD) with a constant learning rate with a value of $\alpha = 0.01$. In the same way, the value of mini-batch size was fixed to 4 and a first-order momentum of 0.9 was considered. Furthermore, a 10-fold cross-validation was used for the classification process and, in order to understand the overall behaviour of the trained models, the average accuracy is calculated.

Software and Hardware

This work has been developed using Python (version 3.9.9), given the flexibility it offers. In addition, it allows the use of PyTorch (version 1.8.1) as well as the helper libraries NumPy (version 1.18.3), Scikit-learn (version 1.0.2), OpenCV (version 4.5.2) and Pandas (version 1.1.4.). In terms of hardware resources, the training and validation process was performed using a computer (Intel® Core™ i7 8^{th} generation, 16 GB) with an NVIDIA® GeForce GTX 1060 6GB GDDR5.

Statistical Analysis

Qualitative variables were presented with their frequency distribution and quantitative variables were summarized with their mean and standard deviation. Quantitative variables showing an asymmetric distribution were summarized with the median and interquartile range.

Comparisons of means between more than two independent groups were performed by analysis of variance (ANOVA), or by the nonparametric Kruskal-Wallis test for asymmetric variables. A significance value of 5% was accepted for all tests. Data processing and analysis were performed using IBM SPSS Statistics v.26 statistical software.

Measurements Interpretation

The final performance of the system was expressed in measures of precision, recall, F1-score and accuracy:

- Precision denotes the proportion of predicted positive cases that are correctly real positives. Consequently, inverse precision is the proportion of predicted negative cases that are indeed real negatives.
- Recall is the proportion of real positive cases that are correctly predicted positive and in a medical context it is referred as the true positive rate. The

inverse recall is thus the proportion of real negative cases that are correctly predicted negative (True Negative Rate).

- F1-score references the true positives as the arithmetic mean of predicted positives and real positives which is the arithmetic mean of precision and recall.
- Accuracy explicitly takes into account the classification of negatives both as a weighted average of precision and inverse precision and as a weighted average of recall and inverse recall.[19]

RESULTS

Demographic features.

A total of 216 eyes of 175 patients were included; mean age was 55.6 ±10.8 years and 70.6% were males. In the gender distribution per group, the percentage of males remained stable: 68.2% in group 1, 81.8% in group 2 and 61.6% in group 3. There were statistically significant differences in mean age between groups (p=0.001), group 1 being the youngest (mean age of 52.6 ±10.5 years old); followed by group 2 (57.1 ±9.2 years) and by group 3 (59.6 ±12.1 years).

The mean baseline SRF height for the whole population was 128.8 ± 78.8 µm. Significant differences were also found in the mean SRF height between groups before PDT: Group 1: 129.5 ± 76,26 µm; Group 2: 150.0 ± 94.9 µm; and Group 3: 99.4 ± 44.7 µm (p=0.007).

Results 1st Approach: Predictive analytics of Group 1 vs. Group 2 vs. Group 3.

In this first approach, 100 patients were included in group 1, 66 in group 2 and 50 in group 3. The results are expressed in measures of precision, recall and F1-score in Table 1. The best precision was found for Group 1 with 0.57 ± 0.07 (mean and standard deviation), followed by Group 2 with 0.54 ± 0.19 and Group 3 with the lowest value of 0.32 ± 0.28. The mean accuracy in the model was 0.53 ± 0.03.

Results 2nd Approach: Predictive analytics of Group 1 vs. Group 2 + 3.

In this scenario, poor responses to PDT were pooled and a total of 116 eyes were included in group 2 and 3. The results of the unbalanced experiment are summarized in Table 2. In this case, both groups present a very similar precision, slightly higher for responses 2 and 3. The recall for detecting responses 2 and 3 was also higher (0.70 ± 0.15) than for detecting responses 1 (0.63 ± 0.18).

Results 3rd Approach: Predictive analytics of Group 2 vs Group 3.

In this last approach, a complementary analysis was performed including cases where the response to PDT was partial (N=66) or null (N=50). The results are summarized in Table 3. The precision for predicting response from group 2 and 3 was similar [(0.74 ± 0.12) and (0.69 ± 0.15) respectively] but the recall was markedly higher for the group 2 (0.75 ± 0.16). The accuracy was 0.68 ± 0.07, what means that for every 100 eyes that the system classifies as non-responder or partial responder, 68 are really non-responders or partial responders.

DISCUSSION

In the present study, an algorithm based on DL was developed to perform a predictive analysis of the response to PDT in patients with chronic CSCR based on the baseline OCT, achieving an accuracy of 53 – 68 %. The system offers a higher precision and accuracy for the 2nd and 3rd approaches, so it is more accurate in predicting the response of patients who will not have a complete SRF resolution after PDT. This represents interesting and valuable information, which enables to establish a more accurate prognosis for patients due to the high clinical variability after this treatment probably due to the multifactorial etiopathogenesis in CSCR.

In the past years, some clinical factors that may predict a poor response to PDT or a high probability of recurrences in patients with chronic CSCR have been described. Inoue et al. reported in a retrospective study with 32 patients that the effectiveness of PDT differed depending on the degree of hyperpermeability on ICGA at baseline and concluded that PDT was not effective in eyes without intense hyperfluorescence.[20] Fujita et al. showed in a retrospective nonrandomized study of 255 eyes that patients with intermediate hyperpermeability on ICGA and lower BCVA at baseline were less likely to respond to half-dose PDT than those with intense hyperpermeability.[9] In agreement, Chung et al. showed in a consecutive series of 61 cases of chronic CSCR treated with half-dose PDT that the baseline BCVA was significantly associated with BCVA post treatment. They also reported that diffuse hyperfluorescence ICGA pattern, shallow irregular retinal pigment epithelium detachments (RPED) and disruption of the ellipsoid zone predicted a poor prognosis.[21] Van Rissent et al. concluded that the absence of intense hyperfluorescence on ICGA is associated with a less favorable response to PDT.[22] Nicolo et al. hypothesized that posterior cystoid retinal degeneration might be another predictive factor of PDT effectiveness.[23]

In addition, different authors such as Haga et al., have shown that advanced age is a negative prognostic factor for response to PDT in CSCR.[24] Van Rissent et al. also showed that patients with CSCR and persistent SRF after PDT were older

compared with the group of patients with successful treatment.[22] In this study, the mean age of the sample is in line with previous studies, as well as the gender distribution, and there are significant differences between the mean age in the groups; the younger patients showed the best response to PDT in the sample. This is consistent with the age and PDT response associations found to date as mentioned previously.

Overall, six negative predictive factors to PDT response in CSCR have been described until now: older age, poor baseline BCVA, an absence of an intense hyperfluorescent area on ICGA, a disruption in the ellipsoid zone in OCT, a diffuse hyperfluorescent pattern on ICGA and the presence of shallow irregular RPED on OCT. In addition to these predictive factors, our algorithm could be an objective and complementary tool to make a prediction of the response to the PDT based only on the baseline OCT.

On the other hand, there exists some variability in the proportion of patients with a complete response after the therapy. Most of studies have reported percentages between 70 – 88 % of complete resorption.[6,9,25,26] However, Lai et al. in a multicentric study with 136 eyes reported a higher percentage 97.1 %.[8] By contrast in the PLACE trial, the values were lower after 7-8 months of follow-up period, finding a 67.2 % of complete resorption of SRF in the group treated with half- fluence PDT.[7] This variability may be due to the differences on the degree of severity of the CSCR between the samples and the presence or absence of negative predictive factors not being considered. In addition, the multifactorial pathophysiology in CSCR could have an impact on the results.

In clinical practice, having objective tools such as these algorithms can serve to compare future therapeutic alternatives in clinical trials in CSCR and to predict more accurately non-responders, in order to design individually targeted therapies and avoid unnecessary secondary adverse effects such as atrophy or choroidal neovascularization (CNV) after PDT.[2] In this regard, early vessel occlusion followed by recanalization has been shown to occur in the first few days after PDT,[27] but sometimes Verteporfin selectively accumulates around the permeable choroidal area leading to reduced blood flow which can produce an irreversible occlusion of the choroidal vessels.[15] Consequently, vascular growth factors (VEGF) can be induced contributing to the development of CNV which is a very important side effect to take into account in these patients.[28] Besides, there are cases reported in the literature in which severe choroidal ischaemia is developed after full PDT.[29] Acute exudative maculopathy (PAEM) is also frequent after PDT but with a favorable evolution as Fernández-Vigo et al. have described in their prospective study.[30] In summary, to avoid these possible complications, DL can be a useful to help the clinician to know in advance which patients are not going to have a good response. Finally, at the time that this

manuscript is being written, there is a worldwide shortage of verteporfin. Therefore, a tool that could elucidate which patients could benefit most from PDT treatment is of great clinical interest.[31]

On the other hand, the use of AI in retinal pathology is growing in this technological era. Diabetic retinopathy, age-related macular degeneration and central venous obstruction are the diseases more commonly explored given their high prevalence and they are based on OCT image or fundus retinography.[13,32,33] DL is also an emerging field of study in CSCR and there are many lines of research.[14,34] Similar to our study, Xu et al. have recently published the first work to predict de VA and OCT images in patients with CSCR treated with laser, SML and PDT using DL with promising results. However, they did not separate patients by acute or chronic form of CSCR and they collect data from the first (416 eyes), third (322 eyes) and sixth month (258 eyes) after treatment. The VA and post-therapeutic OCT images predicted by AI models were compared with the ground truth and they developed three simplified prediction models; the first model was based on different clinical data and all OCT features; the second model was trained with VA and five OCT features (ellipsoid zone baseline integrity, central macular thickness, retinal neuroepithelial layer, double layer sign and choroidal thickness); the third model was only based on the five OCT features. Their first and second simplified models achieved a promising level of predictive power in terms of mean absolute error, whereas the short-term predictive power of model three declined slightly. They showed that for patients with CSCR the most significant predictor of short-term VA was the most recent VA measurement and for the long-term VA predictions, the retinal integrity. They also supported that the choice of conventional laser treatment, SML treatment or PDT is less important[16] in contrast with what the PLACE study demonstrated in 2018.[7]

As can be seen, prediction is a major challenge in the development of machine learning-based systems in medical image analysis. On one hand, the acquisition of non-standardized medical images using different scanning protocols provides OCT images with different characteristics in terms of brightness, contrast, size, scale and spatial resolution. This requires the use of sophisticated machine learning techniques, such as DL, to address these challenges and attempt to mitigate most of these problems. On the other hand, morphological changes associated with treatment response in individuals are very faint in some cases, which makes assessment by visual inspection a difficult and tedious task, even for clinical experts with many years of experience. In this sense, diagnostic support systems allow the automatic extraction of objective and valuable information, facilitating analysis and decision-making in clinical practice.

As mentioned above, this algorithm shows an accuracy above 50%, but is variable between the groups. This is because CSCR is a very heterogeneous and multifactorial entity that depends on external factors that have not been studied in this work, such as stress levels, corticosteroid treatments or personality type.[35] Differences are also noted in age and height of SRF between the groups in this study. Future research with larger sample sizes and more homogeneous groups are needed to increase the validity of these results. Another limitation is that DL does not allow us to know with certainty what parameters of the images the algorithm uses to make its predictions and therefore this study uses activation maps, where the warmer colors correspond to the areas with SRF confirming that it is one of the key parameters to take into account in this pathology.

Finally, it is necessary to point out that CSCR prevalence is increasing, being the fifth macular disease more common at present time but with the peculiarity that it mainly affects patients of working age.[36] The chronic form can severely affect patient's quality of life with a severe loss of BCVA that in some cases may lead to work incapacity with the psychological, social and economic repercussions that this can entail. This DL system can support the clinician in providing realistic expectations and establishing a more accurate visual prognosis of each patient. Besides, it is based on non-invasive OCT imaging, which is useful, quick and applicable in our daily clinical practice. In summary, predicting PDT response in chronic CSCR using OCT scans is a very complex problem and, although there is still a major problem with dimensionality, the results shown here are promising.

In conclusion, this is the first DL-based algorithm that offers an objective and promising tool to complement clinical practice and therapeutic decisions based on the prediction of response to PDT in patients with chronic CSCR.

Figure legends

Fig. 1. Spectral domain optical coherence tomography (SD-OCT) images (Heidelberg Spectralis, Heidelberg Engineering, Heidelberg, Germany) from patients with chronic central serous chorioretinopathy (CSCR) before photodynamic therapy (PDT) and 3 months later, classified according to the subretinal fluid (SRF) resolution after PDT. A,B: Patient from Group 1, pre TFD (A) and post PDT (B) that shows a total resorption of SRF. C,D: Patient from Group 2, pre TFD (C) and post TFD (D) with a partial resolution of SRF. E, F: Patient from Group 3 pre TFD (E) and post TFD (F) without response post PDT.

Fig. 2. Overall graphical description of the proposed methodology. For each scenario, our algorithm receives as input an OCT scan and obtains as output a value associated to the prediction (Group 1, 2 or 3) which is the possible value of the estimated response.

Fig. 3. Activation map representing the importance of each region in the prediction process with a scale showing the degree of confidence of each colour; between 0 (cold colours) and 1 (warm colours). Areas with subretinal fluid are shown in red, which could mean that they have been more important to make the final prediction to our algorithm.

Fig. 4. Schematic illustration of the DenseNet-121 architecture employed.

[1] A. Daruich, A. Matet, A. Dirani, E. Bousquet, M. Zhao, N. Farman, F. Jaisser, F. Behar-Cohen, Central serous chorioretinopathy: Recent findings and new physiopathology hypothesis., Prog. Retin. Eye Res. 48 (2015) 82–118. https://doi.org/10.1016/j.preteyeres.2015.05.003.

[2] T.J. van Rijssen, E.H.C. van Dijk, S. Yzer, K. Ohno-Matsui, J.E.E. Keunen, R.O. Schlingemann, S. Sivaprasad, G. Querques, S.M. Downes, S. Fauser, C.B. Hoyng, F.C. Piccolino, J.K. Chhablani, T.Y.Y. Lai, A.J. Lotery, M. Larsen, F.G. Holz, K.B. Freund, L.A. Yannuzzi, C.J.F. Boon, Central serous chorioretinopathy: Towards an evidence-based treatment guideline., Prog. Retin. Eye Res. 73 (2019) 100770. https://doi.org/10.1016/j.preteyeres.2019.07.003.

[3] J.I. Fernández-Vigo, F.J. Moreno-Morillo, H. Shi, F. Ly-Yang, B. Burgos-Blasco, N. Güemes-Villahoz, J. Donate-López, J. García-Feijóo, Assessment of the anterior scleral thickness in central serous chorioretinopathy patients by optical coherence tomography., Jpn. J. Ophthalmol. 65 (2021) 769–776. https://doi.org/10.1007/s10384-021-00870-4.

[4] M. Cho, A. Athanikar, J. Paccione, K.J. Wald, Optical coherence tomography features of acute central serous chorioretinopathy versus neovascular age-related macular degeneration., Br. J. Ophthalmol. 94 (2010) 597–9. https://doi.org/10.1136/bjo.2008.149724.

[5] T.J. van Rijssen, D. Mohabati, G. Dijkman, T. Theelen, E.K. de Jong, E.H.C. van Dijk, C.J.F. Boon, Correlation between redefined optical coherence tomography parameters and best-corrected visual acuity in non-resolving central serous chorioretinopathy treated with half-dose photodynamic therapy., PLoS One. 13 (2018) e0202549. https://doi.org/10.1371/journal.pone.0202549.

[6] F.J. Moreno-Morillo, J.I. Fernández-Vigo, N. Güemes-Villahoz, B. Burgos-Blasco, L. López-Guajardo, J. Donate-López, Update on the management of chronic central serous chorioretinopathy., Arch. Soc. Esp. Oftalmol. 96 (2021) 251–264. https://doi.org/10.1016/j.oftal.2020.07.023.

[7] E.H.C. van Dijk, S. Fauser, M.B. Breukink, R. Blanco-Garavito, J.M.M. Groenewoud, J.E.E. Keunen, P.J.H. Peters, G. Dijkman, E.H. Souied, R.E. MacLaren, G. Querques, S.M. Downes, C.B. Hoyng, C.J.F. Boon, Half-Dose Photodynamic Therapy versus High-Density Subthreshold Micropulse Laser Treatment in Patients with Chronic Central Serous Chorioretinopathy: The PLACE Trial., Ophthalmology. 125 (2018) 1547–1555. https://doi.org/10.1016/j.ophtha.2018.04.021.

[8] F.H.P. Lai, D.S. Ng, M. Bakthavatsalam, V.C.K. Chan, A.L. Young, F.O.J. Luk, C.W. Tsang, M.E. Brelén, A Multicenter Study on the Long-term Outcomes of Half-dose Photodynamic Therapy in Chronic Central Serous Chorioretinopathy., Am. J. Ophthalmol. 170 (2016) 91–99. https://doi.org/10.1016/j.ajo.2016.07.026.

[9] K. Fujita, Y. Imamura, K. Shinoda, C.S. Matsumoto, Y. Mizutani, K.

Hashizume, A. Mizota, M. Yuzawa, One-year outcomes with half-dose verteporfin photodynamic therapy for chronic central serous chorioretinopathy., Ophthalmology. 122 (2015) 555–61. https://doi.org/10.1016/j.ophtha.2014.09.034.

[10] J.I. Lim, A.R. Glassman, L.P. Aiello, U. Chakravarthy, C.J. Flaxel, R.F. Spaide, R. and E.C. and W.C. Macula Society CSC Collaborative Study Group, Collaborative retrospective macula society study of photodynamic therapy for chronic central serous chorioretinopathy., Ophthalmology. 121 (2014) 1073–8. https://doi.org/10.1016/j.ophtha.2013.11.040.

[11] R. Poplin, A. V Varadarajan, K. Blumer, Y. Liu, M. V McConnell, G.S. Corrado, L. Peng, D.R. Webster, Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning., Nat. Biomed. Eng. 2 (2018) 158–164. https://doi.org/10.1038/s41551-018-0195-0.

[12] V. Gulshan, L. Peng, M. Coram, M.C. Stumpe, D. Wu, A. Narayanaswamy, S. Venugopalan, K. Widner, T. Madams, J. Cuadros, R. Kim, R. Raman, P.C. Nelson, J.L. Mega, D.R. Webster, Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs., JAMA. 316 (2016) 2402–2410. https://doi.org/10.1001/jama.2016.17216.

[13] J. De Fauw, J.R. Ledsam, B. Romera-Paredes, S. Nikolov, N. Tomasev, S. Blackwell, H. Askham, X. Glorot, B. O'Donoghue, D. Visentin, G. van den Driessche, B. Lakshminarayanan, C. Meyer, F. Mackinder, S. Bouton, K. Ayoub, R. Chopra, D. King, A. Karthikesalingam, C.O. Hughes, R. Raine, J. Hughes, D.A. Sim, C. Egan, A. Tufail, H. Montgomery, D. Hassabis, G. Rees, T. Back, P.T. Khaw, M. Suleyman, J. Cornebise, P.A. Keane, O. Ronneberger, Clinically applicable deep learning for diagnosis and referral in retinal disease., Nat. Med. 24 (2018) 1342–1350. https://doi.org/10.1038/s41591-018-0107-6.

[14] Y. Zhen, H. Chen, X. Zhang, X. Meng, J. Zhang, J. Pu, ASSESSMENT OF CENTRAL SEROUS CHORIORETINOPATHY DEPICTED ON COLOR FUNDUS PHOTOGRAPHS USING DEEP LEARNING., Retina. 40 (2020) 1558–1564. https://doi.org/10.1097/IAE.0000000000002621.

[15] W.-M. Chan, D.S.C. Lam, T.Y.Y. Lai, B.S.M. Tam, D.T.L. Liu, C.K.M. Chan, Choroidal vascular remodelling in central serous chorioretinopathy after indocyanine green guided photodynamic therapy with verteporfin: a novel treatment at the primary disease level., Br. J. Ophthalmol. 87 (2003) 1453–8. https://doi.org/10.1136/bjo.87.12.1453.

[16] F. Xu, C. Wan, L. Zhao, S. Liu, J. Hong, Y. Xiang, Q. You, L. Zhou, Z. Li, S. Gong, Y. Zhu, C. Chen, L. Zhang, Y. Gong, L. Li, C. Li, X. Zhang, C. Guo, K. Lai, C. Huang, D. Ting, H. Lin, C. Jin, Predicting Post-Therapeutic Visual Acuity and OCT Images in Patients With Central Serous Chorioretinopathy by Artificial Intelligence., Front. Bioeng. Biotechnol. 9 (2021) 649221. https://doi.org/10.3389/fbioe.2021.649221.

[17] R. Selvajaru, A. Cogswell, R. Vedantam, D. Parikh, D. Batra, Explanations

from Deep Networks via Gradient-Based Localization, IEEE International Conference on Computer Vision (ICCV) (2017) 618–26.

[18] G. Huang, Z. Liu, L. Van den Maaten, K. Winberger, Densely connected convolutional networks, Proc IEEE Conf Comput Vis Pattern Recognit. (2017) 2261–7.

[19] D. Powers, Evaluation: From Precision, Recall and F-Factor to ROC, Informedness, Markedness & Correlation, Mach. Learn. Technol. 2 (2008).

[20] R. Inoue, M. Sawa, M. Tsujikawa, F. Gomi, Association between the efficacy of photodynamic therapy and indocyanine green angiography findings for central serous chorioretinopathy., Am. J. Ophthalmol. 149 (2010) 441-6.e1–2. https://doi.org/10.1016/j.ajo.2009.10.011.

[21] C.Y. Chung, Y.Y. Chan, K.K.W. Li, Angiographic and Tomographic Prognostic Factors of Chronic Central Serous Chorioretinopathy Treated with Half-Dose Photodynamic Therapy., Ophthalmologica. 240 (2018) 37–44. https://doi.org/10.1159/000484100.

[22] T.J. van Rijssen, E.H.C. van Dijk, G. Dijkman, C.J.F. Boon, Clinical characteristics of chronic central serous chorioretinopathy patients with insufficient response to reduced-settings photodynamic therapy., Graefe's Arch. Clin. Exp. Ophthalmol. 256 (2018) 1395–1402. https://doi.org/10.1007/s00417-018-4003-z.

[23] M. Nicolò, D. Zoli, M. Musolino, C.E. Traverso, Association between the efficacy of half-dose photodynamic therapy with indocyanine green angiography and optical coherence tomography findings in the treatment of central serous chorioretinopathy., Am. J. Ophthalmol. 153 (2012) 474-480.e1. https://doi.org/10.1016/j.ajo.2011.08.015.

[24] F. Haga, R. Maruko, C. Sato, K. Kataoka, Y. Ito, H. Terasaki, Long-term prognostic factors of chronic central serous chorioretinopathy after half-dose photodynamic therapy: A 3-year follow-up study., PLoS One. 12 (2017) e0181479. https://doi.org/10.1371/journal.pone.0181479.

[25] M. Nicoló, C.M. Eandi, C. Alovisi, F.M. Grignolo, C.E. Traverso, D. Musetti, F. Cardillo Piccolino, Half-fluence versus half-dose photodynamic therapy in chronic central serous chorioretinopathy., Am. J. Ophthalmol. 157 (2014) 1033–7. https://doi.org/10.1016/j.ajo.2014.01.022.

[26] D. Mohabati, E.H. van Dijk, T.J. van Rijssen, E.K. de Jong, M.B. Breukink, J.P. Martinez-Ciriano, G. Dijkman, C.B. Hoyng, S. Fauser, S. Yzer, C.J. Boon, Clinical spectrum of severe chronic central serous chorioretinopathy and outcome of photodynamic therapy., Clin. Ophthalmol. 12 (2018) 2167–2176. https://doi.org/10.2147/OPTH.S174573.

[27] J.I. Fernández-Vigo, F.J. Moreno-Morillo, B. Burgos-Blasco, L. López-Guajardo, J. Donate-López, Early vessel occlusion and recanalization after photodynamic therapy in central serous chorioretinopathy by OCT angiography., Eur. J. Ophthalmol. (2021) 11206721211027060. https://doi.org/10.1177/11206721211027060.

[28] Z. Zhang, X. Bao, Z. Wu, J. Zhang, Choroidal neovascularization secondary to half-dose photodynamic therapy for chronic central serous chorioretinopathy: A case report., Medicine (Baltimore). 100 (2021) e24790. https://doi.org/10.1097/MD.0000000000024790.

[29] P.Y. Lee, K.S. Kim, W.K. Lee, Severe choroidal ischemia following photodynamic therapy for pigment epithelial detachment and chronic central serous chorioretinopathy., Jpn. J. Ophthalmol. 53 (2009) 52–56. https://doi.org/10.1007/s10384-008-0613-z.

[30] J.I. Fernández-Vigo, F.J. Moreno-Morillo, A. Valverde-Megías, B. Burgos-Blasco, L. López-Guajardo, J. Donate-López, ACUTE EXUDATIVE MACULOPATHY AND BACILLARY LAYER DETACHMENT IN PATIENTS WITH CENTRAL SEROUS CHORIORETINOPATHY AFTER PHOTODYNAMIC THERAPY., Retina. 42 (2022) 859–866. https://doi.org/10.1097/IAE.0000000000003404.

[31] M.J. Sirks, E.H.C. van Dijk, N. Rosenberg, C.E.M. Hollak, S. Aslanis, C.M.G. Cheung, I. Chowers, C.M. Eandi, K.B. Freund, F.G. Holz, P.K. Kaiser, A.J. Lotery, K. Ohno-Matsui, G. Querques, Y. Subhi, R. Tadayoni, C.C. Wykoff, D. Zur, R.M.H. Diederen, C.J.F. Boon, R.O. Schlingemann, Clinical impact of the worldwide shortage of verteporfin (Visudyne®) on ophthalmic care., Acta Ophthalmol. (2022). https://doi.org/10.1111/aos.15148.

[32] Y. Wang, Y. Zhang, Z. Yao, R. Zhao, F. Zhou, Machine learning based detection of age-related macular degeneration (AMD) and diabetic macular edema (DME) from optical coherence tomography (OCT) images., Biomed. Opt. Express. 7 (2016) 4928–4940. https://doi.org/10.1364/BOE.7.004928.

[33] F. Antaki, R.G. Coussa, G. Kahwati, K. Hammamji, M. Sebag, R. Duval, Accuracy of automated machine learning in classifying retinal pathologies from ultra-widefield pseudocolour fundus images., Br. J. Ophthalmol. (2021). https://doi.org/10.1136/bjophthalmol-2021-319030.

[34] J. Yoon, J. Han, J.I. Park, J.S. Hwang, J.M. Han, J. Sohn, K.H. Park, D.D.-J. Hwang, Optical coherence tomography-based deep-learning model for detecting central serous chorioretinopathy., Sci. Rep. 10 (2020) 18852. https://doi.org/10.1038/s41598-020-75816-w.

[35] R. Kaye, S. Chandra, J. Sheth, C.J.F. Boon, S. Sivaprasad, A. Lotery, Central serous chorioretinopathy: An update on risk factors, pathophysiology and imaging modalities., Prog. Retin. Eye Res. 79 (2020) 100865. https://doi.org/10.1016/j.preteyeres.2020.100865.

[36] M. Wang, I.C. Munch, P.W. Hasler, C. Prünte, M. Larsen, Central serous chorioretinopathy., Acta Ophthalmol. 86 (2008) 126–45. https://doi.org/10.1111/j.1600-0420.2007.00889.x.

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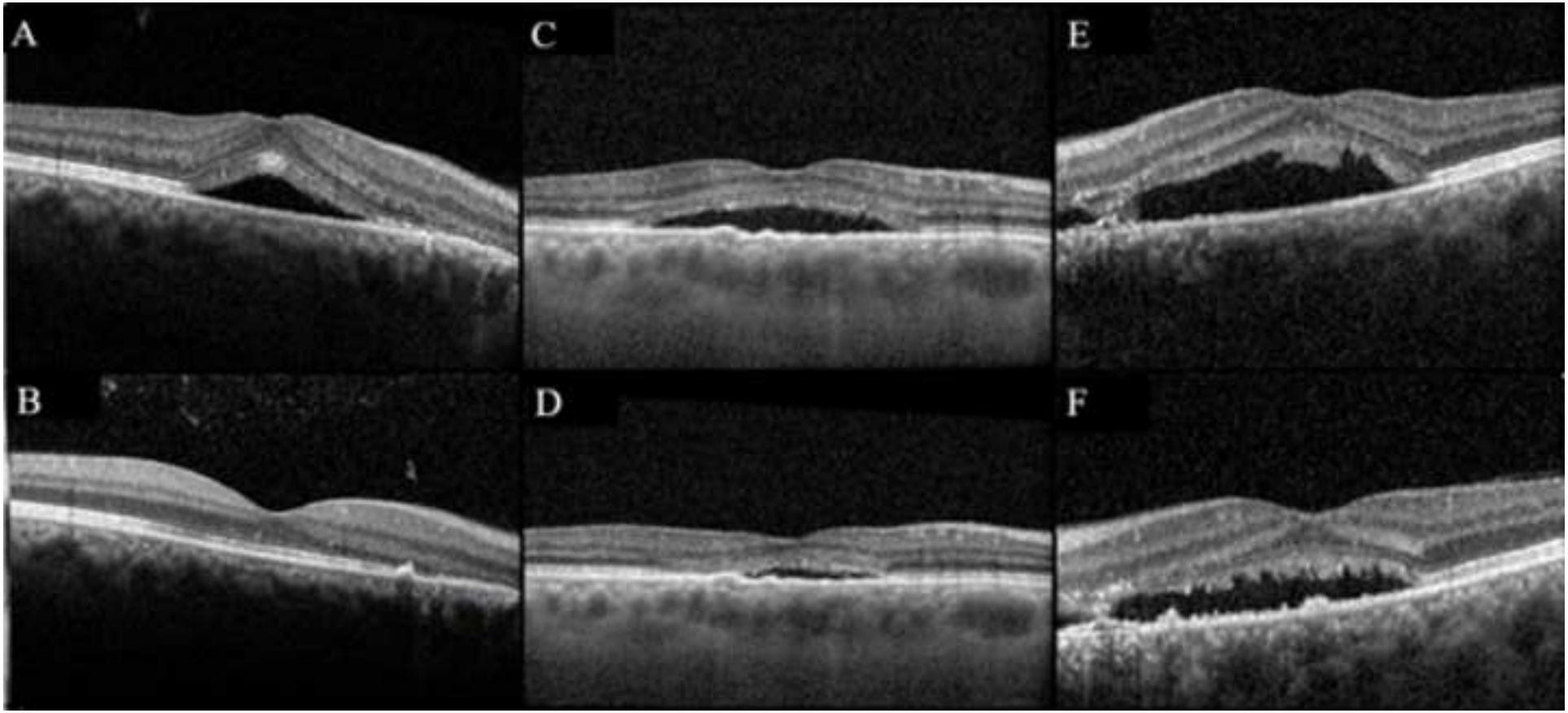

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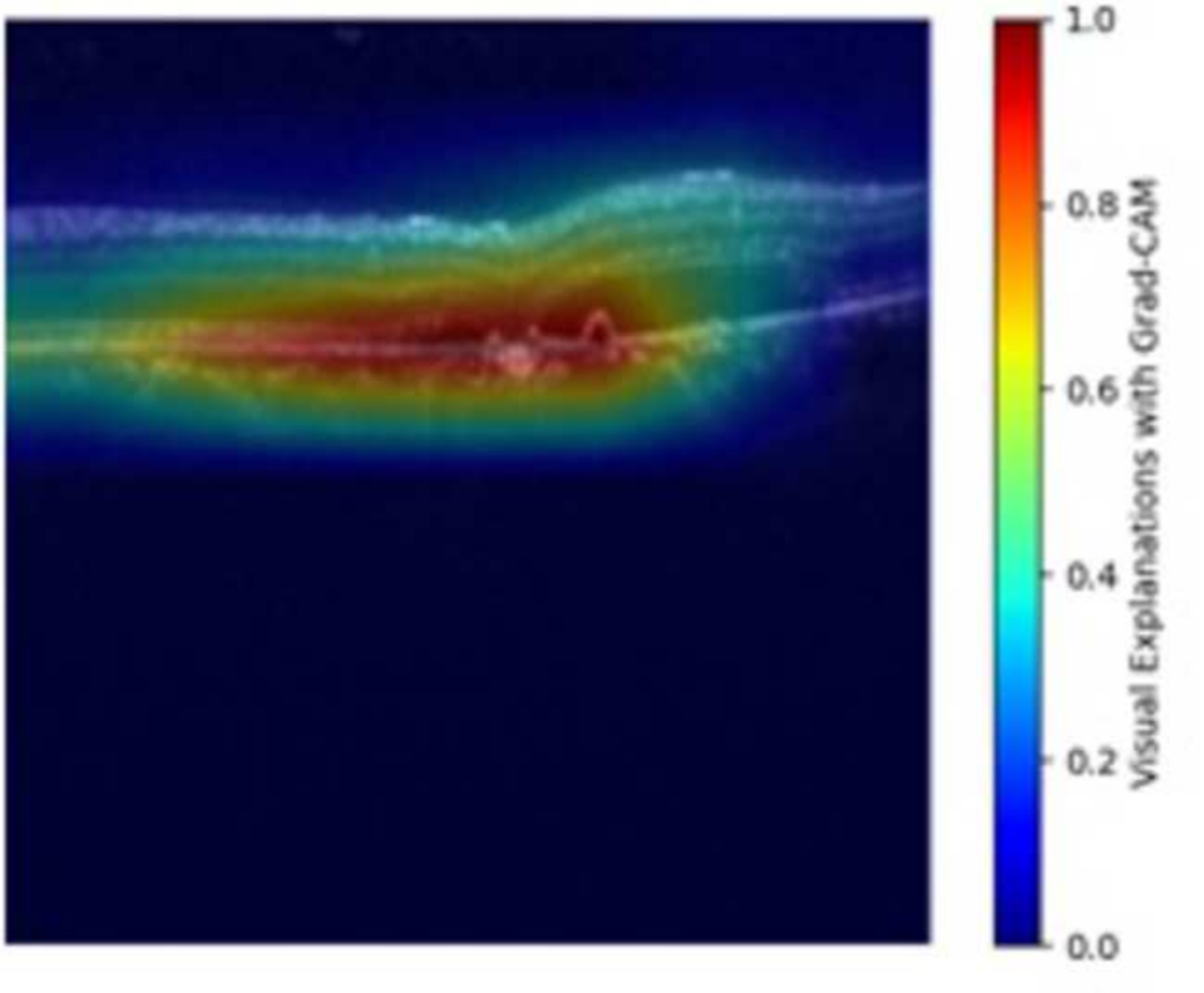

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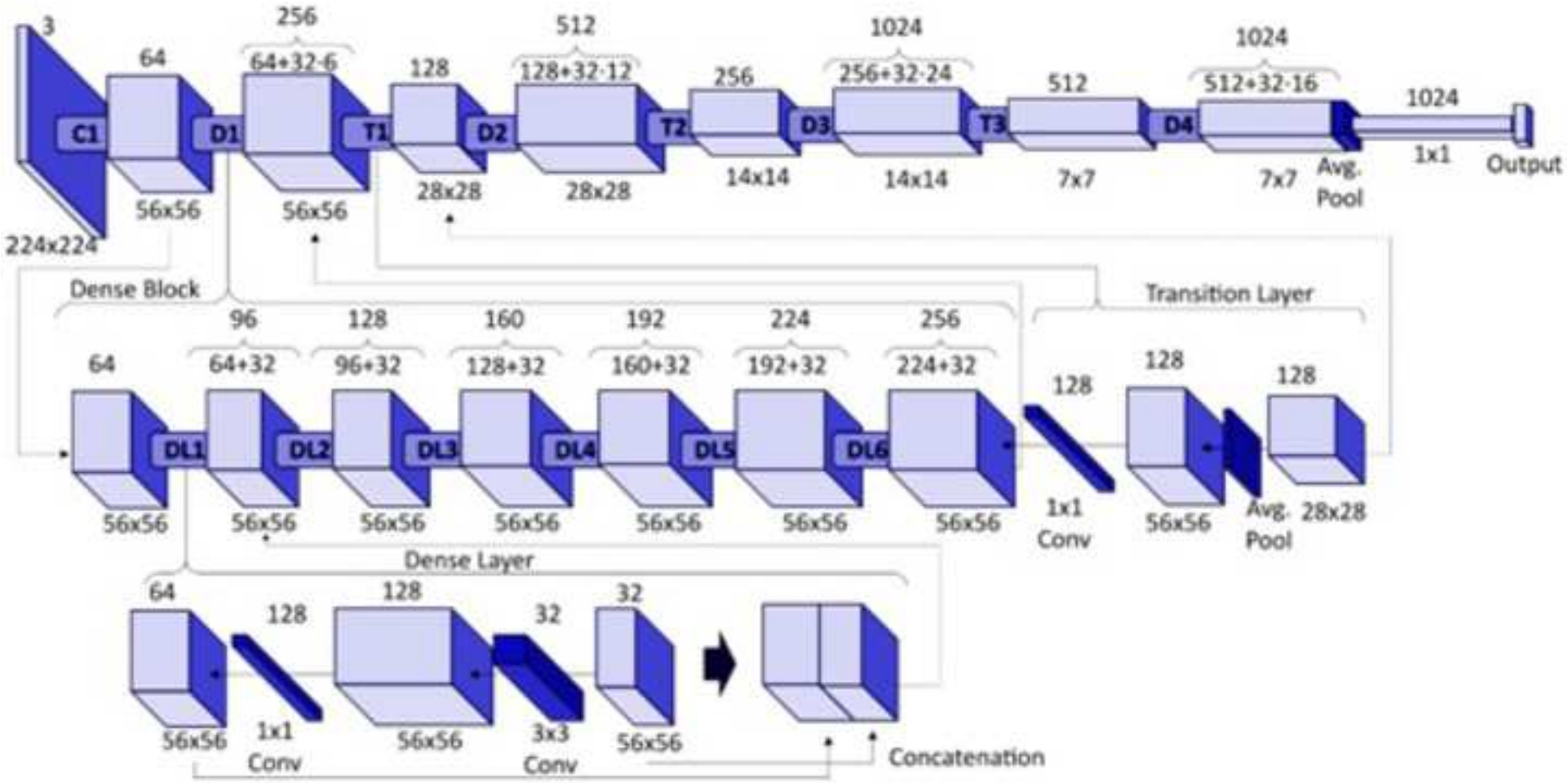

Table 1. Outcome variables in predictive analytics of Group 1 (complete subretinal fluid (SRF) resorption) vs. group 2 (partial SRF resorption) vs. group 3 (absence of any SRF resorption).

	Precision (μ ± σ)		Recall (μ ± σ)		F1-score (μ ± σ)		Accuracy (μ ± σ)	
Group 1	0.57	0.07	0.77	0.22	0.63	0.08	0.53	0.03
Group 2	0.54	0.19	0.37	0.20	0.39	0.12		
Group 3	0.32	0.28	0.27	0.25	0.29	0.26		

Table 2. Outcome variables of predictive analytics of Group 1 (complete subretinal fluid (SRF) resorption) vs Group 2 + 3 (partial SRF resorption + absence of any SRF resorption).

	Precision (μ ± σ)		Recall (μ ± σ)		F1-score (μ ± σ)		Accuracy (μ ± σ)	
Group 1	0.66	0.07	0.63	0.18	0.63	0.10	0.67	0.05
Group 2+3	0.71	0.09	0.70	0.15	0.69	0.07		

Table 3. Outcome variables of predictive analytics of Group 2 vs. Group 3 (partial SRF resorption vs absence of any SRF resorption).

	Precision (μ ± σ)		Recall (μ ± σ)		F1-score (μ ± σ)		Accuracy (μ ± σ)	
Group 2	0.74	0.12	0.75	0.16	0.73	0.06	0.68	0.07
Group 3	0.69	0.15	0.60	0.29	0.58	0.21		