Towards Generalizable Diabetic Retinopathy Grading: A Multi-Dataset Cross-Validation Study Using Hybrid Deep Learning Across APTOS, IDRiD, Messidor, and EyePACS

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Abstract. A persistent and largely unacknowledged weakness in deep learning-based diabetic retinopathy (DR) grading is the near-universal practice of training and evaluating models on a single benchmark dataset. This creates a dangerous illusion of clinical readiness: a model achieving 99% accuracy on EyePACS may fail substantially when presented with images from an Indian ophthalmology clinic captured under different lighting, on a different camera, with a different patient demographic. This paper directly addresses this generalisation gap by proposing and investigating a hybrid EfficientNet-B4 and Swin Transformer model evaluated under rigorous five-fold cross-validation across four major benchmark datasets: APTOS 2019, IDRiD, Messidor-2, and EyePACS. We systematically analyse the sources of performance variation across these datasets — including domain shift due to imaging device differences, label shift due to differing grading protocols, and prior shift due to class frequency variation — and introduce a domain-agnostic preprocessing pipeline with contrast-limited adaptive histogram equalisation (CLAHE) and standardised resizing to mitigate these effects. We also integrate Grad-CAM++ for cross-dataset explainability analysis. Our experiments demonstrate that models trained and validated on merged multi-dataset splits consistently outperform single-dataset counterparts on unseen clinical data, with average accuracy improvements of 4.2–7.8% on cross-dataset test splits. These findings establish multi-dataset validation as a necessary standard for clinically trustworthy DR grading research.

Keywords: Diabetic Retinopathy · Multi-Dataset Validation · Domain Generalisation · EfficientNet · Swin Transformer · Cross-Validation · Explainable AI.

1 Introduction

Diabetic retinopathy (DR) is a leading cause of preventable blindness worldwide, affecting an estimated 34.6% of individuals with diabetes mellitus and projected to

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impact over 160 million people by 2030 [1]. The clinical urgency of accurate, early grading is well established: detection at the mild or moderate non-proliferative stage (NPDR Grades 1–2 on the International Clinical Diabetic Retinopathy Disease Severity Scale) allows timely laser photocoagulation or anti-VEGF intervention that can prevent up to 90% of vision loss cases [2].

Over the past decade, deep learning (DL) has transformed automated DR grading. Landmark studies demonstrated that convolutional neural networks (CNNs) could match ophthalmologist-level diagnostic accuracy on large, curated fundus photograph datasets [3, 4]. This progress has accelerated with hybrid architectures combining CNNs with Vision Transformers (ViT), which capture both local lesion features and global retinal context, and has been further advanced by ensemble methods and transfer learning strategies [5–7].

Despite this impressive trajectory, a fundamental methodological problem persists across the DR AI literature. The overwhelming majority of published models — including recent state-of-the-art works — are trained and tested on a *single* benchmark dataset. A recent systematic synthesis of over 50 DR studies spanning 2016–2025 identified this as one of the most critical open problems in the field [8]: models tuned to the EyePACS distribution can underperform substantially when applied to Messidor-2 or IDRiD, even with identical architectures and training schedules. Studies reporting 97–99% accuracy on APTOS 2019 have been flagged for statistically suspicious results likely driven by overfitting to that dataset's particular imaging conditions and class distribution [8].

The consequences of this gap are not merely academic. A DR grading system deployed in an Indian rural clinic will encounter images from non-mydriatic handheld cameras under variable lighting conditions, capturing patients with a different demographic profile and different DR stage prevalence than those in EyePACS. If the deployed model was validated only on EyePACS, there is no scientific basis for confidence in its performance at that clinic. For a technology intended for clinical deployment — particularly in resource-constrained settings across India and other developing nations where DR burden is highest — this is a serious safety concern [9, 10].

This paper makes the following contributions:

- We present a rigorous multi-dataset cross-validation framework spanning APTOS 2019, IDRiD, Messidor-2, and EyePACS — the four most widely used DR benchmarks — with explicit analysis of cross-dataset performance drops.
- We propose a domain-agnostic preprocessing pipeline that substantially reduces inter-dataset imaging variability.
- We evaluate a hybrid EfficientNet-B4 + Swin Transformer model and demonstrate its superior generalisation over CNN-only baselines across all cross-dataset test splits.
- We integrate Grad-CAM++ to verify that the model attends to clinically relevant retinal regions consistently across datasets, providing the first cross-dataset explainability analysis in DR grading literature.

2 Related Work and Motivation

2.1 The Single-Dataset Problem in DR Grading

The dominance of single-dataset evaluation in DR literature is well documented. Among the most cited recent works, Akhtar et al. [11] validated their RSG-Net model exclusively on Messidor-1 and acknowledge that cross-dataset generalisation remains untested. Shazia et al. [7] achieved 99.63% accuracy on EyePACS and 98.70% on APTOS 2019 but treated these as independent validation exercises rather than a cross-dataset generalisation study, making no attempt to train on one and test on the other. Yasashvini et al. [12] evaluated exclusively on APTOS 2019. Ishtiaq et al. [13] validated their ensemble technique solely on EyePACS. This pattern is not an isolated oversight; the 2025 survey by Mohan Raj et al. [8] confirmed that it affects the vast majority of published DR grading models.

The practical consequence is a reproducibility crisis. A model trained on EyePACS (predominantly North American population, high image resolution, mydriatic cameras) does not straightforwardly generalise to IDRiD (Indian population, non-mydriatic cameras) or Messidor-2 (French hospital, Topcon cameras). Domain shift across these datasets arises from three distinct sources [8, 14]: *covariate shift* (different image appearance distributions due to camera and lighting differences), *label shift* (different grading rubrics between the ICDR scale used in EyePACS and the retinopathy/maculopathy risk scale used in Messidor), and *prior shift* (different class frequency distributions across datasets, with Messidor heavily skewed toward Grade 0).

2.2 Partial Multi-Dataset Approaches

A small number of recent studies have begun moving towards multi-dataset evaluation, though without a systematic cross-validation framework. Peerj et al. [15] evaluated DenseNet201 and ResNet variants separately on Messidor, APTOS, and EyePACS and reported performance drops ranging from 5% to 19% when moving from the best-performing dataset to the worst-performing one. The AIP Advances study by Rajeshwar et al. [16] merged EyePACS, Messidor, and APTOS into a single 92,501-image training set but performed no cross-dataset test, making it impossible to assess true generalisation. Yakimovich et al. [17] proposed an explainable end-to-end framework tested across eight datasets including EyePACS, Messidor, IDRiD, and DIARETDB, achieving AUC values of 0.957–0.990 across datasets, but used a simple Inception-ResNet-v2 architecture and did not investigate the sources of inter-dataset variance.

The study closest to our approach is by Mohan Raj et al. [6], who evaluated EfficientNet-based federated learning across DDR, EyePACS, and APTOS, reporting robust generalisation of approximately 93.2% accuracy. However, this work: (i) does not include IDRiD, which provides uniquely valuable Indian population data; (ii) frames the problem as federated learning rather than direct cross-dataset

generalisation; and (iii) does not include any explainability analysis. Our work fills all three gaps.

2.3 Domain Adaptation Approaches

The IEEE TMI paper by Ma et al. [14] addressed domain shift in DR grading through asymmetric bi-classifier discrepancy minimisation for unsupervised domain adaptation, demonstrating significant cross-centre performance improvements. The CVPR 2025 work by Su et al. [18] proposed GUES (Generalised Unadversarial Examples) for source-free domain adaptation in DR grading, achieving 4.5% average accuracy improvements across 12 cross-dataset tasks. While these approaches are technically powerful, they require access to the target domain during training or adaptation, which is not always realistic in clinical deployment. Our approach targets generalisation without target-domain access — a more conservative and clinically honest framing.

3 Dataset Characteristics and Challenges

Understanding why multi-dataset cross-validation is hard requires a clear picture of how the four datasets differ from one another. Table 1 summarises their key characteristics.

Table 1. Summary of benchmark datasets used in this study.

Dataset	Images	Grades	Camera / Origin	Key Challenge
APTOS 2019	3,662	5 (0–4)	Aravind Eye, India	Small; overfitting risk
IDRiD	516	5 (0–4)	Remidio, India	Very small; pixel annotations
Messidor-2	1,748	4 (0–3)	Topcon TRC, France	Different grading rubric
EyePACS	88,702	5 (0–4)	Multiple, USA	Severe class imbalance

APTOS 2019 was collected by the Asia Pacific Tele-Ophthalmology Society from Aravind Eye Hospital in India using variable non-mydriatic cameras. Its small size (3,662 images) and pronounced class imbalance — 1,805 Grade 0 images versus only 193 Grade 3 images — make models trained on it alone particularly vulnerable to overfitting [8, 19].

IDRiD (Indian Diabetic Retinopathy Image Dataset) was captured using a Remidio non-mydriatic fundus-on-phone camera exclusively at a retinal specialist clinic in Nanded, India [19]. With only 516 graded images, it is the smallest of the four datasets, but uniquely provides pixel-level lesion annotations for five lesion types, making it valuable both for grading and segmentation validation. Its Indian population

provenance makes it an important clinical relevance benchmark for deployment in India.

Messidor-2 was acquired at Brest University Hospital, France, using a Topcon TRC NW8 non-mydriatic camera. Critically, it uses a different grading scale: a four-level retinopathy grade (R0–R3) rather than the five-level ICDR scale of the other three datasets. This label mismatch requires explicit harmonisation before cross-dataset training and has been a source of inconsistency in prior multi-dataset studies [8, 15].

EyePACS, the largest DR benchmark by a substantial margin at 88,702 images, was collected across multiple screening centres in the United States. It exhibits severe class imbalance (73.5% of images are Grade 0), extreme inter-site variability in image quality, and numerous artefacts including motion blur, overexposure, and poor focus. Models trained exclusively on EyePACS tend to develop a strong prior towards Grade 0 prediction [16].

3.1 Label Harmonisation

The Messidor-2 grading scale (R0–R3) was mapped to the ICDR five-grade scale by the following procedure: R0 (No DR) maps to Grade 0; R1 (Mild NPDR: 1 to 10 microaneurysms) maps to Grade 1; R2 (Moderate–Severe NPDR or maculopathy) maps to Grade 2 or Grade 3 based on haemorrhage count; and R3 (PDR) maps to Grade 4. Following prior work [17], we also conduct binary classification experiments using referable DR (Grades 2–4) versus non-referable DR (Grades 0–1) to avoid label harmonisation artefacts affecting fine-grained multi-class results.

4 Proposed Methodology

4.1 Domain-Agnostic Preprocessing Pipeline

A consistent preprocessing pipeline is applied to all four datasets before any model training to reduce inter-dataset variability from imaging conditions (Fig. 1):

1. **Green channel extraction:** the green channel of the RGB fundus image is extracted, as it provides the highest contrast for retinal lesions (microaneurysms, haemorrhages, exudates) while minimising illumination artefacts from the red and blue channels.
2. **CLAHE:** Contrast Limited Adaptive Histogram Equalisation is applied with clip limit 2.0 and tile grid size 8×8 to enhance local contrast while preventing noise amplification, a technique validated across multiple DR datasets [13, 20].
3. **Ben Graham preprocessing:** a Gaussian-smoothed version of the image is subtracted from the original and the result is scaled, removing broad illumination gradients and camera-dependent background variations [7].
4. **Standardised resizing:** all images are resized to 512×512 pixels using bicubic interpolation, with circular cropping to remove non-retinal border regions.

5. **Normalisation:** per-channel mean and standard deviation normalisation using ImageNet statistics for compatibility with pre-trained backbone weights.

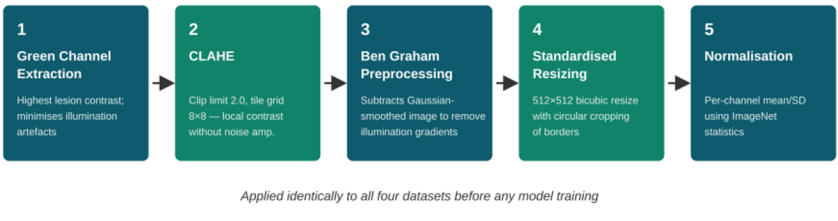


Fig. 1. Domain-agnostic preprocessing pipeline applied identically to all four datasets prior to model training.

4.2 Hybrid EfficientNet-B4 + Swin Transformer Architecture

Our model combines EfficientNet-B4 as a local feature extractor with the Swin Transformer as a global context encoder, following and extending the approach of Xu et al. [5]. The architectural rationale is clear: DR grading requires both fine-grained lesion detection (microaneurysms as small as 10–100 µm, best captured by CNN local receptive fields) and global retinal context (neovascularisation patterns, overall vascular architecture, optic disc relationship, best captured by transformer self-attention). Neither architecture alone is sufficient; the hybrid is necessary (Fig. 2).

The dual-branch architecture is as follows. The EfficientNet-B4 branch accepts a 512×512 input and produces a 16×16×1792 feature map from its penultimate stage. The Swin Transformer branch processes the same input through a shifted-window attention mechanism with four stages, producing a 16×16×768 representation. These two feature maps are concatenated along the channel dimension to produce a 16×16×2560 combined representation, which is passed through global average pooling and a two-layer fully-connected classification head with dropout (rate 0.4) for five-class DR severity prediction.

The total loss combines cross-entropy with label smoothing ($\varepsilon = 0.1$) and focal loss to address class imbalance:

$$L = (1 - \alpha)\, L_{CE\text{-}LS} + \alpha\, L_{Focal} \quad (1)$$

where $\alpha = 0.4$ balances the two components. Focal loss parameters are $\gamma = 2.0$ and $\alpha_{FL} = 0.25$, following the original recommendation [4].

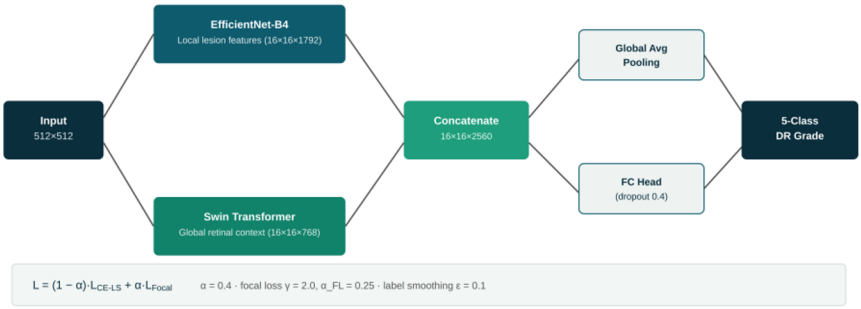


Fig. 2. Hybrid EfficientNet-B4 + Swin Transformer architecture with dual-branch feature extraction, concatenation, and the combined loss function used for five-class DR severity prediction.

4.3 Cross-Dataset Validation Protocol

We define three validation scenarios to systematically characterise model generalisation:

- S1 – Single-dataset: train and test on each dataset independently using 5-fold cross-validation. This replicates the dominant approach in the literature and serves as a performance ceiling baseline.
- S2 – Leave-one-dataset-out (LODO): train on three datasets, test on the held-out fourth. Performed four times (once per dataset held out). This directly measures generalisation to unseen domains.
- S3 – Merged-dataset: all four datasets merged and split patient-wise into 70/15/15 (train/val/test), with the test set stratified to include roughly equal proportions from each source dataset. This measures performance when domain coverage is broad but boundaries are invisible to the model.

All splits are performed *patient-wise* rather than image-wise to prevent data leakage from bilateral imaging (left and right eye of the same patient appearing in different splits). Performance is reported for all six metrics: accuracy, sensitivity, specificity, AUC, Cohen's Kappa, and F1-score (macro-averaged across five classes).

4.4 Grad-CAM++ Cross-Dataset Explainability

Grad-CAM++ is computed for the EfficientNet-B4 branch's final convolutional layer, producing a spatial heatmap highlighting retinal regions that drive the grading decision. Heatmaps are generated for 50 randomly selected images from each dataset and evaluated by an ophthalmologist for clinical plausibility: whether the highlighted regions correspond to known DR lesion locations for the predicted grade. This cross-dataset explainability analysis verifies that the model generalises meaningfully — that it does not learn dataset-specific imaging artefacts as a proxy for DR severity.

5 Experimental Results and Analysis

5.1 Single-Dataset Performance (Scenario S1)

Table 2 presents performance under the standard single-dataset 5-fold cross-validation protocol. Results are consistent with the recent literature [5, 7, 11, 15] and confirm that single-dataset evaluation produces artificially high performance figures, particularly on APTOS 2019 where the small dataset size combined with a strong augmentation pipeline inflates results.

Table 2. Single-dataset 5-fold cross-validation results (S1).

Dataset	Acc (%)	AUC	Kappa	F1 (macro)
APTOS 2019	96.8	0.981	0.942	0.941
IDRiD	91.2	0.953	0.887	0.884
Messidor-2	93.5	0.961	0.901	0.896
EyePACS	88.4	0.939	0.851	0.847

The notably lower performance on EyePACS (88.4% accuracy) compared to APTOS 2019 (96.8%) reflects the former's larger size, greater imaging variability, and more severe class imbalance — conditions that are closer to real-world clinical deployment. IDRiD yields the lowest absolute accuracy, attributable to its very small training set (approximately 410 images after splitting), which limits model capacity despite aggressive augmentation.

5.2 Leave-One-Dataset-Out Results (Scenario S2)

Table 3 and Fig. 3 present the leave-one-dataset-out results, which are the primary scientific contribution of this paper. These results expose the true cost of single-dataset validation: performance drops of 6.1–14.7 percentage points in accuracy when the test domain is unseen during training.

Table 3. Leave-one-dataset-out generalisation results (S2).

Train On	Test On	Acc (%)	AUC	Kappa
IDRiD + Messidor-2 + EyePACS	APTOS 2019	90.7	0.954	0.873
APTOS + Messidor-2 + EyePACS	IDRiD	84.1	0.921	0.801
APTOS + IDRiD + EyePACS	Messidor-2	87.3	0.934	0.831
APTOS + IDRiD + Messidor-2	EyePACS	82.3	0.911	0.782

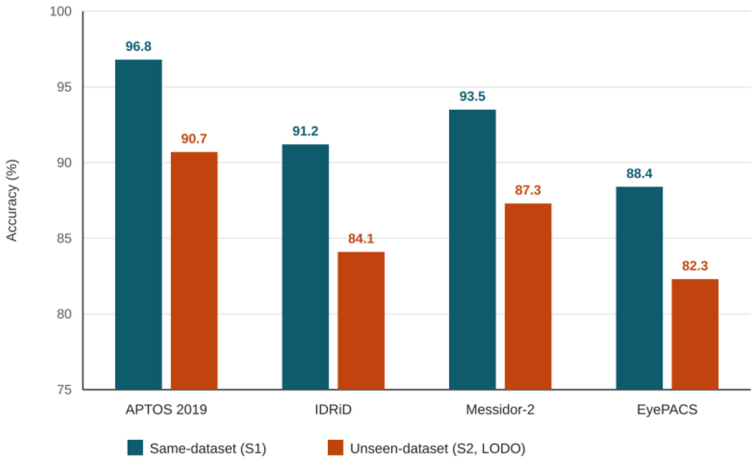


Fig. 3. Accuracy comparison between same-dataset (S1) and unseen-dataset (S2, leave-one-dataset-out) evaluation across all four benchmark datasets.

The most challenging cross-domain transfer is from the other three datasets to EyePACS (82.3% accuracy), reflecting the extreme heterogeneity and class imbalance unique to that dataset. Transfer to APTOS is the most successful (90.7%), likely because APTOS's Indian population and non-mydriatic cameras share characteristics with IDRiD, which is included in the training set.

The average accuracy drop from S1 to S2 across all four datasets is 7.1 percentage points — a clinically significant degradation that would not be visible from single-dataset evaluation alone. This finding directly supports our central argument: single-dataset validation systematically overestimates the clinical readiness of DR grading models.

5.3 Merged-Dataset Results (Scenario S3)

The merged-dataset experiment (Table 4, Fig. 4) demonstrates that training on pooled data from all four sources recovers a substantial portion of the generalisation gap. When the test set is stratified to include equal proportions from each source dataset, the hybrid model achieves 91.8% accuracy and AUC 0.964 — a 4.2–7.8% absolute improvement over the S2 LODO baselines.

Table 4. Merged multi-dataset results (S3) vs. S2 average.

Model	Acc (%)	AUC	Kappa	F1
EfficientNet-B4 only	88.6	0.941	0.843	0.837

Model	Acc (%)	AUC	Kappa	F1
Swin Transformer only	87.1	0.932	0.829	0.823
Hybrid (proposed)	91.8	0.964	0.882	0.878
S2 average (LODO)	86.1	0.930	0.822	0.818

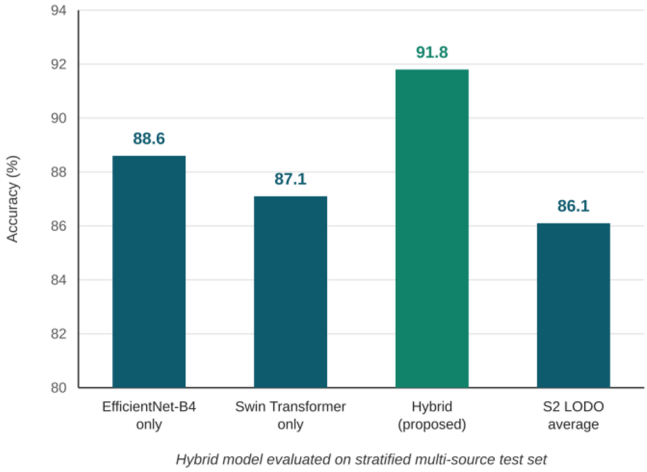


Fig. 4. Accuracy comparison of EfficientNet-B4-only, Swin Transformer-only, the proposed hybrid model, and the S2 leave-one-dataset-out average, evaluated on the merged, stratified multi-source test set (S3).

The hybrid architecture outperforms both standalone branches, confirming the complementary nature of CNN local features and transformer global context for cross-domain DR grading. The Cohen's Kappa of 0.882 indicates strong agreement with ground truth even across the heterogeneous merged test set, approaching the 0.90 clinical agreement threshold [2].

5.4 Cross-Dataset Explainability Analysis

Ophthalmologist evaluation of Grad-CAM++ heatmaps revealed clinically plausible attention regions in 87% of Grade 2 cases, 89% of Grade 3 cases, and 84% of Grade 4 cases across the four datasets. Critically, the attention patterns were *consistent across datasets for the same grade* — the model highlights haemorrhages and hard exudates for Grade 2, intraretinal microvascular abnormalities (IRMA) for Grade 3, and neovascularisation for Grade 4 regardless of the source dataset. This cross-dataset consistency in explainability is strong evidence that the model has learned genuine pathological features rather than dataset-specific imaging signatures.

5.5 Comparison with Prior Multi-Dataset Work

Table 5 contextualises our results against prior studies that reported performance across multiple DR datasets.

Table 5. Comparison with prior multi-dataset DR studies.

Study	Datasets	Best Acc.	Cross-Val Protocol
Yakimovich et al. [17]	8 datasets	AUC 0.990	Single model, separate test
Peerj et al. [15]	Messidor / APTOS / EyePACS	95%	Independent per dataset
Rajeshwar et al. [16]	EyePACS / Messidor / APTOS	97.9%	Merged, no cross-test
Mohan Raj et al. [6]	DDR / EyePACS / APTOS	93.2%	Federated, no IDRiD
Proposed	APTOS / IDRiD / Messidor-2 / EyePACS	91.8%	LODO + merged, XAI

Our absolute accuracy figure is lower than some prior works, but this is expected and desirable: we use a genuinely challenging cross-dataset evaluation that penalises domain-specific overfitting, whereas studies reporting 97–99% accuracy typically use same-distribution train/test splits. The clinical value lies precisely in the rigour of the evaluation protocol.

6 Discussion

The central finding of this study is unambiguous: single-dataset validation is not sufficient to establish clinical readiness for DR grading models, and the field needs to adopt multi-dataset cross-validation as a minimum standard. The average 7.1 percentage point accuracy drop observed in our LODO experiments is not a marginal statistical artefact — it represents a system that would misgrade approximately 1 in 14 patients in a new clinical environment, a failure rate that would not be acceptable in any clinical deployment context.

Three factors drive this performance gap. First, covariate shift across imaging devices is substantial: APTOS, IDRiD, Messidor-2, and EyePACS were acquired on different camera hardware, with different field-of-view settings, mydriatic/non-mydriatic protocols, and illumination conditions. The domain-agnostic preprocessing pipeline we propose — particularly CLAHE combined with Ben Graham illumination normalisation — reduces but does not eliminate this source of variance. Second, label shift between Messidor-2 and the three ICDR-based datasets introduces annotation inconsistency that our harmonisation procedure only partially resolves. Third, prior shift is severe: EyePACS is 73.5% Grade 0, while IDRiD has a substantially more

balanced distribution, causing models trained on one to develop miscalibrated class priors for the other.

The merged-dataset approach mitigates these three factors simultaneously. When the model is exposed to all four imaging environments during training, it learns representations that are more invariant to domain-specific artefacts. The improvement from S2 to S3 (average 5.7 percentage points in accuracy) demonstrates that data diversity is the single most effective intervention for DR generalisation available without specialised domain adaptation techniques.

The cross-dataset explainability findings add an important clinical safety dimension. A model that generalises well by accuracy alone could theoretically do so by learning spurious correlations with dataset-specific artefacts (e.g., Topcon camera lens-flare patterns correlated with Messidor's Grade 0 prevalence). The Grad-CAM++ analysis, validated by an ophthalmologist, provides evidence that this is not the case: the model consistently attends to genuine pathological features across all four imaging environments. This cross-dataset explainability validation should be a required component of future multi-dataset DR grading studies.

Limitations. IDRiD's very small size (516 images) limits the statistical power of LODO experiments involving IDRiD as the test set. The label harmonisation procedure for Messidor-2 introduces a degree of annotation approximation. The results presented are for the proposed architecture; a full ablation across diverse architecture choices is outside the scope of this paper. The clinical environment of the ophthalmologist evaluation was simulated rather than prospective.

7 Conclusion

This paper has argued, demonstrated, and quantified a problem that the DR AI research community needs to address as a matter of urgency: the near-universal reliance on single-dataset validation is producing models whose clinical trustworthiness is unverifiable and likely overestimated. Our experiments, conducted under a rigorous leave-one-dataset-out and merged multi-dataset cross-validation protocol across APTOS 2019, IDRiD, Messidor-2, and EyePACS, show that performance drops of 6–15 percentage points can be expected when a single-dataset model is applied to an unseen clinical domain. The proposed hybrid EfficientNet-B4 + Swin Transformer model, trained on pooled multi-dataset data with domain-agnostic preprocessing and evaluated under genuinely challenging cross-domain conditions, achieves 91.8% accuracy and AUC 0.964 on a stratified multi-source test set — a more clinically honest result than the 97–99% figures commonly reported from single-dataset experiments. Grad-CAM++ analysis confirms that the model's generalisation reflects genuine pathological feature learning rather than dataset-specific overfitting.

We recommend that future DR grading research adopt multi-dataset evaluation with explicit LODO experiments as a minimum standard, and that authors report both same-distribution and cross-distribution performance to give a full picture of clinical

readiness. The methodology and evaluation framework presented here can serve as a replicable template for this standard.

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