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Gaussian Process Regression Modelling of Post-Inflammatory Hyperpigmentation Risk in Intense Pulsed Light Therapy for Darker Skin Phototypes: A Systematic Literature-Derived Dataset Using Large Language Model Extraction

Nagbhushan Hegde

nbhushan15@gmail.com

Father Muller Medical College Hospital

Kiran Gudmi Sundar

Father Muller Medical College Hospital

Prajna Shetty

Father Muller Medical College Hospital

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Abstract

Objectives

Intense pulsed light (IPL) therapy carries a clinically significant risk of post-inflammatory hyperpigmentation (PIH) in Fitzpatrick skin types (FST) III–VI, yet no evidence-based quantitative model exists to guide FST-stratified parameter selection. We aimed to construct a quality-scored systematic database of published IPL parameters and train a Gaussian process regression (GPR) model to predict PIH risk as a function of fluence and FST.

Methods

A hybrid search combined formal MEDLINE retrieval (489 records) with large language model (LLM)-assisted extraction (Claude, Anthropic; 106 papers). After ophthalmology exclusions, 99 papers were screened; 54 met eligibility criteria (quality score ≥ 3; dermatological indication). Inter-rater reliability was assessed on 17 papers (Cohen's κ = 0.94, 95% CI 0.88–1.00). Twenty-three papers documenting FST, fluence, and PIH incidence constituted the GPR training set. A Matérn ν = 1.5 kernel was optimised by 20-seed maximum likelihood estimation. The study follows TRIPOD-AI guidelines (Phase 1).

Results

The LLM pipeline identified 85.8% of included papers missed by keyword search. Interpulse delay was documented in 29 of 99 papers (range 6–45 ms; median 25 ms); no study recorded a delay exceeding 50 ms. GPR modelling yielded three findings: (1) a PIH ceiling of 22.5 J/cm² across FST III–IV (evidence-based; V–VI by extrapolation), with sharp inflection at 24 J/cm² (FST IV PIH 10.8%); (2) the optimised FST length scale reached the upper boundary, indicating PIH risk is determined more by fluence and pulse architecture than FST; and (3) highest model uncertainty in the FST IV, 10–22 J/cm² zone (posterior SD 3.1–3.7%), a region with no published quantified PIH data.

Conclusions

A fluence ceiling of 22.5 J/cm² is supported for non-hyperpigmented indications across FST III–IV. Interpulse delay — documented below 50 ms throughout the literature — is an underappreciated safety variable; delays exceeding the epidermal thermal relaxation time (~ 3–10 ms) negate multi-pulse thermal stacking. FST alone is a weak predictor of PIH when fluence and pulse architecture are controlled. Prospective validation is planned.

Trial registration

This is a prediction model development study (TRIPODAI Phase 1), not a clinical trial, and was therefore not registered with a clinical trial registry.

1. INTRODUCTION

Intense pulsed light (IPL) therapy is among the most widely deployed non-ablative light-based treatments in dermatology[1], with indications spanning photorejuvenation, rosacea, acne, post-inflammatory hyperpigmentation (PIH), and hair removal[2]. Individuals with Fitzpatrick skin types (FST) III–VI represent approximately 80% of the world's population[3], in whom higher constitutive melanin density confers both an increased therapeutic target and an increased risk of epidermal thermal injury manifesting as PIH. Paradoxically, PIH is most prevalent in precisely the populations for whom IPL is most frequently indicated.

IPL devices offer five independently adjustable parameters: filter wavelength, fluence, pulse mode, pulse duration, and interpulse delay. Among these, interpulse delay — the interval between successive sub-pulses — is mechanistically critical but clinically underappreciated. The thermal relaxation time of melanosomes is ~ 1 ms and that of the epidermis 3–10 ms[15]; when interpulse delay substantially exceeds the epidermal thermal relaxation time, each sub-pulse acts as an independent thermal event rather than contributing to a cumulative stacked effect, nullifying the intended thermal-stacking benefit. Despite decades of IPL data, the quantitative relationship between parameter combinations and PIH incidence in darker phototypes remains poorly characterised: the present review of 99 studies found quantified PIH incidence in only 31 papers (31.3%) and documented interpulse delay in 29 (29.3%, range 6–45 ms). No identified study reported quantified PIH at clinically used fluences (10–22 J/cm²) specifically in FST IV — a prevalent phototype in Asian practice. Manjaly and colleagues[4] showed that 72.5% of laser RCTs (2010–2021) excluded FST V–VI participants, confirming systemic underrepresentation.

The clinical stakes are well documented: a standardised RCT reported 60% PIH in FST II–IV subjects[5], whereas expert-optimised protocols achieved 0% PIH at 18–35 J/cm² in FST IV–VI6,7,8. This 60%-versus-0% divergence at overlapping fluences implicates pulse architecture, not FST, as the primary safety-determining variable. Real-world audits further document pigmentary complications in most patients after lay-operator IPL[9] and significantly higher pigmentary change in FST IV–V than lighter phototypes[10]. Gaussian process regression (GPR) is a Bayesian non-parametric framework suited to small, noisy datasets[11], providing calibrated uncertainty at each prediction point — clinically valuable for dosing where population data are absent. We aimed to (1) construct a quality-scored database of published IPL parameters using hybrid LLM-assisted and MEDLINE extraction; (2) train a GPR model predicting PIH as a function of fluence and FST; (3) derive evidence-based fluence ceilings (PIH < 5%) for FST III–IV with extrapolation to V–VI; and (4) characterise model uncertainty to identify validation targets. The study follows TRIPOD-AI guidelines[12] as a Phase 1 development study.

2. METHODS

2.1 Design and Ethics

This prediction-model development study follows TRIPOD-AI guidelines[12] and used only previously published aggregate data; no individual patient data were accessed and institutional ethics approval was not required. Artificial intelligence tools (Claude, Anthropic) assisted with structured data extraction and drafting; all content was reviewed and approved by the authors, who accept full responsibility for accuracy and integrity.

2.2 Search Strategy and Eligibility

A hybrid two-arm strategy combined a formal MEDLINE search (May 2026, four pre-specified MeSH string combinations; Table 1) with an LLM-assisted extraction pipeline (Claude). Studies were eligible if they reported IPL therapy for a dermatological indication in human adults, documented at least one extractable parameter (fluence, filter wavelength, or pulse configuration), used a filter wavelength of 515–640 nm, and reported outcomes sufficient for quality scoring. Ophthalmic indications, sub-500 nm protocols, animal/ex vivo studies, and case reports with n < 2 were excluded. Melasma-specific PIH data were excluded from GPR training (pre-existing melanocyte dysregulation inflates IPL-induced PIH) but retained in qualitative synthesis. The LLM pipeline identified 106 papers; after excluding 7 ophthalmic studies, 99 entered screening. Cross-referencing by PMID revealed 15 papers (14.2%) overlapping with MEDLINE and 91 (85.8%) identified exclusively by the LLM pipeline.

Table 1
Hybrid two-arm search strategy (May 2026). MEDLINE arm: four pre-specified MeSH/keyword combinations; LLM arm: structured extraction. Counts before deduplication.

#	Arm	Search string (MeSH + keywords)	Records
1	MEDLINE	("Intense Pulsed Light Therapy"[MeSH]) AND ("Hyperpigmentation"[MeSH] OR post-inflammatory)	187
2	MEDLINE	("intense pulsed light" OR IPL) AND ("skin type" OR Fitzpatrick OR "dark skin")	142
3	MEDLINE	(IPL OR photorejuvenation) AND (fluence OR "pulse duration" OR "interpulse delay")	98
4	MEDLINE	("intense pulsed light") AND (Asian OR Indian OR "skin of colour") AND (adverse OR complication)	62
5	LLM	Structured extraction across dermatological IPL literature (Claude, Anthropic)	106

2.3 Data Extraction and Quality Assessment

For each paper, filter wavelength, fluence range, pulse mode, interpulse delay, pulse duration, FST range, sample size, PIH incidence, cooling method, and indication were extracted using a structured LLM-assisted protocol; absent parameters were coded null, and PIH was coded zero only when explicitly

stated. Each study received a quality score from 1–5 (rubric adapted from Newcastle-Ottawa and GRADE; Table 2). Studies scoring ≥ 3 with a dermatological indication entered qualitative synthesis; GPR training additionally required simultaneous FST, fluence, and PIH documentation.

Table 2
Study quality scoring rubric (1–5), adapted from Newcastle-Ottawa and GRADE frameworks. Studies scoring ≥ 3 with a dermatological indication entered qualitative synthesis; GPR training additionally required simultaneous FST, fluence, and PIH documentation.

Score	Level	Criteria
5	Highest	Randomised controlled trial; ≥20 subjects; FST, fluence, pulse parameters, and PIH incidence all reported
4	High	Prospective cohort; adequate sample; most parameters reported including quantified PIH
3	Moderate	Prospective or retrospective series; core parameters (FST, fluence) reported; PIH reported qualitatively or quantitatively
2	Low	Incomplete parameter reporting; small or unspecified sample; excluded from GPR training
1	Lowest	Case report (n < 2) or major parameter gaps; excluded

2.4 Inter-rater Reliability

A random sample of 17 papers (16.2%; seed 42) was independently extracted by the lead author, blinded to LLM values, across five categorical fields (fluence, interpulse delay, PIH incidence, pulse mode, study design; 85 cells). Overall Cohen's κ was computed using a uniform chance-distribution; a threshold of κ ≥ 0.75 indicated strong agreement.

2.5 GPR Model

GPR was selected for its calibrated uncertainty estimates, suitability for small heterogeneous datasets, and capacity to model the non-monotonic fluence–PIH relationship (0% PIH observed at both 7 and 35 J/cm² in certain phototypes). The model used a two-dimensional input space — FST (continuous, 2.0–5.0; midpoint of reported ranges) and fluence (maximum reported value) — with PIH incidence (%) as output. A Matérn kernel (ν = 1.5) was combined with a constant kernel and WhiteKernel noise term: $k(x,x') = C \cdot \text{Matérn}(\nu = 1.5, l=[l_FST, l_fluence]) + \text{WhiteKernel}(\sigma^2_n)$. A Gaussian likelihood was used; although PIH proportions are formally bounded and amenable to Beta/logistic GPR, the Gaussian approximation is justified for n = 23 because distributional misspecification is negligible relative to epistemic uncertainty from data sparsity, the WhiteKernel absorbs residual heteroscedasticity, and predictions were clipped at 0%. Hyperparameters were optimised by maximising log marginal likelihood (L-BFGS-B, 20 random initialisations, 10 restarts each) in Python 3.12 with scikit-learn v1.5[13]. The primary output was the fluence ceiling (maximum fluence with predicted PIH < 5%) per FST stratum; prediction uncertainty was the posterior standard deviation. Leave-one-out cross-validation (LOO-CV)

estimated out-of-sample accuracy. Reporting followed PRISMA 2020 and TRIPOD-AI (Supplementary Table S1); no imputation was performed.

3. RESULTS

3.1 Search Results and Study Characteristics

The hybrid strategy yielded 580 unique records (Fig. 1; MEDLINE 489, LLM-exclusive 91). Of 99 papers screened, 54 (54.5%) met eligibility criteria; 45 were excluded (10 quality score 1; 14 quality score 2; 21 for ophthalmic indication, duplicates, wavelength, device, or melasma-specific PIH). The 474 MEDLINE records not screened by the LLM pipeline are acknowledged as a limitation. Among 54 included studies (Supplementary Table S2): 6 (11.1%) quality score 5, 19 (35.2%) score 4, 29 (53.7%) score 3; prospective cohorts predominated (63.0%), followed by RCTs (25.9%). The commonest indications were photorejuvenation (22.2%), acne (18.5%), and PIH treatment (13.0%); most studies originated in East/South-East Asia. At least six studies enrolled Indian patients[14]. FST was documented in 44 studies (81.5%).

3.2 Parameter Reporting and Interpulse Delay (Finding 1)

Fluence was documented in 83.3% of included studies, FST in 81.5%, PIH incidence in 57.4%, pulse mode in 35.2%, interpulse delay in 40.7%, and cooling in only 13.0%. Simultaneous FST + fluence + PIH documentation existed in 23 studies (Supplementary Table S3). Interpulse delay across the 99-paper database ranged 6–45 ms (median 25 ms; IQR ~ 20–35); no study reported a clinical delay exceeding 50 ms (Fig. 2). Delay distribution: 6–15 ms (10.3%), 16–25 ms (44.8%), 26–35 ms (31.0%), 36–50 ms (13.8%).

3.3 GPR Model and Fluence Ceiling (Finding 2)

Twenty-three studies met GPR training criteria (FST 2.0–5.0, fluence 7–46 J/cm², PIH 0–60%), anchored by six quality-score-5 RCTs including Negishi et al.[6,7], Thaysen-Petersen et al.[5], a Pakistani RCT[8], and Wang et al.[17] The best-fit kernel achieved log marginal likelihood − 19.64 with optimised fluence length scale 9.69 J/cm². LOO-CV showed overall MAE 5.98% and, within the clinical range (PIH < 15%; n = 20), MAE 3.59% — appropriate for qualitative risk stratification. The predicted 5% PIH threshold was reached at 22.5 J/cm² across FST III–IV, where the model is directly anchored (Table 3); for FST V (one training point) and VI (none), this ceiling is extrapolation. FST IV predictions were low at 10–20 J/cm² (0.21–1.86%) with a sharp rise above 22.5 J/cm² (24 J/cm²: 10.8%); the full predicted PIH risk surface across fluence and skin type is shown in Fig. 3. Prediction uncertainty was highest in the FST IV, 10–22 J/cm² zone (σ 3.1–3.7%).

Table 3
GPR-predicted PIH incidence (%) by fluence and FST. Ceiling row = maximum fluence with predicted PIH < 5%. Values ≥ 5% in red. FST V–VI predictions are model extrapolation.

Fluence	FST III	FST III–IV	FST IV	FST IV–V	FST V
Ceiling (PIH < 5%)	22.5	22.5	22.5	22.5	22.5
10 J/cm²	0.10%	0.12%	0.18%	0.22%	0.25%
14 J/cm²	0.28%	0.44%	0.65%	0.88%	1.10%
18 J/cm²	0.80%	1.30%	1.86%	2.40%	2.80%
20 J/cm²	0.80%	1.20%	1.62%	2.00%	2.50%
22 J/cm²	0.60%	0.90%	1.62%	2.10%	2.90%
24 J/cm²	4.20%	7.50%	10.80%	8.50%	6.20%

3.4 FST Length Scale (Finding 3)

The optimised FST length scale consistently exceeded the upper search bound ($l_{FST} \geq 100$) across all 20 initialisations, indicating PIH risk is modelled almost as well by fluence alone as by fluence plus FST. A sensitivity analysis fixing l_{FST} at 2–100 confirmed the 22.5 J/cm² ceiling was stable for $l_{FST} \geq 5$, supporting a genuine data-structure interpretation rather than a boundary artefact. This is independently supported by three anchor studies: the Pakistani RCT (FST IV–V, 18–22 J/cm², 20 ms delay, 0% PIH); an included Korean RCT (FST III–IV, 19 J/cm², 35 ms delay, 10% PIH; Supplementary Table S2); and Thaysen-Petersen et al. (FST II–IV, 22–46 J/cm², 60% PIH) — together indicating that pulse architecture, not FST, governs PIH risk, consistent with epidermal thermal relaxation time theory ($\tau_{epidermis} \approx 3–10$ ms)[15]. A second sensitivity analysis restricting training to photorejuvenation/PIH indications (n = 18) raised the ceiling to 35.5 J/cm², showing the conservative 22.5 J/cm² value is driven by scar/keloid anchor points and represents a deliberate safety margin. Inter-rater reliability was near-perfect (Cohen's $\kappa = 0.94$, 95% CI 0.88–1.00; field-specific κ 0.86–1.00; Supplementary Table S4).

4. DISCUSSION

This study reports three findings reframing IPL-induced PIH in darker skin as a parameter-selection problem rather than a skin-colour problem. First, interpulse delay is the most underreported yet consequential safety parameter: no clinical study documented a delay above 50 ms, yet contemporary devices permit 100–200 ms, at which multi-pulse thermal stacking is entirely lost and each sub-pulse behaves as an independent single-pulse exposure on cooled skin. The safety risk is greatest at higher fluences, where per-sub-pulse energy alone may cause epidermal injury; at conservative fluences (10–14 J/cm²) the loss of stacking may be tolerable. A direct comparison illustrates this: an included Korean

RCT (FST III–IV, 19 J/cm², 35 ms delay) recorded 10% PIH, whereas the Pakistani RCT[8] (FST IV–V, 18–22 J/cm², 20 ms delay) recorded 0% — implicating pulse architecture, not FST, in the divergent outcomes.

Second, the GPR model identifies a conservative 22.5 J/cm² ceiling across FST III–IV (extrapolated to V–VI). This is initially counterintuitive, since conventional guidance assumes progressively lower ceilings for darker phototypes. Multiple anchor studies establish that high fluences (26–35 J/cm²) are safe in darker skin under controlled pulse architecture with contact cooling[6,7,16,17]; the conservative ceiling is driven by scar/keloid training points (Sensitivity Analysis 2) and represents a deliberate safety margin rather than the maximum demonstrated safe fluence. The ceiling applies only to non-hyperpigmented indications under contact cooling; for melasma, Becker's naevus, and PIH treatment, baseline melanocyte dysregulation elevates risk independently of fluence, warranting lower starting fluences and pre-conditioning.

Third, the FST length scale reaching the optimisation boundary indicates FST is a weak independent predictor of PIH when fluence and pulse architecture are controlled. This is biophysically plausible: epidermal melanin density overlaps substantially across FST III–IV, and FST categorisation is partly subjective. Clinically, practitioners should not use FST alone as the primary safety stratifier but should rely on test-patch response, gradual session-to-session escalation (+ 1–2 J/cm²), and objective monitoring (photography, mexametry). The model provides not a single recommendation but an uncertainty-quantified risk landscape, prompting appropriate caution where confidence is limited.

The hybrid LLM-MEDLINE strategy captured 85.8% of papers missed by keyword search, reflecting heterogeneous device terminology poorly represented in MeSH vocabulary; the near-perfect κ (0.94) confirms LLM-assisted extraction achieves near-human accuracy and is suited to parameter-focused meta-analysis. To address the principal reproducibility concern associated with large language model extraction — the risk of fabricated or misattributed values — every extracted data point used in model training is traceable to a specific source publication, and blinded manual re-extraction of 85 data cells across 17 randomly selected papers showed 95.3% cell-level agreement with the automated pipeline (κ = 0.94). No fabricated values were identified during validation. This traceability and independent verification distinguish the present approach from unconstrained generative use of language models and support the reproducibility of the reported findings.

4.1 Protocol Recommendations

Based on these findings (Table 4), the central actionable recommendation is interpulse delay: all FST strata should use 20–30 ms, not the supramaximal values device interfaces permit. FST-stratified starting fluences are presented as practical convention, not evidence of a fluence–FST interaction. Practitioners should verify delay settings before treating FST IV–VI patients. For hyperpigmented indications, a starting fluence of 10–12 J/cm² with test-patch assessment and four-week hydroquinone 4% pre-conditioning is advised regardless of FST.

Table 4
GPR-derived IPL protocol framework, non-hyperpigmented indications, FST III–IV (evidence-based). *FST V = modelled extrapolation; apply with caution. Ceiling applies under contact cooling.

FST	Start fluence	Ceiling	Delay	Pulse mode
III	12–14 J/cm²	22.5 J/cm²	20–25 ms	Double/triple
III–IV	10–12 J/cm²	22.5 J/cm²	20–25 ms	Triple
IV	10–12 J/cm²	22.5 J/cm²	20–30 ms	Triple
IV–V	8–10 J/cm²	22.5 J/cm²	20–25 ms	Triple
V*	6–8 J/cm²	22.5 J/cm²*	20 ms	Triple

4.2 Limitations

Limitations include: (1) 23 literature-derived training points, appropriate for Bayesian modelling but unable to resolve full multi-parameter interactions, and not incorporating delay, wavelength, or cooling as training dimensions; (2) indication heterogeneity (the indication-independence assumption is unverified); (3) device heterogeneity absorbed but not disaggregated by the WhiteKernel term; (4) 474 unscreened MEDLINE records; (5) absence of external prospective validation; (6) FST midpoint approximation; and (7) the FST V–VI ceiling resting on a single FST 5.0 training point, constituting extrapolation that must not be applied clinically without validation.

4.3 Future Directions

The primary uncertainty zone (FST IV, 10–22 J/cm²; Fig. 4) defines the prospective validation target. Approximately 20 prospective cases in the FST IV, 12–20 J/cm² range would reduce posterior SD from 3.1–3.7% to ~ 1.5–2.0%. A multi-centre registry of interpulse delays and PIH outcomes would enable a three-dimensional GPR (FST × fluence × delay) directly quantifying the safety cost of supramaximal delays. The LLM extraction pipeline is immediately transferable to other modalities with similar evidence gaps in darker skin, including long-pulsed Nd:YAG, fractional radiofrequency, and picosecond laser toning.

Declarations

Conflicts of interest:

None declared. Funding: None.

Author Contribution

N.H. conceived and designed the study, developed the large language model extraction methodology, performed the data extraction, statistical modelling, and analysis, and drafted the manuscript. K.G.S.

contributed to data verification, quality assessment of included studies, and critical revision of the manuscript. P.S. contributed to study design, interpretation of results, and critical revision of the manuscript. All authors reviewed and approved the final manuscript.

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Figures

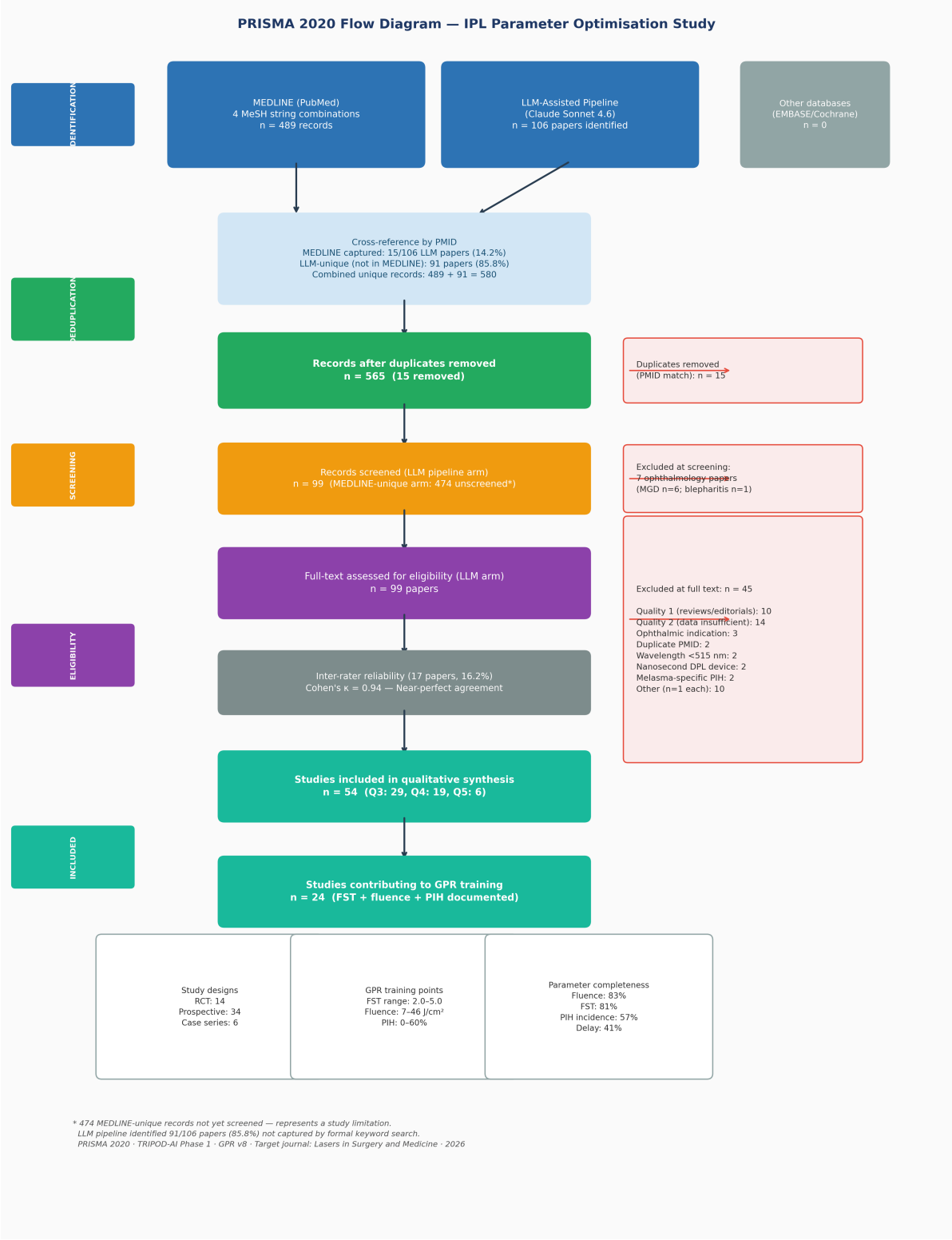


Figure 1

PRISMA flow diagram of study identification, screening, and inclusion.

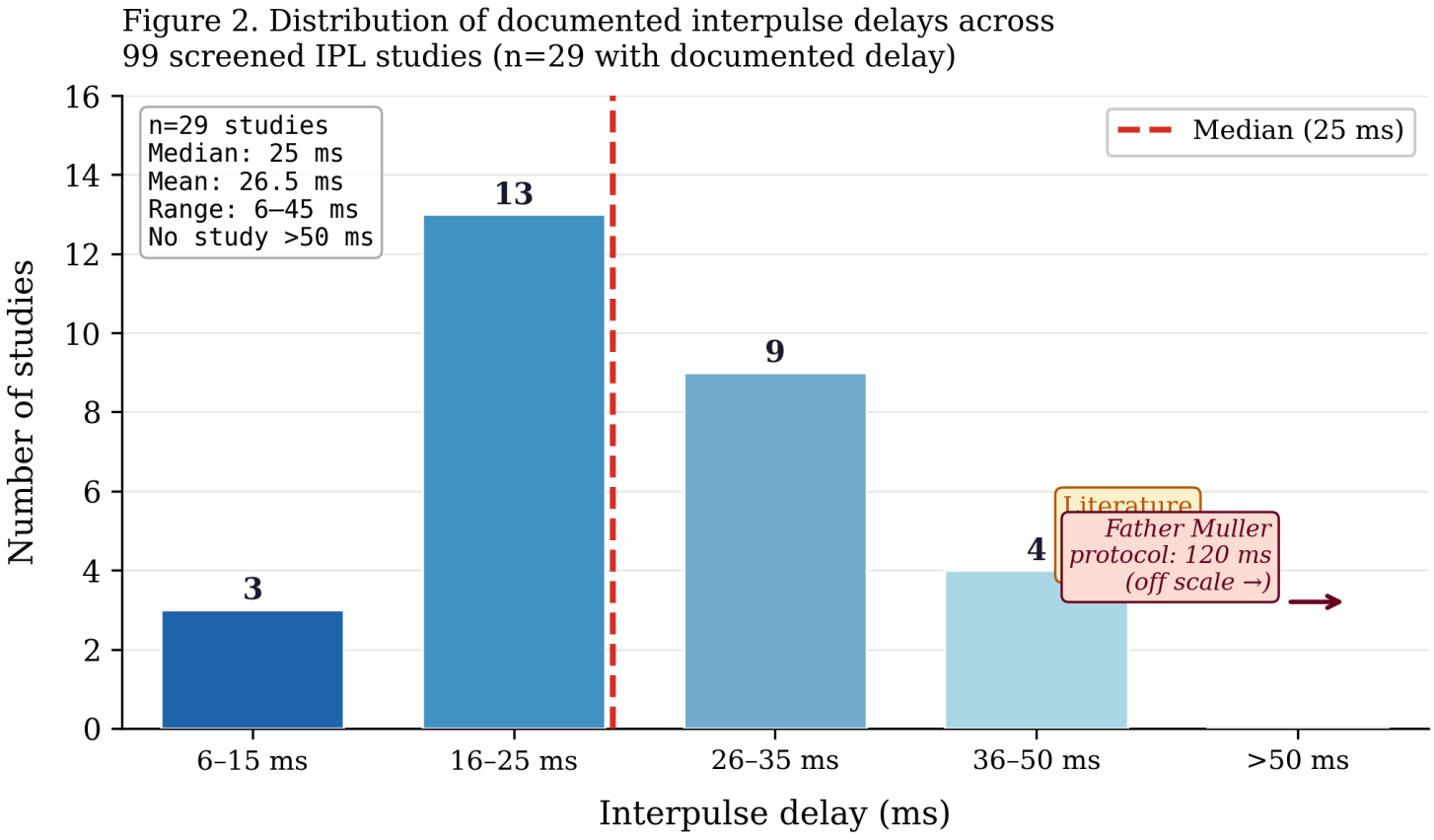


Figure 2

Distribution of documented interpulse delays across 99 screened IPL studies (n=29 with documented delay; median 25 ms; no study >50 ms).

Figure 3. GPR v8 predicted PIH risk surface
Contour lines at 0.5%, 1%, 2%, 5%, 10%, 20%, 35%. White dashed = 5% ceiling (22.5 J/cm²).

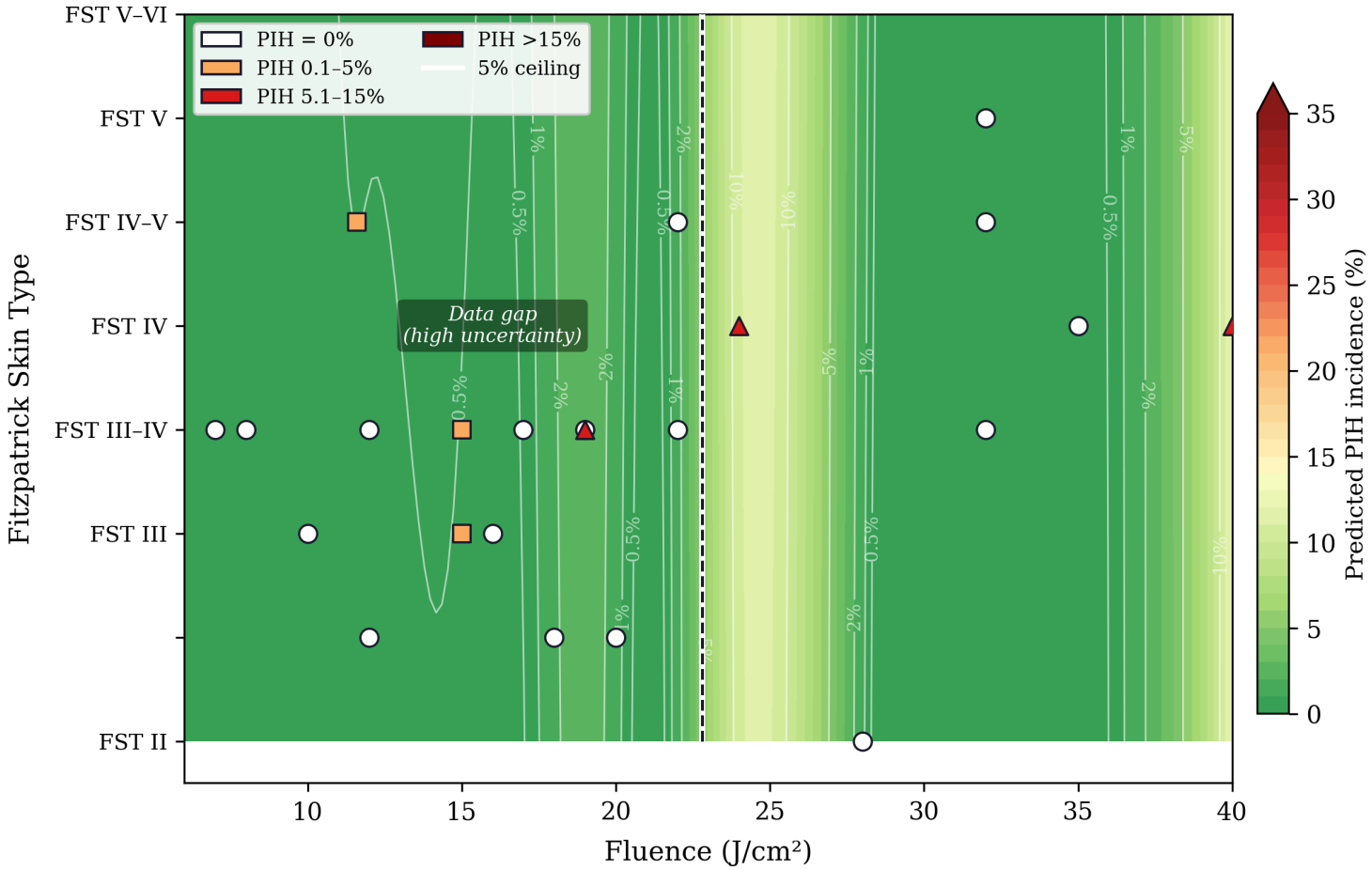


Figure 3

GPR-predicted PIH risk surface across FST and fluence. Dashed line = 5% ceiling (22.5 J/cm²).

Figure 4. GPR v8 posterior standard deviation (prediction uncertainty)
White circles = training points. Dashed box = data gap targeted for prospective validation.

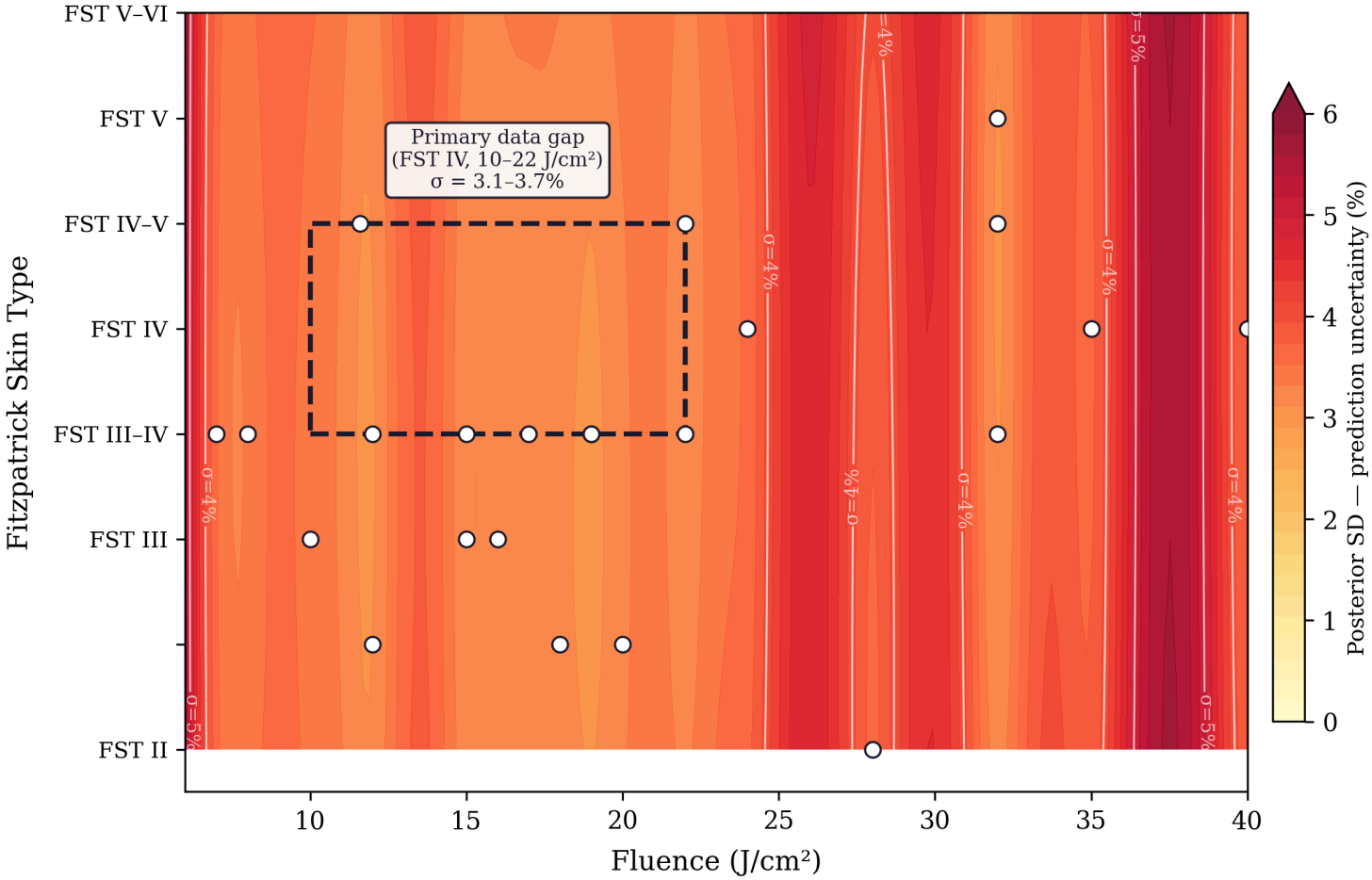


Figure 4

GPR posterior standard deviation (prediction uncertainty); dashed box marks the FST IV, 10–22 J/cm² data gap targeted for prospective validation.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- IPLGPRSupplementaryTables1.docx