Stage-specific risk stratification of diabetic retinopathy progression based on integration of OCT parameters and systemic biomarkers of inflammation and endothelial dysfunction

Mogilevskyy S. Yu. [1], Serdiuk A. V. [2], Serdiuk V. N. [2], Babenko M. S. [3], Ziablitsev S. V. [3]

[1] Shupyk National University of Health Care of Ukraine, Kyiv (Ukraine)
[2] Dnipro State Medical University, Dnipro (Ukraine)
[3] Bogomolets National Medical University, Kyiv (Ukraine)

Стадія-специфічна стратифікація ризику прогресування діабетичної ретинопатії на основі інтеграції ОКТ-параметрів і системних біомаркерів запалення та ендотеліальної дисфункції

Могілевський С. Ю. [1], Сердюк А. В. [2], Сердюк В. Н. [2], Бабенко М. С. [3], Зябліцев С. В. [3]

[1] Національний університет охорони здоров'я України імені П. Л. Шупика, Київ (Україна)
[2] Дніпровський державний медичний університет, Дніпро (Україна)
[3] Національний медичний університет імені О. О. Богомольця, Київ (Україна)

Abstract

Purpose. *To assess the prognostic value of clinical and instrumental parameters and serum biomarkers of inflammation and endothelial dysfunction for the development of stage-specific risk stratification of rapid progression of diabetic retinopathy (DR) and prediction of treatment failure in patients with type 2 diabetes.*

Material and methods. *A prospective study (2 years of follow-up) included 358 patients with type 2 diabetes and DR: 189 with nonproliferative (NPDR), 96 with preproliferative (PPDR) and 73 with proliferative (PDR). Biomarker analysis was performed in a subgroup (n=136). General clinical indicators, OCT parameters – central retinal thickness (CRT) and macular volume (MV) and serum biomarker levels – von Willebrand factor (vWF), L-selectin (LS), E-selectin (ES), endothelin-1 (ET-1), high-sensitivity C-reactive protein, endothelial-monocyte activating polypeptide II (EMAP II), endothelial NO synthase (eNOS), tumor necrosis factor α (TNF-α), interleukin-1β and -6 (IL-1β, IL-6), NO metabolites were determined. Patients received stage-specific treatment (conservative, laser, anti-VEGF, vitrectomy or their combination). Ineffectiveness of therapy (rapid progression of DR) was assessed using multivariate logistic regression and ROC-analysis.*

Results. *Among the clinical and instrumental parameters, the highest independent prognostic value was possessed by OCT indices, glycosylated hemoglobin (HbA1c), the presence of maculopathy and diabetic macular edema. The maximum discriminatory ability of CRT and MV was observed in PPDR (AUC 0.834 and 0.824, respectively). Among the biomarkers, the most informative were LS, EMAP II, ES, IL-1β and eNOS. The best stage-specific accuracy was found in: LS in NPDR (AUC 0.979), IL-1β in PPDR (AUC 0.990), as well as EMAP II (AUC 0.988) and eNOS (AUC 0.952) in PDR. The use of optimized thresholds allowed to identify high-risk groups, where the proportion of rapid progression exceeded 80–85% regardless of the chosen treatment method.*

Conclusion. *Treatment failure in DR in patients with T2DM is markedly stage-specific. Integration of OCT parameters with serum biomarkers of inflammation and endothelial*

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Corresponding Author: Serdiuk A. V., PhD, Ophthalmologist, Dnipro State Medical University, Dnipro, (Ukraine).
Email: anton777serdiyk@gmail.com

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dysfunction provides clinically meaningful risk stratification and can be used for early identification of patients with a high probability of rapid disease progression on standard initial therapy.

Keywords: *diabetic retinopathy; type 2 diabetes; optical coherence tomography; biomarkers; inflammatory mediators; vascular endothelium; treatment failure.*

Резюме

Мета. *Оцінити прогностичну цінність клініко-інструментальних параметрів і сироваткових біомаркерів запалення та ендотеліальної дисфункції для розробки стадія-специфічної стратифікації ризику швидкого прогресування діабетичної ретинопатії (ДР) і прогнозування неефективності лікування у хворих на цукровий діабет 2-го типу.*

Матеріал та методи. *У проспективне дослідження (два роки спостереження) включено 358 пацієнтів із ЦД2 та ДР: 189 із непроліферативною (НПДР), 96 із препроліферативною (ППДР) і 73 із проліферативною (ПДР). Біомаркерний аналіз проведено у підгрупі (n=136). Визначали загальноклінічні показники, параметри ОКТ – центральну товщину (ЦТС) і макулярний об'єм (МО) та рівні сироваткових біомаркерів – фактор фон Віллебранда (vWF), L-селектин (LS), E-селектин (ES), ендотелін-1 (ET-1), високочутливий С-реактивний протеїн, ендотеліально-моноцитарний активуючий поліпептид II (EMAP II), ендотеліальну NO-синтазу (eNOS), фактор некрозу пухлин α (TNF-α), інтерлейкін-1β та -6 (IL-1β, IL-6), метаболіти NO. Пацієнти отримували стадія-специфічне лікування (консервативне, лазерне, анти-VEGF, вітректомія або їх комбінація). Неефективність терапії (швидке прогресування ДР) оцінювали за допомогою багатофакторної логістичної регресії та ROC-аналізу.*

Результати. *Серед клініко-інструментальних параметрів найвищу незалежну прогностичну цінність мали показники ОКТ, глікозильований гемоглобін (HbA1c), наявність макулопатії та діабетичного макулярного набряку. Максимальна дискримінаційна здатність ЦТС і МО спостерігалася при ППДР (AUC 0,834 та 0,824 відповідно). Серед біомаркерів найінформативнішими були LS, EMAP II, ES, IL-1β та eNOS. Найкращу стадія-специфічну точність виявили: LS при НПДР (AUC 0,979), IL-1β при ППДР (AUC 0,990), а також EMAP II (AUC 0,988) та eNOS (AUC 0,952) при ПДР. Застосування оптимізованих порогів дозволило ідентифікувати групи високого ризику, де частка швидкого прогресування перевищувала 80–85% незалежно від обраного методу лікування. Висновки. Неефективність лікування при ДР у хворих на ЦД2 має виражений стадія-специфічний характер. Інтеграція ОКТ-параметрів із сироватковими біомаркерами запалення та ендотеліальної дисфункції забезпечує клінічно значущу стратифікацію ризику й може бути використана для раннього виявлення пацієнтів із високою ймовірністю швидкого прогресування захворювання на тлі стандартної стартової терапії.*

Ключові слова: *діабетична ретинопатія; цукровий діабет 2-го типу; оптична когерентна томографія; біомаркери; медіатори запалення; судинний ендотелій; неефективність лікування.*

Introduction

Diabetic retinopathy (DR) is still a major microvascular complication of diabetes mellitus (DM) and a leading cause of visual loss among working-age individuals. Despite substantial advances in screening, imaging and treatment, DR is characterized by substantial clinical heterogeneity, making prognosis in an individual patient difficult [1–4].

Current clinical guidelines provide clear recommendations for managing patients based on the stage of DR, presence of diabetic macular edema, ischemic changes and neovascularization, and using particularly optimal systemic control, intravitreal anti-vascular endothelial growth factor (VEGF) agents and vitreoretinal surgery [2, 3]. However, not all patients show an expected anatomical and clinical response even to standard treatment algorithms. This points to the limited nature of a purely phenotype-based ophthalmoscopic stratification and further necessitates a search for tools that would allow a pre-treatment separation of groups at high risk for fast disease progression and failure of initial therapeutic strategy [4, 5].

DR has been increasingly recognized not only as local microvascular injury to the retina, but also as a clinically heterogenous neurovascular disorder involving ischemia, chronic low-grade inflammation, blood-retinal barrier breakdown, endothelial dysfunction and microcirculation remodeling [4, 6–9]. It is for this reason that combining the two parameter groups in predictive models is of special interest. The first group of parameters reflects the local structural and functional status of the retina, primarily based on optical coherence tomography (OCT). The second group of parameters characterizes the systemic pathobiochemical processes that may model the course of retinal damage in various stages of DR [5, 6, 10].

Today, OCT is a routine tool for assessing macular changes in DR, whereas the morphometric parameters (particularly, central retinal thickness (CRT) and macular volume (MV)) and macular involvement in DR have clear clinical value for characterizing the severity of diabetic retinal lesions [6, 11, 12]. Recent reviews, however, have demonstrated that the prognostic role of particular OCT parameters is not universal, with their relationships with functional consequences and treatment response varying depending on the lesion phenotype, therapy used and method of their standardization [11, 12]. This means that even informative OCT parameters should be interpreted only in the context of the stage of DR and associated systemic mechanisms.

Inflammation and endothelial dysfunction hold a central place among these mechanisms. Hyperglycemia, oxidative stress, accumulation of advanced glycation-end products, activation of pro-inflammatory cytokines and impaired vascular tone regulation contribute to retinal endothelial injury, increased vascular wall permeability, leukostasis, capillary occlusion and further ischemic progression [7–9]. In this context, serum biomarkers appear clinically promising, since they potentially enable minimally invasive assessment of the processes that are not always completely characterized by only ophthalmic signs [6, 10].

The most promising candidates include soluble adhesion molecules, anti-inflammatory mediators and markers of endothelial reactivity. Selectins play a key role in the early interaction of leukocytes with endothelial cells; L-selectin (LS) is associated with leukocyte activation and recruitment, whereas E-selectin (ES) reflects the activation of endothelial cells [13–15]. Soluble ES stands out as a potential predictor for development of retinopathy in type 2 diabetes [16]. Interleukin-1β (IL-1β) is a main mediator of inflammasome-mediated inflammation that has been increasingly recognized as a component of DR progression [8, 9, 17]. Endothelial nitric oxide synthase (eNOS) is pivotal for maintaining vascular homeostasis and regulating retinal blood flow, whereas impaired nitric oxide (NO)-dependent mechanisms are considered a component of endothelial dysfunction in diabetic microvascular lesions [7, 18]. Endothelial monocyte activating polypeptide II (EMAP-II) is a multifunctional pro-inflammatory mediator that has been associated previously with microvascular diabetic complications; however, its role in risk stratification in patients with DR has been covered to a limited extent [19].

Therefore, although the data available support the concept of multimodal prediction of the course of DR, most publications are related to (a) individual biomarkers or (b) the prediction of the presence or severity of DR or the response to treatment of narrow clinical phenotypes, most commonly, diabetic macular edema (DME) [5, 6, 10–12]. However, clinically useful prediction models integrating clinical and instrumental parameters of the retina with serum inflammatory and endothelial dysfunction biomarkers and taking into account the stage of DR remain insufficiently developed.

The purpose of this study was to assess the prognostic value of clinical and instrumental markers and serum inflammatory and endothelial dysfunction biomarkers for designing the stage-specific stratification of the risk for fast progression of DR and predicting treatment failure in type 2 diabetics.

Material and Methods

This was a single-center prospective longitudinal cohort study with a 24-month follow-up.

The procedures followed were in accordance with the ethical standards of the Helsinki Declaration (1964, amended most recently in 2013) of the World Medical Association. The study was conducted in compliance with the requirements of the Council of Europe Convention on Human Rights and Biomedicine, and relevant laws of Ukraine. The study was approved by the Bioethics Committee of the Shupyk National Healthcare University of Ukraine.

Informed consent was obtained from all participants of the study. The inclusion criteria were 50–75-year-old male and female type 2 diabetics with any stage of DR and being born and permanently living in Ukraine. The exclusion criteria were patients with other types of diabetes; patients with severe comorbidity that was not a complication of type 2 diabetes; patients with acute or chronic dental and jaw or ear, nose and throat disorders; patients with acute or chronic infection, uveitis, congenital or acquired glaucoma, or a history of eye trauma or surgery.

Totally, 358 type 2 diabetics with DR were included in the study. Of these, a subgroup of 136 patients was used for a detailed biomarker analysis. DR was classified into nonproloferative diabetic retinopathy (NPDR; group 1; n = 189), preproliferative diabetic retinopathy (PPDR; group 2; n = 96) and proliferative diabetic retinopathy (PDR; group 3; n = 73), as per recommendations by Kohner and Porta [20, 21].

At baseline, detailed histories were taken, and clinical and demographic data (age, gender, diabetes duration expressed in years, smoking status, and systolic and diastolic blood pressures), pattern of glucose-lowering therapy used, and any systemic comorbidities (complications like polyneuropathy, diabetic foot, nephropathy, encephalopathy, microangiopathy, and/or hepatopathy) were recorded. Patients underwent eye examination including visual acuity assessment with a chart projector (CCP-3100; Huvitz Corp, Gunpo, Korea) and phoropter (HDR 7000, Huvitz Corp); static Humphrey perimetry (Humphrey Field Analyzer model 740i, Carl Zeiss Meditec Inc, Dublin, CA); refractometry with an autorefractor/ keretometer (HRK-700, Huvitz Corp); tonometry with a non-contact air-puff tonometer (HNT-7000, Huvitz Corp); corneal pachymetry with a biometer (Pentacam AXL, Oculus, Werzlar, Germany); slit-lamp biomicroscopy (SLM-2ER, Chongqing Kanghua Ruiming Science Technology Co, Ltd, Chongqing, China); gonioscopy with a Goldmann three-mirror lens (Ocular Instruments, Bellevue, WA, USA); ophthalmoscopy with Volk digital wide-field lens (Volk Optical, Mentor, OH) and Goldmann three-mirror lens (Ocular Instruments); and OCT with RTVue RT-100 apparatus (Optovue Inc., Fremont, CA). Fundus photohraphy (TRS-NW7SF; TOPCON, Tokyo, Japan) and fluorescein angiography were performed, if indicated. The presence of any active ocular treatment at baseline was recorded. OCT-based quantitative parameters, central retinal thickness (CRT), expressed in mm, and macular volume (MV), expressed in mm3, were determined. Manifestations of diabetic maculopathy (DMP) were assigned a binary value (ie,

"0" if absent, or "1" if present) and considered an integral characteristic of macular lesions [21, 22]. Moreover, the presence of diabetic macular edema (DME), if any, was recorded [23].

Blood samples were randomly taken in 136 patients, including 60 patients in group 1 (NPDR), 42 patients in group 2 (PPDR), and 34 patients in group 3 (PDR), to determine biomarkers. Serum levels of fasting glucose, glycosylated hemoglobin (HbA1c), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglycerides, and fibrinogen were determined colorimetrically using commercially available kits on a Cobas c311 biochemical analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Coagulation hemostasis was evaluated with an extended panel of parameters including activated recalcification time (ART), prothrombin time, prothrombin index, Quick prothrombin time, international normalized ratio (INR), activated partial prothrombin time (aPPT) and thrombin time using standardized laboratory techniques [24]. Serum levels of specific markers were determined using enzyme-linked immunosorbent assays (ELISA) for advanced studies on systemic inflammation and endothelial dysfunction. Photometric measurements were performed on an ELISA plate reader (Stat Fax 303 Plus, Awareness Technology Inc, Palm City, FL). Particularly, we examined baseline levels of von Willebrand factor (vWF), LS and ES (Peninsula Laboratories, Inc., San Carlos, CA), endothelin-1 (ET-1), highly-sensitive C-reactive protein (hsCRP; Monobind Inc., Lake Forest, CA), EMAP-II (Biosource, Camarillo, CA), eNOS (BCM Diagnostics, USA), and tumor necrosis factor alpha (TNF-α), IL-1β and IL-6 (Bender Medsystems, Vienna, Austria). Serum nitric oxide levels were determined biochemically via nitric oxide metabolism end products, nitrites (NO2-) and nitrates (NO3-), using the acidic Griess reaction [25].

In the follow-up, patients received differential initial therapy depending on the stage of the disease. Conservative treatment was administered mostly to patients in group 1 and sometimes to patients in group 2 and included hypoglycemic medications, restoration of homeostasis, and vasoprotection. Additionally, fibrates, statins and metabolic therapy were administered, if required. Groups 1 and 2 had laser treatment including panretinal laser photocoagulation (PRP) and, if required, focal laser photocoagulation (FLP). Anti-VEGF therapy was used predominantly in groups 2 and 3 and included an intravitreal anti-VEGF injection once monthly. After the first five monthly loading injections, anti-VEGF treatment intervals were determined according to a treat-and-extend regimen. Patients began receiving PRP one month after the first aflibercept injection. Up to five PRP sessions were performed, with a subsequent PRP session administered only in the presence of ischemic areas. Laser settings utilized pulse durations from 100 to 200 ms, pulse-to-pulse periods of 100 to 150 ms, and powers from 100 to 200 mW.

Surgical treatment was performed mostly in patients in group 3 and included a 25-G three-port subtotal pars plana vitrectomy (PPV) plus PRP session, epiretinal membrane removal and endotamponade with 18% C3F8 or silicone oil 5700 centistokes, depending on the stage of the process.

A combination of intravitreal anti-VEGF medications, PRP and 25-G subtotal PPV was used mostly in patients in groups 2 and 3.

No DR progression (grade 0) was defined as the stability of ophthalmological characteristics at two years. Slow DR progression (grade 1) was defined as the worsening of some ophthalmological characteristics at two years. Fast DR progression (grade 2) was defined as worsening from NPDR to PPDR, worsening from PPDR to PDR, or the substantial worsening of the most ophthalmological characteristics in patients with PDR at two years. Treatment effect was defined as no DR progression or slow DR progression at 2 years. Treatment failure was defined as fast DR progression at 2 years.

Statistical analysis was performed with EZR version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical interface for R (The R Foundation for Statistical Computing, version 4.03, R Foundation for Statistical Computing, Vienna, Austria) [26]. A complete case analysis was used to address missing data. Significance was established at $P < 0.05$ for all two-tailed tests. The analysis included three stages and was aimed at (1) stratifying patients with each DR stage into progression risk and (2) comparing various treatment strategies for efficacy in the selected subgroups. In phase 1 of the statistical analysis, binary logistic regression was used to assess the prognostic value of each marker with regard to fast DR progression (grade 2 versus grades 0 to 1), with correction for age, gender, diabetes duration, DR stage at baseline, and the presence of active initial treatment. The informativeness of the marker was assessed by an increase in the likelihood ratio (LR) $\chi 2$, compared to the basic model, with the Benjamini-Hochberg false discovery rate (FDR) applied for multiple comparisons. In phase 2 of the statistical analysis, stage-specific Receiver Operating Characteristic (ROC) analysis was conducted for the most informative markers: ROC curves were built separately for NPDR, PPDR and PDR, which allowed removing the effect of stage-to-stage variability in the distribution of markers. For each subgroup, the area under curve (AUC) and 95% confidence interval (CI) were calculated by the DeLong method, and the Youden's index was used to determine cut-off values. In phase 3 of the statistical analysis, patients with each stage of DR were divided into high-risk and low-risk subgroups based on the stage-specific marker threshold value. The percentage of patients with fast DR progression was calculated in each of the subgroups created for each of the methods of initial treatment. Data were presented as descriptive portions;

the difference between methods as a result of comparison was not interpreted as evidence of superiority of one of the methods due to the absence of randomization.

Results

During prospective observation of a complete cohort (n = 358) and the subgroup selected for biomarker analysis (n = 136), we assessed the clinical trajectory of DR after the initial treatment was administered. In phase 1 of our statistical analysis, in order to identify the most significant predictors of treatment failure (fast DR progression), we used a binary-regression-based screening analysis, with correction for age, gender, diabetes duration, DR stage at baseline, and the presence of active primary treatment. A hierarchy of informativeness of the parameters examined was established based on the increase in the LR $\chi 2$, with the FDR applied for multiple comparisons.

OCT parameters, CRT and MV, were found to have the highest prognostic value among general clinical and ophthalmological markers, which indicated the development of various manifestations of DMP ($q < 0.05$ for all comparisons). Characteristics of endothelial dysfunction and inflammation (LS, EMAP II, ES, IL-1β and eNOS) showed the highest prognostic potential among the biomarkers determined. It is these characteristics that were selected for further, more detailed analysis.

In phase 2 of our statistical analysis, stage-specific ROC analysis was conducted to quantitatively and accurately assess the prognostic value of the selected markers and determine cut-off points (Table 1).

Prognostic accuracy of general clinical parameters substantially depended on the stage of DR at baseline (Table 1). Thus, the discriminative capacity of the quantitative characteristics of macular edema (CRT and MV) was high in PPDR (AUC > 0.82) but moderate in NPDR and PDR.

A similar stage-specific pattern was observed in the analysis of biomarkers (Table 2).

Serum biomarkers demonstrated higher prognostic accuracy (with AUC > 0.82 for most of the biomarkers; Table 2) compared to general clinical characteristics. Interestingly that, among the serum biomarkers, L-selectin had the highest accuracy in NPDR, whereas EMAP II and IL-1β had the highest accuracy (AUC > 0.94) in PPDR and PDR. The Youden's index-based cut-off values for each marker in each DR stage made the basis for the final phase of the study, stage-specific stratification of the risk for fast progression of DR.

In phase 3 of our statistical analysis, stage-specific thresholds were used to divide the cohort into low-risk and high-risk subgroups, and the efficacy of various initial treatment methods was assessed. Figure 1 shows the examples of implementing this approach for the best instrumental marker (CRT) and the best early biomarker (L-selectin).

The analysis of stratified results found two stable and clinically significant patterns that were reproduced regardless of whether we used an instrumental marker or a biomarker for discrimination. First, in high-risk subgroups (at any stage of DR), the percentage of patients with fast DR progression (i.e., treatment failure) was critically high and predominantly exceeded 80–85%. This pattern was observed regardless of the type of treatment strategy selected (conservative, laser, surgical, anti-VEGF therapy or combined), indicating an aggressive phenotype of the disease which was resistant to standard treatments. Second, a completely different pattern was seen in low-risk subgroups, with substantially better treatment response. Additionally, in low-risk subgroups of patients with PPDR and PDR, surgical or combined treatment strategy was associated with a smaller percentage of patients with fast DR progression compared to monotherapy strategy. Therefore, the use of determined stage- specific cut-off values enabled clearly identifying a cohort of patients who are highly likely to fail conventional treatment algorithms, which may justify the need for revising these algorithms or adjusting them early.

Discussion

This study demonstrated that the prediction of initial treatment failure (which corresponded to fast DR progression in this study) in type 2 diabetics with DR cannot be based on a set of features universally applicable to all stages of DR. The major finding was that of a stage-dependent change in the most prognostically informative parameters. OCT parameters were found to be the most prognostically informative among clinical and instrumental parameters; among serum biomarkers, LS showed the best discrimination in patients with NPDR, whereas EMAP-II, IL-1β, ES and eNOS, in patients with PPDR and PDR. This agrees well with a current concept of DR as a dynamic neurovascular condition in which local retinal structural changes are combined with systemic signs of inflammation and endothelial dysfunction while the prognostic weight of individual markers changes with disease progression [5, 6, 10, 27, 28].

Is seems pathophysiologically intuitive that we found that CRT, MV and other clinical signs of DMP had the highest independent values among general clinical and ophthalmological characteristics in our cohort of patients. The superiority of OCT parameters over HbA1c indicates that direct signs of retinal lesion activity are more important than average metabolic control characteristics in the prognosis of treatment failure. It is especially telling that CRT and MV showed the best discriminative capacity in patients with PPDR. It is likely that it is at this stage of DR macular edematous and ischemic components are sufficiently marked to exert an effect on further clinical trajectory, but are not yet "overlapped" by a complex array of fibrous proliferative and tractional changes characteristic of the later stage, PDR. Such an interpretation is consistent with understanding a phenotype-dependent role of OCT parameters in diabetic macular lesions [11, 12, 29, 30]. On the other hand, the development of these unfavorable

Table 1. Stage-specific results of ROC analysis of general clinical markers for predicting fast progression of diabetic retinopathy (a complete cohort, n = 358)

Marker	Stage of DR	n	AUC (95% CI)*	Optimal cut-off	Sensitivity, %	Specificity, %	Youden J
MV, mm³	NPDR	189	0.683 (0.576–0.789)	> 0.23	31.2	96.8	0.281
	PPDR	96	0.824 (0.733–0.915)	> 0.21	89.4	70.0	0.594
	PDR	73	0.664 (0.518–0.811)	> 0.35	60.8	77.3	0.381
CRT, µm	NPDR	189	0.682 (0.576–0.788)	> 298	31.2	96.8	0.281
	PPDR	96	0.834 (0.747–0.921)	> 271	89.4	70.0	0.594
	PDR	73	0.659 (0.507–0.810)	> 317	68.6	72.7	0.414
DMP	NPDR	189	0.634 (0.551–0.717)	= 1	31.2	95.5	0.268
	PPDR	95	0.705 (0.606–0.804)	= 1	67.7	73.3	0.410
	PDR	73	0.707 (0.592–0.822)	= 1	68.6	72.7	0.414
DME	NPDR	189	0.615 (0.538–0.692)	= 1	25.0	98.1	0.231
	PPDR	96	0.529 (0.439–0.619)	= 1	25.8	80.0	0.058
	PDR	73	0.560 (0.434–0.686)	= 1	52.9	59.1	0.120
HbA1c, %	NPDR	189	0.604 (0.497–0.711)	> 7.7	78.1	42.7	0.208
	PPDR	96	0.693 (0.587–0.800)	> 9.6	62.1	80.0	0.421
	PDR	73	0.574 (0.434–0.714)	> 11.2	56.9	63.6	0.205

Notes: From the ROC analysis, optimal cut-off values were calculated using the Youden Index. AUC 95% confidence intervals were calculated using the DeLong method. Qualitative characteristics were represented with binary variables, such as maculopathy and DME, with "= 1" denoting the presence of a feature. Abbreviations: AUC, area under curve; CI, confidence interval; CRT, central retinal thickness; DME, diabetic macular edema; DMP, diabetic maculopathy; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PPDR, pre-proliferative diabetic retinopathy; ROC, receiver operating curve

Table 2. Stage-specific results of ROC analysis of biomarkers of inflammation and epithelial dysfunction for predicting fast progression of diabetic retinopathy (a biomarker subgroup, n = 136)

Marker	Stage of DR	n	AUC (95% CI)*	Optimal cut-off	Sensitivity, %	Specificity, %	Youden J
LS, ng/mL	NPDR	60	0.979 (0.949–1.000)	> 33.4	94.4	95.2	0.897
	PPDR	42	0.929 (0.846–1.000)	> 49.0	93.9	77.8	0.717
	PDR	34	0.774 (0.551–0.997)	> 59.6	75.0	83.3	0.583
EMAP II, ng/mL	NPDR	60	0.769 (0.648–0.889)	> 3.59	94.4	54.8	0.492
	PPDR	42	0.943 (0.878–1.000)	> 7.04	84.8	100.0	0.848
	PDR	34	0.988 (0.960–1.000)	> 8.65	92.9	100.0	0.929
ES, ng/mL	NPDR	60	0.695 (0.514–0.876)	> 32.5	61.1	88.1	0.492
	PPDR	42	0.902 (0.807–0.997)	> 50.0	84.8	100.0	0.848
	PDR	34	0.920 (0.820–1.000)	> 58.6	89.3	83.3	0.726
IL-1β, pg/mL	NPDR	60	0.580 (0.403–0.757)	> 64.5	33.3	92.9	0.262
	PPDR	42	0.990 (0.968–1.000)	> 77.2	97.0	100.0	0.970
	PDR	34	0.917 (0.822–1.000)	> 192.2	82.1	100.0	0.821
eNOS, pmol/mL	NPDR	60	0.708 (0.566–0.851)	< 206	72.2	73.8	0.460
	PPDR	42	0.747 (0.599–0.896)	< 193	57.6	100.0	0.576
	PDR	34	0.952 (0.883–1.000)	< 121	89.3	100.0	0.893

Notes: From the ROC analysis, optimal cut-off values were calculated using the Youden Index. *AUC 95% confidence intervals were calculated using the DeLong method. Abbreviations: AUC, area under curve; CI, confidence interval; DR, diabetic retinopathy; EMAP II, endothelial-monocyte-activating polypeptide II; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; IL-1β interleukin-1β; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PPDR, pre-proliferative diabetic retinopathy; ROC, receiver operating curve

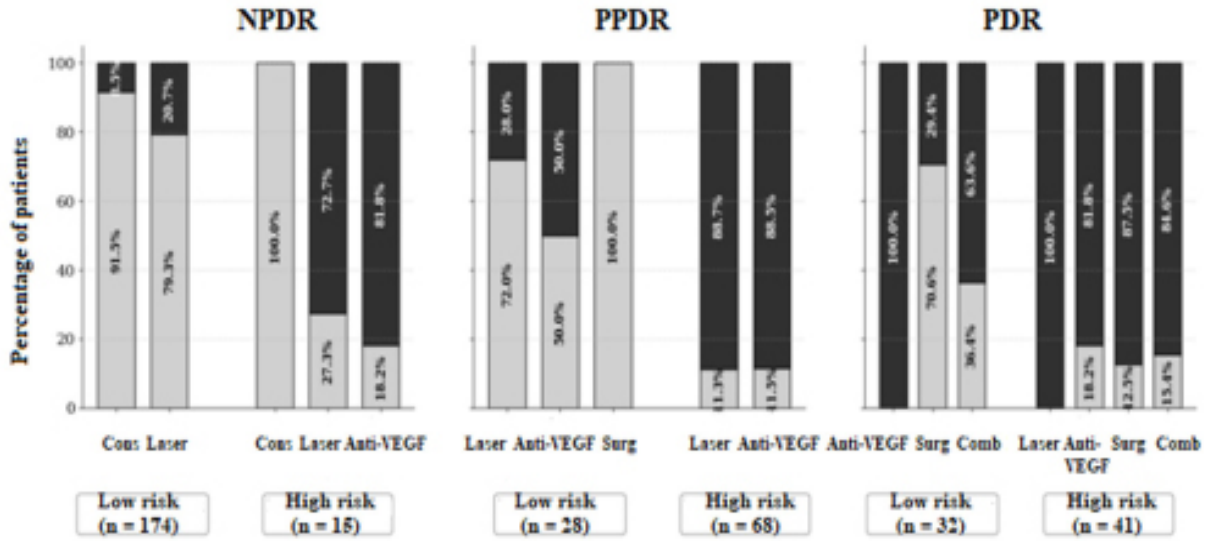

Fig. 1. Efficacy of methods of initial treatment for diabetic retinopathy depending on stage-specific stratification of the risk of diabetic retinopathy progression based on central retinal thickness (CRT). Light-grey bar segments represent percentages of patients with no or slow disease progression (grades 0 to 1), and dark-grey bar segments, percentages of those with fast disease progression (grade 2; treatment failure) in a complete cohort (n = 358). Separation into low-risk and high-risk subgroups was based on stage-specific CRT cut-off values determined by ROC analysis: ≤298 and >298 µm for NPDR; ≤271 and >271 µm for PPDR; and ≤317 and >317 µm for PDR, respectively. The n values under the abscissa represent numbers of patients in each risk subgroup. Comparisons of treatment strategies are only descriptive in nature. Abbreviations: Cons, conservative treatment; Comb, combination treatment; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PPDR, pre-proliferative diabetic retinopathy; Surg, surgical treatment.

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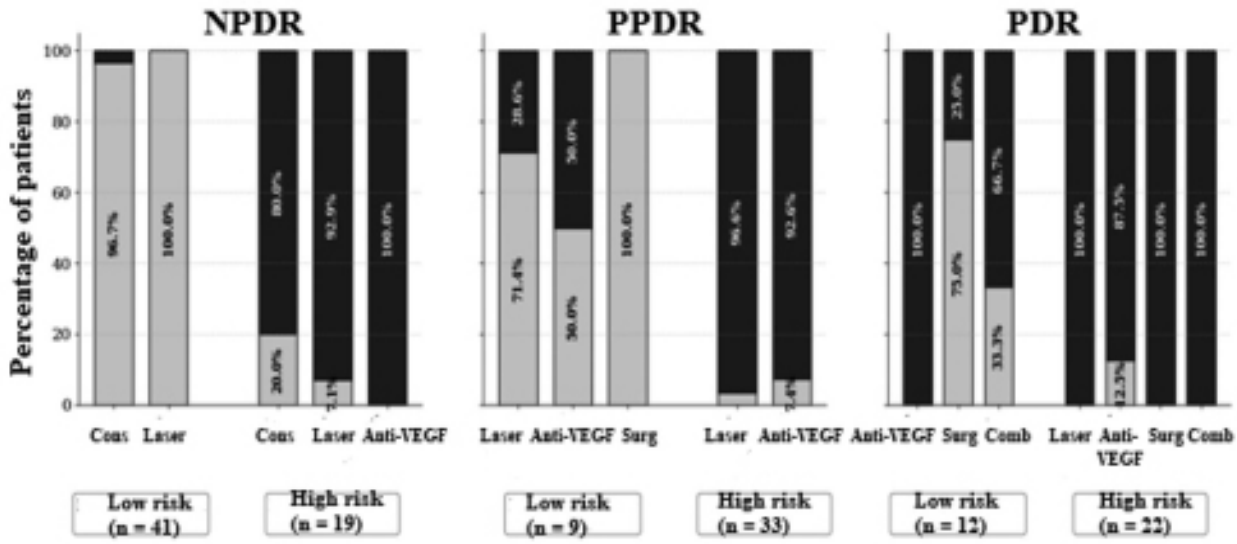

Fig. 2. Efficacy of methods of initial treatment for diabetic retinopathy depending on stage-specific stratification of the risk of diabetic retinopathy progression based on serum L-selectin (LS) level. Light-grey bar segments represent percentages of patients with no or slow disease progression (grades 0 to 1), and dark-grey bar segments, percentages of those with fast disease progression (grade 2; treatment failure) in the biomarker subgroup (n = 136). Separation into low-risk and high-risk subgroups was based on stage-specific LS cut-off values determined by ROC analysis: ≤33.4 and >33.4 ng/mL for NPDR; ≤49.0 and >49.0 ng/mL for PPDR; ≤59.6 and >59.6 ng/mL for PDR, respectively. The n values under the abscissa represent numbers of patients in each risk subgroup. Comparisons of treatment strategies are only descriptive in nature. Abbreviations: Cons, conservative treatment; Comb, combination treatment; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PPDR, pre-proliferative diabetic retinopathy; Surg, surgical treatment.

changes in the retinal structure of patients with DR is closely associated with systemic metabolic abnormalities. As we have demonstrated in our recent study, atherogenic dyslipidemia (particularly, increased LDL-C, VLDL-C and non-HDL-C levels) is a "profound" systemic predictor of the development of DME and worsened OCT parameters [31]. This further underlines the need for a comprehensive approach to risk stratification, with the involvement of local retinal characteristics and the systemic metabolic profile.

We found LS to be the most informative serous marker of early risk stratification in DR. This observation has a convincing biological basis since (1) selectins are key mediators in the early interaction of leukocytes with endothelial cells, and (2) leukostasis is believed to be an early component of retinal microvascular damage in diabetes [7, 13–15, 28, 32–35]. A high prognostic value of LS in NPDR may reflect the situation when irreversible proliferative changes are not yet clinically dominant, but mechanisms of leukocyte adhesion, local inflammation and blood-retinal barrier breakdown are already actively involved in the disease process. While demonstrating the role of HbA1c, lipoprotein cholesterols and coagulation characteristics in DR progression, we have previously pointed out that it is at the non-proliferative stage of DR that identifying predictors of this progression is especially important [36]. Findings of the current study complement these results, demonstrating that, among the specialized panel of inflammation and endothelial dysfunction markers, it is soluble L-selectin that is the earliest and most sensible indicator of the transition to an unfavorable course of DR. An increased role of ES in PPDR and PDR is also reasonable because this marker directly reflects the activation of endothelial cells proper, that is, the vascular stress that expectedly increases with increasing severity of DR [7, 13–15, 28, 32–35].

Out results, however, should not be interpreted as the confirmation of the absolute universality of circulating adhesion molecules in all populations of patients. Some studies found no persuasive association between soluble adhesion molecules and the development of DR [16]. Most likely, such variability may be due to differences in design, type of diabetes, distribution of DR stages in the sample, selected endpoints and/or no division of the sample into groups with various baseline stages of DR. It is telling that prospective and cohort studies, however, support the prognostic value of endothelial dysfunction and low-grade inflammation in the development and progression of DR [16, 28, 37–39]. In this context, our results do not contradict previous data, but rather clarify the conditions under which these markers are actually clinically informative.

More important appears to be a shift in "leading biomarkers" with the transition from NPDR to PPDR and PDR. High discriminative capacity of EMAP-II and IL-1β in these stages of DR supposes that, with the progression of DR, a chronic pro-inflammatory environment and a deeper endothelial lesion become more decisive than early leukocyte adhesion. This interpretation is especially convincing for IL-1β, because this cytokine is a central effector of the inflammasome-mediated response associated with pyroptosis, increased vascular permeability and retinal lesion progression [8, 9, 17, 40]. Although data are still limited on the role of EMAP-II in the context of DR, it is known to mediate the interaction of monocytes with endothelial cells and be involved in apoptosis and pathological vascular remodeling [19, 41, 42]. This is why its high discriminative capacity in PPDR and PDR is one of the most interesting findings of this study. Equally telling was the finding that low eNOS was an informative predictor of PDR. This is consistent with the idea of the depletion of NO-dependent vasoprotective mechanisms, loss of endothelial reactivity and loss of vascular homeostasis under conditions of severe microangiopathy [7, 18]. The present study is a logical continuation of our previous study [43] in which we (1) developed a model for predicting the efficacy of treating DR in type 2 diabetes on the basis of determination of markers of endothelial dysfunction and (2) demonstrated high sensitivity and specificity of EMAP II and eNOS. The present study, however, substantially expands this understanding by demonstrating that the prognostic values of these endothelial factors are not constant and it is in late stages (pre-proliferative and proliferative) of DR that they reach their maximum.

Taken together, our findings allow us to build a consistent pathobiological scheme, from early leukocyte-endothelial activation (to which LS is sensitive) via an increased endothelial response with an increased expression of ES, to persistent inflammatory amplification associated with IL-1β and EMAP-II, and, finally, to the depleted endothelial reserve which is reflected by a reduced expression of eNOS.

This scheme is backed by experimental evidence: leukostasis, intercellular adhesion and inflammation are directly involved in the development of vascular permeability, capillary occlusion and endothelial cell death in diabetic retina [34, 44–46]. The practical implications of our findings are not so much the selection of the best method of treatment of DR as the identification of the aggressive phenotype of DR prior to therapy initiation. The fact that the percentage of patients with fast DR progression in high-risk subgroups predominantly exceeded 80–85% regardless of the type of initial treatment strategy selected indicates the limitedness of a conventional step-by-step approach to treatment strategy selection in this category of patients. At the same time, better outcomes in low-risk than high-risk subgroups and lower frequency of fast DR progression in patients with PPDR/PDR that received surgical or combined treatment strategy should be interpreted carefully, because, in this study, comparisons of treatment strategies were only descriptive in nature. However, the very possibility of separating patients for whom early revision of treatment strategy, more intensive

monitoring or multimodal management may be appropriate would have a direct clinical value [2, 3, 5, 9, 11, 30].

Advantages of this study include its prospective design, a clinically relevant endpoint, combination of general clinical data with a detailed biomarker analysis in a biomarker subgroup, and determination of practical cut-off values for each DR stage.

Results of the present study should be interpreted with some limitations. First, because the biomarker subgroup was of a moderate size, further studies with larger sample sizes are required to confirm the accuracy of individual assessments. Second, the levels of all the serum markers were determined at baseline only, whereas the dynamics of these levels in the presence of treatment would add some prognostic value. Third, the proposed cut-off values are of a pragmatic nature for this cohort and should be externally validated prior to wide implementation. Finally, because this work did not aim to compare individual treatment strategies for efficacy, any conclusions with regard to advantages of a particular intervention would be incorrect. The present study, however, demonstrates that integration of OCT parameters with serum biomarkers of inflammatory and endothelial dysfunction may provide a basis for more accurate personalized stratification of the risk of initial treatment failure in DR.

Conclusions

First, in type 2 diabetics with DR, the prognostic value of markers of initial treatment failure (which in this study was defined as fast disease progression) is of an apparently stage-specific nature; using a universal set of predictors for all stages of DR will be insufficiently informative.

Second, among clinical ophthalmological parameters, OCT parameters (CRT and MV) and signs of various manifestations of DMP were found to have the highest independent prognostic value, with CRT and MV demonstrating the highest discriminative capacity in the PPDR stage of DR.

Third, serum biomarkers of inflammatory and endothelial dysfunction generally demonstrated a higher prognostic accuracy than general clinical characteristics. LS was the most informative marker in NPDR; IL-1β and EMAP II, in PPDR, whereas EMAP II and eNOS, in PDR.

Fourth, the determination of the stage-specific cut-off values for the most informative clinical-and-instrumental and laboratory markers provided a separation of patients into subgroups with a low and high risk of initial treatment failure, respectively, with the percentage of patients with fast DR progression in high-risk subgroups predominantly exceeding 80–85%.

Finally, integrating OCT parameters with serum biomarkers of inflammatory and endothelial dysfunction provides a justified approach to personalized stage-specific stratification and may be used for early separation of DR patients with a high probability of initial treatment failure.

Author contributions

SYM: Conceptualization, Project Administration, Data Analysis and Interpretation; AVS: Data Curation, Investigation, Data Analysis and Interpretation, Writing - original draft preparation, Writing – Review and Editing; VNS: Data Curation, Investigation; BMS: Investigation, Data Analysis and Interpretation, Writing - original draft preparation; SVZ: Conceptualization, Data Analysis and Interpretation. All authors have read and approved the final version of the manuscript.

Ethical Declaration

This study involved human subjects, was approved by the local bioethics committee, and followed ethical standards as outlined in the Declaration of Helsinki. Informed consent was obtained from all subjects. This study did not include animal experiments.

Disclaimer

This manuscript reflects the views of the authors and may not reflect the views of their institutions.

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None.

Conflict of interest

All authors declare no conflict of interest that could influence their views on the subject matter or materials described and discussed in this manuscript.

Data Availability Declaration

All the data obtained or examined during this study has been incorporated into this published article.

Abbreviations

AUC, area under curve; CI, confidence interval; DME, diabetic macular edema; DM, diabetic mellitus; DR, diabetic retinopathy; EMAP II, endothelial-monocyte-activating polypeptide II; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; HbA1c, glycated hemoglobin; hs-CRP, highly sensitive C-reactive protein; IL-1β, interleukin 1β; IL-6, interleukin 6; NO, nitric oxide; NOx, nitric oxide metabolites; NPDR, non-proliferative diabetic retinopathy; OCT, optical coherence tomography; OR, odds ratio; PDR, proliferative diabetic retinopathy; PPDR, pre-proliferative diabetic retinopathy; PRP, panretinal laser photocoagulation.

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