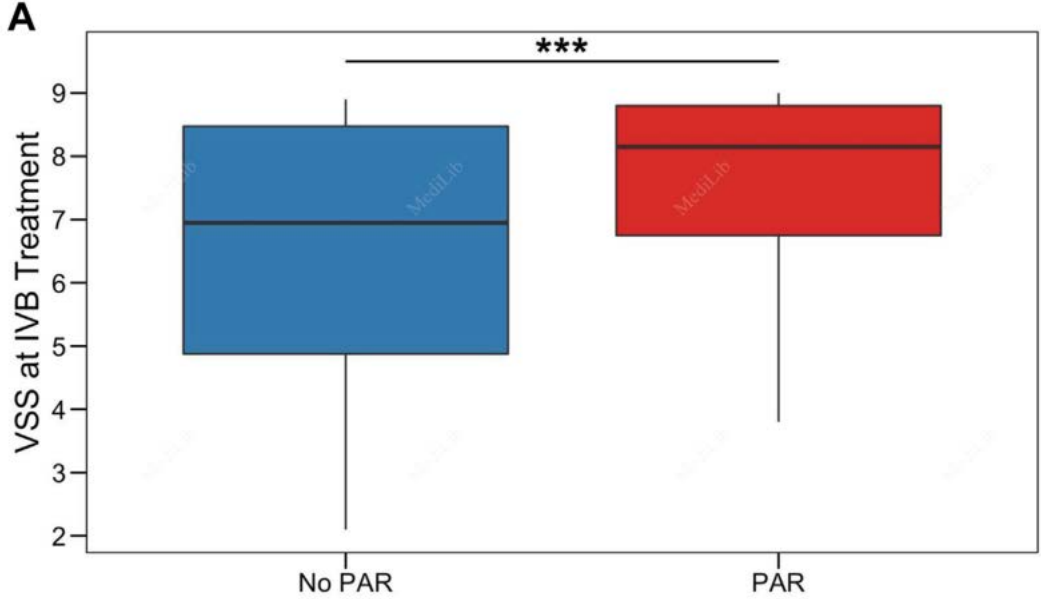
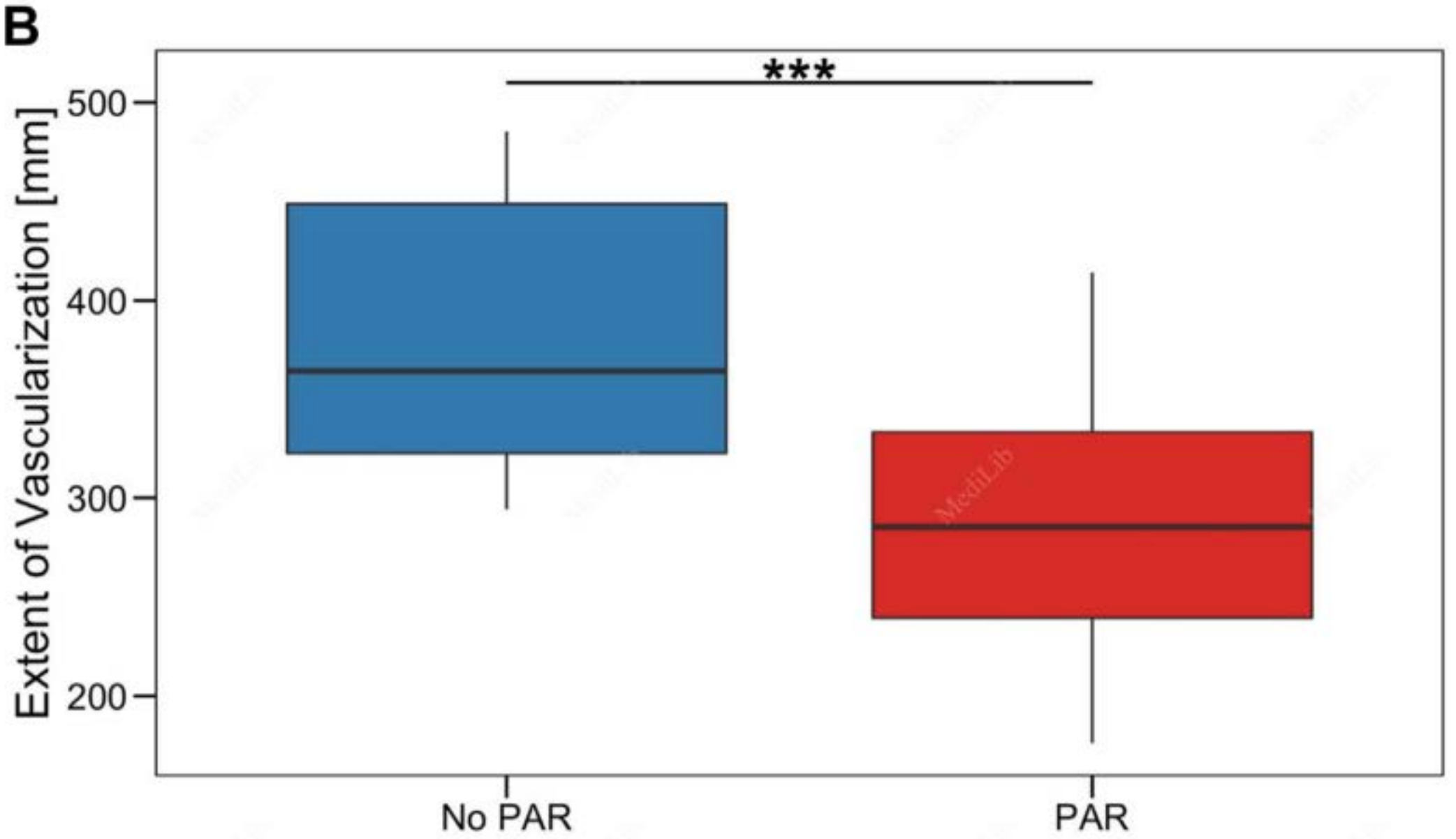
Imaging Features Associated with Persistent Avascular Retina in Retinopathy of Prematurity

The use of anti-VEGF therapy as the primary treatment for retinopathy of prematurity (ROP) has generated attention to the potential for long-term avascularity of the peripheral retina after initial treatment. The most recent International Classification of Retinopathy of Prematurity, Third Edition, formally termed this finding "persistent avascular retina" (PAR) and recognized that it can occur after spontaneous regression or anti-VEGF treatment.[1] A potential benefit of anti-VEGF primary treatment compared with laser is increased vascularized area, potentially enlarging the functional visual field long term. However, this treatment also has the potential to reactivate and cause atypical ROP-related retinal detachments in infancy, as well as increasing the long-term risk of detachment.[2] A better understanding of which babies are at highest risk of PAR could help risk stratify who would benefit most from more frequent examinations and possibly laser.

Recent work has demonstrated that a higher vascular severity score (VSS), derived from the artificial intelligence–based Imaging and Informatics in ROP deep learning algorithm, is associated with more posterior disease, higher disease stage and extent, and higher risk of treatment failure with laser.[3] In this report, we evaluate whether imaging-based quantitative metrics such as the VSS or the measured posterior extent of retinal vascularization at the time of treatment with intravitreal bevacizumab (IVB) may be associated with disease reactivation or failure to fully vascularize (PAR).

Although BW, GA, and PMA were not statistically different between groups, the median (IQR) VSS in the PAR group was significantly higher (8.2 [2.1]) than in the No PAR group (7.0 [3.6], $P < 0.001$, Fig 2A). Likewise, the median (IQR) length of vascularized retina for all eyes was 310.4 (90.0) mm but was shorter in the PAR group (285.3 [94.2] mm) compared with the No PAR group (364.6 [126.3] mm, $P < 0.001$, Fig 2B). This coincided with the finding that zone I ROP was significantly associated with PAR ($P < 0.001$). A post hoc analysis revealed that the time to reactivation for eyes that would eventually develop PAR was associated with the extent of the retinal vasculature measured at initial IVB treatment (Fig 2C). The median (IQR) length of vascularized retina for eyes requiring re-treatment at 0–6 weeks, 6–12 weeks, and 12 or more weeks was 194.0 (41.9), 269.0 (88.4), and 310.0 (69.2), respectively. All groups were significantly different from one another ($P < 0.001$).


A
***
VSS at IVB Treatment
9
8
7
6
5
4
3
2
No PAR
PAR


B
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Extent of Vascularization [mm]
500
400
300
200
No PAR
PAR

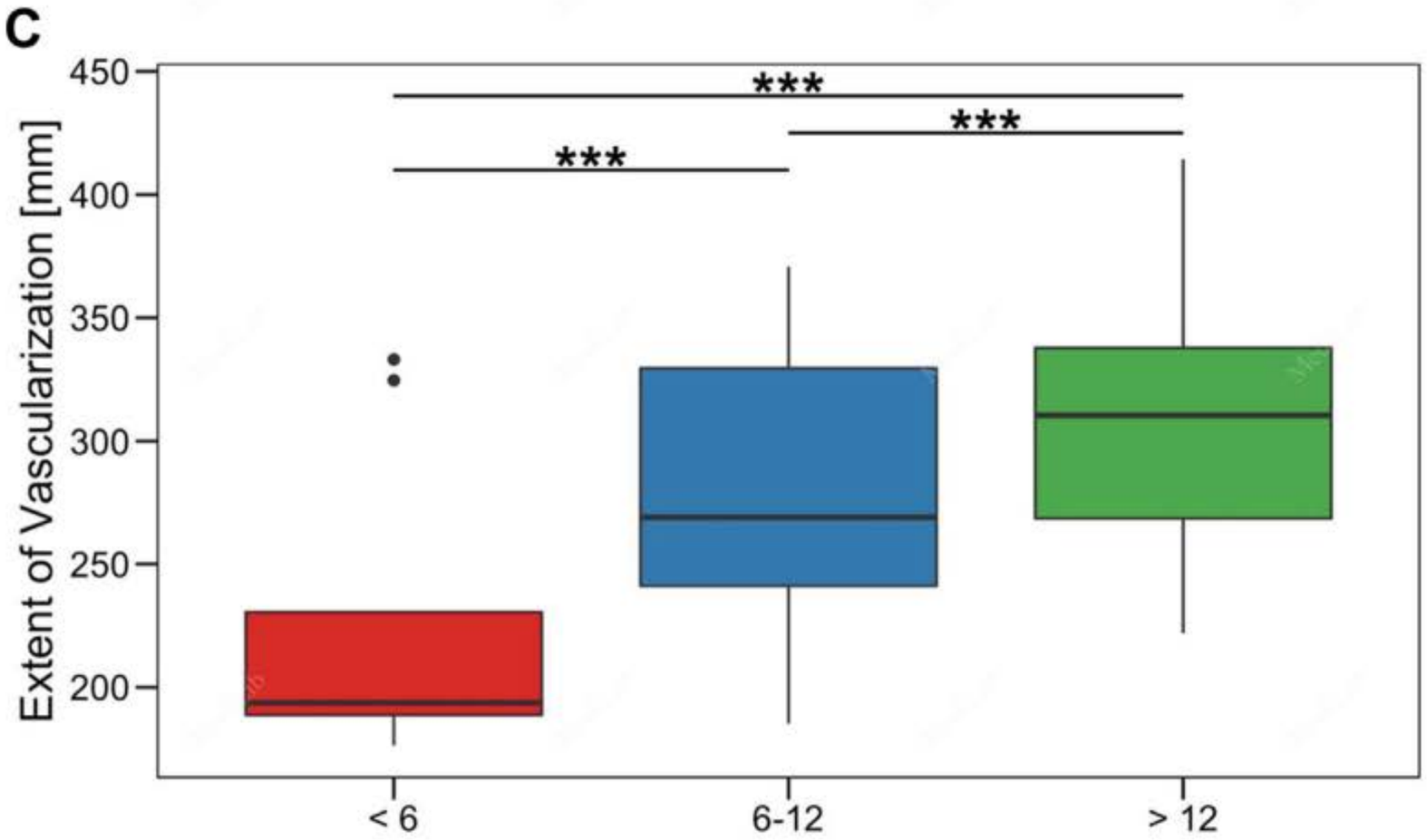

Figure 2. Comparisons between eyes with no persistent avascular retina (PAR) and eyes with PAR. Box plots suggest that the **(A)** median vascular severity score (VSS) and **(B)** extent of vascularization at the time of intravitreal bevacizumab (IVB) between groups are different. Generalized estimating equations (GEEs) confirmed these results ($P < 0.001$). Additionally, plots also suggested that of the eyes with PAR, **(C)** time to reactivation was dependent on the extent of vascularization at the time of IVB. This was also confirmed by GEE ($P < 0.001$).

The results of this study suggest that quantitative assessment of imaging features, using either objective assessment of vascular severity or measurement of the posterior extent of retinal vascularization, may help identify babies at highest risk of reactivation or PAR. These results are consistent with prior clinical studies that zone I eyes are at highest risk of treatment failure or reactivation. Notably, in this study, although the clinical grading of zone did not differ for the majority of eyes, objective assessment of the posterior

vascular border did, suggesting that objective metrics of disease severity may be more precise than clinical examination and that ophthalmic imaging may be beneficial.