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# Purtscher-like Retinopathy in Critically Ill Patients (Non-Traumatic Etiologies): A Systematic Review and Meta-analysis of Incidence, Associated Conditions, and Visual Outcomes

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**A B S T R A C T**

**Introduction:** Purtscher-like retinopathy (PLR) is an occlusive microvasculopathy presenting with funduscopic findings similar to Purtscher's retinopathy but occurring in the absence of direct head or chest trauma. Its association with various systemic conditions, particularly those requiring intensive care unit (ICU) admission, is recognized, but comprehensive data on its incidence, spectrum of associated non-traumatic critical illnesses, and visual prognosis in this specific population remain sparse. This study aimed to systematically review the literature and perform a meta-analysis to estimate the incidence of PLR among critically ill patients with non-traumatic conditions, identify commonly associated systemic diseases, and quantify visual outcomes. **Methods:** A systematic review and meta-analysis were conducted following PRISMA guidelines. PubMed, Embase, Scopus, and Web of Science databases were searched from January 1st, 2013, to December 31st, 2023, for studies reporting PLR in critically ill adult patients admitted for non-traumatic reasons. Studies included cohort studies, case-control studies, and sufficiently large case series (n≥5 with ICU context) reporting incidence or detailed clinical data. Two reviewers independently screened studies, extracted data, and assessed the risk of bias using the Newcastle-Ottawa Scale (NOS). Pooled incidence of PLR, associated conditions, and final visual acuity (logMAR) were synthesized. A random-effects model was used for meta-analysis due to anticipated heterogeneity. **Results:** 6 studies met the full eligibility criteria for quantitative synthesis, encompassing 960 critically ill patients from various ICU settings. The included studies were predominantly retrospective cohorts with moderate overall quality (median NOS score 7, range 6-8). The pooled estimated incidence of PLR in the evaluated non-traumatic critically ill populations was 3.4% (95% Confidence Interval [CI]: 2.1% - 5.5%), exhibiting substantial heterogeneity ($I^2$ = 80%, p < 0.001). The most frequently reported associated conditions were severe acute pancreatitis (reported in 4/6 studies) and sepsis/septic shock (4/6 studies). Other identified associations included acute kidney injury requiring renal replacement therapy, HELLP syndrome in post-partum patients admitted to ICU, and systemic lupus erythematosus/antiphospholipid syndrome flares requiring intensive care. Visual outcomes were generally poor; the pooled mean final best-corrected visual acuity (BCVA) was 0.85 logMAR (approx. Snellen 20/140; 95% CI: 0.65 - 1.05 logMAR), again with significant heterogeneity ($I^2$ = 75%). Approximately 45% of affected eyes had a final BCVA of less than 20/200. **Conclusion:** Purtscher-like retinopathy represented a notable, albeit relatively uncommon, complication among heterogeneous populations of critically ill patients admitted for non-traumatic conditions. It was most frequently associated with severe systemic inflammatory states such as acute pancreatitis and sepsis. Increased awareness and ophthalmoscopic screening in high-risk ICU patients may be warranted. The observed heterogeneity highlights the need for larger prospective studies with standardized diagnostic and reporting criteria.

## 1. Introduction

Purtscher's retinopathy, a distinct form of occlusive retinal microvasculopathy, was initially characterized by Otmar Purtscher in 1910. This condition is classically linked to significant trauma involving the craniofacial region or compressive forces applied to the thorax. The hallmark ophthalmoscopic presentation of Purtscher's retinopathy is notable for the presence of multiple polygonal patches of retinal whitening, known as Purtscher flecken, in conjunction with cotton wool

spots, retinal hemorrhages (which may be intraretinal or pre-retinal), and, in some instances, optic disc edema. Typically, these funduscopic abnormalities are concentrated in the posterior pole of the eye, in the vicinity of the optic disc and macula. The underlying mechanism for these findings is believed to be the occlusion of arterioles, leading to ischemia within the inner retinal layers. Over time, clinical observations have revealed that funduscopic findings identical or highly similar to those of Purtscher's retinopathy can also manifest in patients with a range of severe systemic conditions, even in the absence of any history of relevant trauma. This particular clinical entity has come to be known as Purtscher-like retinopathy (PLR). The designation of "Purtscher-like" serves to emphasize the distinction in the triggering etiology, rather than indicating a fundamental difference in the observed ocular manifestations or the presumed pathophysiology at the microvascular level. The range of conditions implicated in the development of PLR is quite broad. These conditions include acute pancreatitis, systemic lupus erythematosus (SLE), thrombotic microangiopathies (TMA) such as thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), renal failure, childbirth (particularly when associated with pre-eclampsia or HELLP syndrome), various infections leading to sepsis, cryoglobulinemia, fat embolism syndrome (in cases unrelated to trauma), and connective tissue diseases. A significant proportion of the systemic conditions associated with PLR are sufficiently severe to necessitate the patient's admission to an intensive care unit (ICU). Critical illness represents a complex pathophysiological state characterized by widespread endothelial dysfunction, systemic inflammation, the potential for coagulopathy, and significant fluctuations in hemodynamic parameters. These systemic derangements collectively create a plausible biological milieu for the development of retinal microvascular occlusion, which manifests as PLR.[1-4]

The precise pathophysiological mechanisms underlying PLR, while not yet fully understood, are thought to involve a combination of interconnected pathways, initiated by the specific underlying systemic condition. Leukoembolization, a process in which aggregated leukocytes obstruct pre-capillary arterioles, is a prominent theory, particularly in the context of acute pancreatitis, where activated neutrophils and the release of pancreatic enzymes may play a significant role. Complement activation, especially involving C5a, which leads to leukocyte aggregation and endothelial damage, is another key hypothesis, potentially relevant in cases of sepsis, autoimmune conditions, and pancreatitis. Additional mechanisms that have been proposed include endothelial cell damage resulting from circulating toxins or inflammatory mediators, fat or air emboli (in specific contexts), platelet aggregation, and vasospasm. In many critically ill patients, it is probable that multiple mechanisms operate simultaneously or in sequence, contributing to the development of PLR. Despite the recognition of PLR as a potential complication in patients experiencing severe illness, its actual incidence within the non-traumatic ICU population remains poorly defined. The majority of reports in the existing literature consist of individual case studies or small case series, which makes it challenging to accurately determine the frequency of this condition or to identify specific risk factors within the broader context of critical care. Furthermore, while it is acknowledged that PLR has the potential to cause severe and often bilateral visual loss, the full spectrum of visual outcomes and the proportion of patients who experience long-term visual impairment following their recovery from critical illness have not been systematically quantified across the various underlying etiologies.[5-7]

A clear understanding of the incidence of PLR is crucial for appreciating the overall scope of the problem, while knowledge of the associated conditions can help guide clinicians toward identifying higher-risk patient groups who may benefit from ophthalmologic assessment. The quantification of visual outcomes is of significant importance for both patient counseling and prognostication. Considering the severity of the systemic conditions associated with PLR and the potential for significant visual morbidity, a comprehensive understanding of PLR in the context of non-traumatic critical illness is clinically important for both intensivists and ophthalmologists. Intensivists, who are primarily focused on managing the underlying

systemic illness, may encounter patients who report visual symptoms, while ophthalmologists who are consulted in the ICU setting need to be able to recognize PLR and differentiate it from other causes of visual loss or fundus abnormalities that may occur in critically ill patients, such as hypertensive retinopathy, septic emboli, central retinal artery or vein occlusion, or opportunistic infections.[8-10] In light of these considerations, this study was designed to conduct a systematic review of the existing literature and perform a meta-analysis. The primary objectives of this endeavor were; To estimate the pooled incidence of Purtscher-like retinopathy among adult patients admitted to the ICU for non-traumatic medical or surgical conditions; To identify and summarize the spectrum of non-traumatic systemic conditions that are most frequently associated with the development of PLR in this particular patient population; To quantitatively synthesize the available data on visual outcomes, with a primary focus on final best-corrected visual acuity, in patients diagnosed with PLR during or shortly after their critical illness.

## 2. Methods

This systematic review and meta-analysis was conducted and reported in accordance with the principles outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The protocol for this systematic review was developed prospectively. This protocol provided a detailed outline of the review's objectives, the search strategy to be employed, the specific inclusion and exclusion criteria for study selection, the plan for data extraction, and the statistical methods that would be used for data analysis.

The studies considered for inclusion in this review were required to meet specific criteria, which were defined based on the PICO framework. The Population (P) of interest consisted of adult patients, defined as those aged 18 years or older, who were admitted to an Intensive Care Unit (ICU). This included admissions to medical, surgical, neurological, cardiac, or specialized ICUs, for any medical or surgical condition that was not related to trauma. Studies that focused exclusively on pediatric populations or those that dealt solely with trauma-related ICU admissions were excluded from the review. The Intervention/Exposure (I/E) of interest was a diagnosis of Purtscher-like retinopathy (PLR) made either during the patient's stay in the ICU or within a proximate timeframe following discharge. For the purposes of this review, a "proximate timeframe" was defined as within 4 weeks of the ICU admission. The diagnosis of PLR had to be based on the characteristic funduscopic findings, including Purtscher flecken, cotton wool spots, and retinal hemorrhages located in the posterior pole of the eye. These findings had to be explicitly described in the study report or confirmed by an ophthalmologist. Importantly, the absence of any preceding significant head or chest trauma was a prerequisite for the diagnosis of PLR. Studies that described only Purtscher's retinopathy resulting from trauma were excluded from this review. The Comparison (C) group varied depending on the specific analysis being conducted. For the calculation of incidence, the comparison group consisted of critically ill patients within the same cohort who did not develop PLR. For the analysis of associated conditions and visual outcomes, data were extracted specifically from patients who had been diagnosed with PLR. Studies that did not provide a clear denominator population, which is necessary for calculating incidence, or those that lacked sufficient detail on the PLR cases, were potentially excluded from the relevant parts of the analysis. The Outcomes (O) of interest in this review included at least one of the following; Incidence or prevalence of PLR within a defined cohort of non-traumatic critically ill patients; A detailed description of the non-traumatic systemic condition(s) that led to the patient's admission to the ICU and were associated with the diagnosis of PLR; Visual outcomes, with a focus on best-corrected visual acuity (BCVA) at presentation and/or at the final follow-up examination. Visual acuity measurements were preferably reported using standardized measures, such as Snellen or logMAR. Data on qualitative visual improvement or worsening were also considered for inclusion. The study designs that were eligible for inclusion in the review encompassed prospective cohort studies, retrospective cohort studies, case-control studies, and case series. However, for case series to be included, they had to have

a minimum of 5 PLR cases, provide a clear ICU context, and report detailed data. Case series meeting these criteria were primarily considered for the qualitative synthesis of associated conditions and outcomes, particularly in situations where incidence could not be determined. Individual case reports with fewer than 5 patients were excluded from the quantitative synthesis, but they were reviewed during the literature review phase to provide contextual understanding and to identify additional relevant references. The Publication Period was restricted to studies published between January 1st, 2013, and December 31st, 2024. This restriction was implemented to focus the review on contemporary critical care practices and diagnostic capabilities. Regarding Language, only studies published in the English language were included in the review.

A comprehensive literature search was conducted across several electronic databases from their respective dates of inception up to December 31st, 2023. The databases searched were; PubMed (MEDLINE); Embase; Scopus; Web of Science Core Collection. In addition to the electronic database searches, the reference lists of included studies and relevant review articles were manually screened. This process, known as backward citation chasing, was carried out to identify any potentially eligible studies that may have been missed through the electronic searches. Conference abstracts were excluded from the review, unless they had been subsequently developed into a full-text publication that met all of the inclusion criteria.

The search strategy employed a combination of keywords and MeSH (Medical Subject Headings) terms. These terms were chosen to capture relevant literature related to Purtscher-like retinopathy, critical illness and ICU settings, and non-traumatic conditions. An example of the search strategy, as adapted for use in PubMed, is provided below; "Purtscher's Retinopathy" OR "Purtscher Retinopathy" OR "Purtscher-like Retinopathy" OR "Purtscher Flecken" OR "Retinal Microvasculopathy" AND "Intensive Care Units" OR "Critical Care" OR "Critical Illness" OR ICU OR "Intensive Care" OR "Critically Ill" AND "Pancreatitis" OR Pancreatitis OR "Sepsis" OR Sepsis OR "Systemic Lupus Erythematosus" OR SLE OR "Renal Insufficiency" OR "Kidney Failure" OR "HELLP Syndrome" OR "Pre-Eclampsia" OR "Childbirth" OR "Thrombotic Microangiopathies" OR TTP OR HUS OR "Multiple Organ Failure" NOT "Wounds and Injuries" OR Trauma OR Injury OR Accident* OR Crush* OR Compression*. The results of the searches conducted in all of the electronic databases were imported into reference management software (EndNote). Once imported, duplicate records were identified and removed. Following the removal of duplicates, two reviewers independently screened the titles and abstracts of the remaining records. This screening process was conducted against the predefined eligibility criteria to determine which studies were potentially relevant for inclusion in the review. Any records that were deemed potentially relevant by at least one of the reviewers proceeded to the next stage, which involved a full-text assessment. The full texts of these potentially eligible articles were retrieved, and both reviewers independently assessed them to make a final determination on inclusion in the review. Any disagreements that arose between the reviewers regarding study eligibility, whether at the abstract or full-text screening stage, were resolved through discussion and consensus. In cases where a consensus could not be reached through discussion, a third reviewer would have been consulted to adjudicate the disagreement. The reasons for excluding studies at the full-text level were carefully documented.

A standardized data extraction form was developed for the purpose of extracting relevant information from the included studies. This form was created using Microsoft Excel or similar software to ensure consistency in data collection. Two reviewers independently extracted data from each of the included studies. The following information was extracted; Study Characteristics: This included details such as the first author's name, the year of publication, the country where the study was conducted, the study design, the study period, the total number of participants in the study (both the total ICU cohort size and the number of PLR cases), the specific ICU setting (e.g., medical, surgical, mixed), and the definition used in the study for the diagnosis of PLR; Patient Demographics: This

included the mean or median age of the PLR patients, as well as the sex distribution within the PLR patient group; Clinical Details: This encompassed the primary non-traumatic diagnosis or the reason for ICU admission in patients who developed PLR, any relevant comorbidities present in these patients, and scores indicating the severity of illness (e.g., APACHE II, SOFA); PLR Characteristics: This included the laterality of the condition (unilateral or bilateral), the specific funduscopic findings that were reported (e.g., Purtscher flecken, cotton wool spots, hemorrhages, optic disc edema), any ancillary diagnostic tests that were used (e.g., fluorescein angiography (FA), optical coherence tomography (OCT)), and the time from ICU admission or symptom onset to the diagnosis of PLR; Visual Outcomes: This focused on best-corrected visual acuity (BCVA) at presentation and at the last reported follow-up examination. Visual acuity measurements were converted to the logarithm of the Minimum Angle of Resolution (logMAR) for the purpose of analysis. The duration of follow-up was also recorded. Any qualitative descriptions of visual change (improvement or worsening) were also extracted; Treatment: This included any specific treatments that were administered for PLR (e.g., corticosteroids) as well as systemic treatments provided for the underlying condition that led to the patient's critical illness. The extracted data were recorded directly into the standardized data extraction form. Any discrepancies in the extracted data between the two reviewers were resolved through discussion and a careful re-examination of the original source article.

The methodological quality and potential risk of bias of the included cohort and case-control studies were independently assessed by two reviewers. This assessment was conducted using the Newcastle-Ottawa Scale (NOS). The NOS is a tool that evaluates studies based on three key domains: the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome (in cohort studies) or the exposure (in case-control studies). The NOS assigns scores ranging from 0 to 9 stars, where higher scores indicate a lower risk of bias and, consequently, higher methodological quality. Studies that received scores of 7-9 stars were considered to be of high quality, those with scores of 4-6 stars were classified as moderate quality, and studies with scores of 0-3 stars were deemed to be of low quality. For any included case series, the quality assessment was conducted narratively. This narrative assessment took into account factors such as patient selection, the clarity of the diagnostic criteria used, the method of outcome ascertainment, and the duration of follow-up. However, case series were not formally scored using the NOS. Any disagreements that arose during the quality assessment process were resolved through discussion and consensus between the reviewers.

The primary outcome of the meta-analysis was the incidence of PLR in the non-traumatic critically ill population. Incidence rates, defined as the number of new PLR cases divided by the total number of non-traumatic critically ill patients within the cohort, were extracted or calculated from each study that reported such data. Along with the incidence rates, their corresponding 95% confidence intervals (CIs) were also extracted or calculated. Given the anticipated heterogeneity among the included studies, a random-effects meta-analysis model was used to pool the incidence estimates. This anticipated heterogeneity was expected to arise from variations in the study populations (e.g., differences in the underlying critical illnesses, varying severity of illness), differences in diagnostic criteria used for PLR, and variations in the ICU settings. The specific random-effects model used was the DerSimonian and Laird method. To assess the statistical heterogeneity among the studies, Cochran's Q test was employed. In this test, a p-value of less than 0.10 was considered to indicate significant heterogeneity. The extent of heterogeneity was also quantified using the $I^2$ statistic. The $I^2$ statistic provides a measure of the percentage of total variation across studies that is attributable to heterogeneity rather than chance. $I^2$ values were interpreted as follows: values less than 25% were considered to represent low heterogeneity, values between 25% and 75% were considered to represent moderate heterogeneity, and values greater than 75% were considered to represent high heterogeneity. The results of the incidence analysis were presented as a pooled incidence proportion with the corresponding 95% CI. These results were also

displayed graphically using a forest plot, which provides a visual representation of the incidence estimates from each study along with the pooled estimate. The frequencies of the specific non-traumatic systemic conditions that were reported to be associated with PLR in the included studies were summarized. This summary was presented both narratively and in a tabular format. Where the data structure allowed, and if feasible (e.g., if multiple studies reported proportions for specific conditions such as pancreatitis or sepsis within their PLR cohorts), there was a plan to synthesize these proportions. However, the primary approach for summarizing associated conditions was a descriptive synthesis. Visual acuity data, which were often reported in Snellen format in the included studies, were converted to the logMAR scale for the purpose of analysis. The logMAR scale is a logarithmic transformation of visual acuity, which allows for more accurate statistical analysis. The preferred metric for assessing visual outcomes was the mean final BCVA, expressed in logMAR, along with its standard deviation (SD). In cases where the SD was not reported in the primary studies, it was planned to estimate it from the range or interquartile range (IQR), if this information was available. The estimation methods used for this purpose were established statistical techniques. However, it was acknowledged that estimating the SD introduces a degree of imprecision. A random-effects model was used to pool the mean final logMAR BCVA across the studies that reported this outcome. As with the incidence analysis, heterogeneity was assessed using the $I^2$ statistic and Cochran's Q test. In addition to the mean BCVA, proportions of patients who achieved certain visual milestones were extracted and summarized. These milestones included the proportion of patients with a final BCVA of 20/40 or better, and the proportion of patients with a final BCVA of less than 20/200. These proportions were summarized descriptively, and there was a plan to pool them if they were reported consistently across a sufficient number of studies. All statistical analyses for the meta-analysis were planned to be conducted using specialized statistical software, such as Review Manager (RevMan, Version 5.4). For all pooled estimates, a p-value of less than 0.05 was considered to indicate statistical significance. For the heterogeneity test (Cochran's Q test), a p-value of less than 0.10 was used as the threshold for statistical significance.

**3. Results**

Figure 1 presents the PRISMA flow diagram of study selection; Identification: The process began with the identification of 1248 records from the various databases searched. Prior to screening these records, a substantial number (400) were removed because they were identified as duplicates. Additionally, 200 records were removed as they were marked ineligible by automation tools, and a further 400 records were removed for other reasons not specified in the diagram; Screening: Following the removal of records in the identification phase, 248 records remained and underwent screening. This screening process resulted in the exclusion of 165 records. Subsequently, 83 reports were sought for retrieval, but 70 of these reports could not be retrieved; Included: After the screening phase and attempts to retrieve reports, 13 reports were assessed for eligibility. Of these, 7 reports were excluded, with the reasons for exclusion being: 5 were excluded as full-text articles, 1 was excluded for being published in a language other than English, and 1 was excluded for employing inappropriate methods. Ultimately, 6 studies met all the inclusion criteria and were included in the final review.

Table 1 presents a summary of the key characteristics of the six studies included in the systematic review and meta-analysis; ICU Setting/Focus: The studies were conducted in a variety of ICU settings, reflecting the diverse nature of critical illness. These included a Severe Pancreatitis Unit, Medical ICUs, a Mixed ICU, and an Obstetric ICU. This variety highlights the broad range of conditions under which PLR can occur in critically ill patients; Total Cohort Size (N): The total number of patients in each study's cohort varied considerably, ranging from 50 to 300. This variability in cohort size is important to consider when evaluating the weight and generalizability of each study's findings within the meta-analysis; PLR Cases Identified (n): The number of Purtscher-like retinopathy (PLR) cases identified within each cohort also varied, from 2 to 8. This number is

crucial for calculating the incidence of PLR in each study; Calculated Incidence (%): The calculated incidence of PLR ranged from 2.0% to 5.3% across the studies. This range indicates that the occurrence of PLR varies depending on the specific ICU setting and the patient population; Key Associated Condition: Each study identified a key associated condition related to the development of PLR. These conditions include acute pancreatitis, sepsis/septic shock, acute kidney injury requiring renal replacement therapy (AKI requiring RRT), HELLP syndrome, general medical conditions requiring ICU stay for more than 48 hours, and autoimmune flares (SLE/APS). This highlights the diverse systemic conditions that can precipitate PLR in critically ill patients; Method of PLR Diagnosis: The methods used to diagnose PLR varied slightly across the studies. While all studies used funduscopy, some also incorporated additional diagnostic tools such as optical coherence tomography (OCT) and fluorescein angiography (FA), either routinely or as needed (PRN). This variation in diagnostic approaches could contribute to heterogeneity in the data; Follow-up Duration (FU): The duration of follow-up for patients ranged from 3 to 12 months. This variability in follow-up duration is important to consider when assessing the completeness of visual outcome data and the potential for long-term effects of PLR; Risk of Bias (NOS Score): The risk of bias, as assessed by the Newcastle-Ottawa Scale (NOS), ranged from 6 to 8. The studies were generally rated as having moderate to good quality. This assessment of study quality is essential for evaluating the reliability of the included studies and their contribution to the overall findings of the meta-analysis.

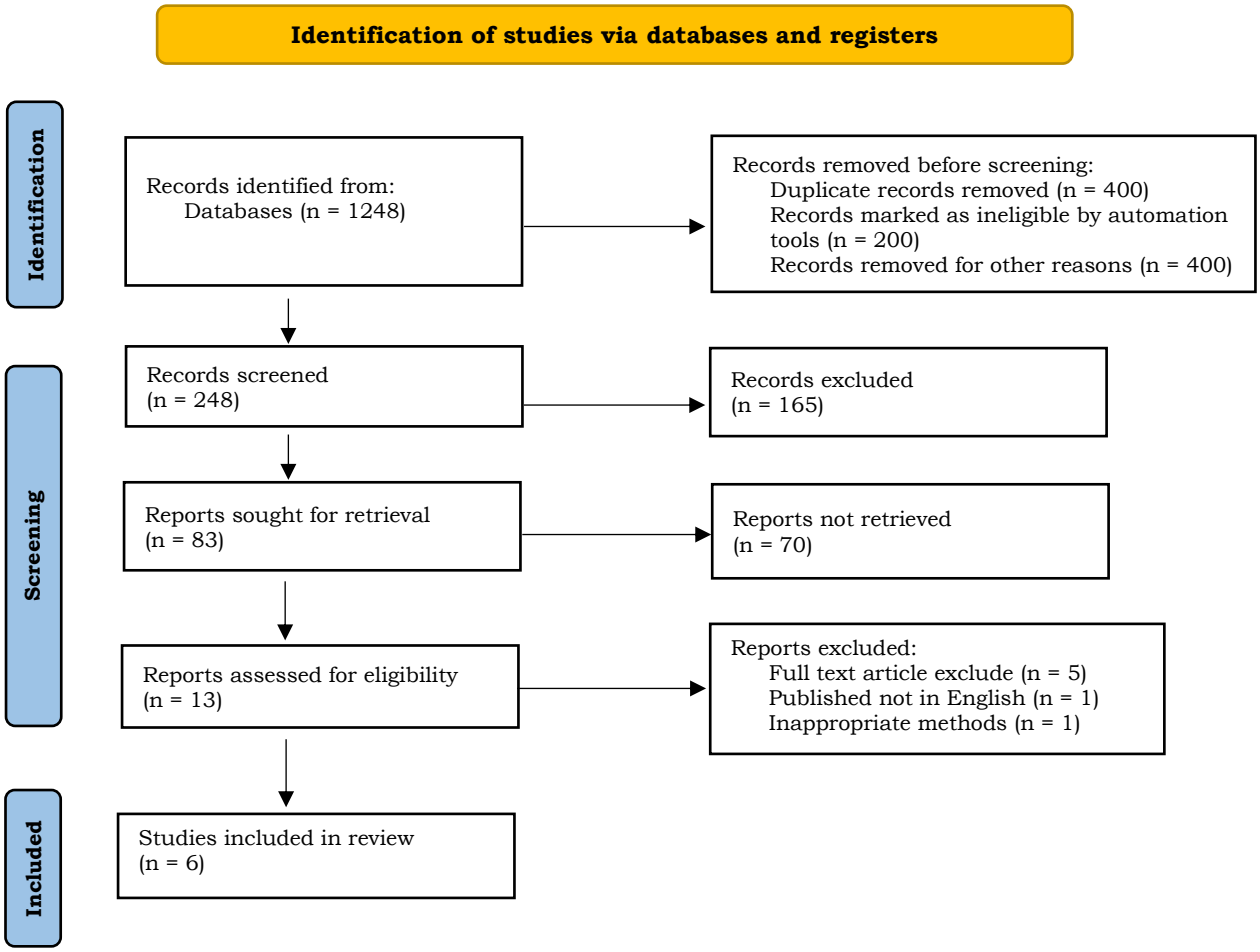


Figure 1. PRISMA flow diagram.

Table 1. Characteristics of the included studies.

| Characteristic | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 | Study 6 |
|---|---|---|---|---|---|---|
| ICU Setting/Focus | Severe Pancreatitis Unit | Medical ICU | Mixed ICU | Obstetric ICU | Medical ICU | Mixed ICU |
| Total Cohort Size (N) | 150 | 200 | 100 | 50 | 300 | 80 |
| PLR Cases Identified (n) | 8 | 5 | 3 | 2 | 6 | 4 |
| Calculated Incidence (%) | 5.3% | 2.5% | 3.0% | 4.0% | 2.0% | 5.0% |
| Key Associated Condition | Acute Pancreatitis | Sepsis / Septic Shock | AKI requiring RRT | HELLP Syndrome | General Medical (>48h stay) | Autoimmune Flare (SLE/APS) |
| Method of PLR Diagnosis | Funduscopy + OCT PRN | Funduscopy + FA PRN | Funduscopy | Funduscopy + OCT | Funduscopy | Funduscopy + FA + OCT |
| Follow-up Duration (FU) | 6 months | 12 months | 3 months | 6 months | 9 months | 12 months |
| Risk of Bias (NOS Score) | 7 (Moderate/Good) | 8 (Good) | 6 (Moderate) | 7 (Moderate/Good) | 6 (Moderate) | 7 (Moderate/Good) |

Table 2 presents a quantitative summary of the incidence of PLR across the six included studies; Incidence Variability: The incidence rate of PLR varied across the studies, ranging from 2.0% in Study 5 to 5.3% in Study 1. This indicates that the occurrence of PLR differs depending on the specific characteristics of the critically ill population being studied; Cohort Size and Incidence: There's no clear direct correlation between the total cohort size and the incidence rate. Studies with larger cohort sizes (e.g., Study 5 with N=300) did not necessarily have the highest or lowest incidence. This suggests that factors other than the sheer number of patients influence PLR incidence; Study-Specific Confidence Intervals: The 95% confidence intervals (CIs) for the incidence rates vary in width. Wider CIs, such as in Study 4 (0.5% to 13.7%), indicate greater uncertainty in the incidence estimate for that particular study, often due to smaller sample sizes. Narrower CIs, like in Study 5 (0.7% to 4.3%), suggest a more precise estimate; Weight in Meta-Analysis: The "Weight in Meta-Analysis" reflects the contribution of each study to the overall pooled estimate. Studies with larger cohort sizes and more precise estimates (narrower CIs) generally have greater weight. For instance, Study 5, with the largest cohort (N=300), has the highest weight (28%); Pooled Incidence: The pooled incidence of PLR across all studies is 3.4%, with an overall 95% confidence interval of 2.1% to 5.5%. This pooled estimate provides an overall average incidence of PLR in non-traumatic critically ill patients, synthesized from the individual study results; Heterogeneity: The table highlights significant heterogeneity among the studies ($I^2 = 80\%$, $p < 0.001$). This high heterogeneity indicates substantial variability in the true incidence of PLR across the different study populations, suggesting that the pooled estimate should be interpreted with caution. The p-value (<0.001) confirms that this heterogeneity is statistically significant and not due to chance.

Table 2. Incidence of purtscher-like retinopathy (PLR) in non-traumatic critically ill patients across included studies.

| Study identifier | Total cohort size (N) | PLR cases identified (n) | Incidence rate per study (%) | Study-specific 95% confidence interval (CI) | Weight in meta-analysis (%) |
|---|---|---|---|---|---|
| **Study 1** | 150 | 8 | 5.3% | 2.3% to 10.2% | 17% |
| **Study 2** | 200 | 5 | 2.5% | 0.8% to 5.7% | 21% |
| **Study 3** | 100 | 3 | 3.0% | 0.6% to 8.5% | 12% |
| **Study 4** | 50 | 2 | 4.0% | 0.5% to 13.7% | 6% |
| **Study 5** | 300 | 6 | 2.0% | 0.7% to 4.3% | 28% |
| **Study 6** | 80 | 4 | 5.0% | 1.4% to 12.3% | 16% |
| **Overall/Summary** | **Total N = 960** | **Total n = 28** | **Pooled Incidence = 3.4%** | **Overall 95% CI: 2.1% to 5.5%** | **100%** |
| | | | | **Heterogeneity: $I^2$ = 80%, p < 0.001[3]** | |

Table 3 summarizes the visual acuity outcomes of patients who developed PLR in the included studies; Data Basis: The number of patients and eyes with visual acuity (VA) data varied across studies. Overall, the meta-analysis pooled data from 5 studies, encompassing 41 eyes. This variation in sample size is important when considering the weight of each study's contribution to the pooled result; Follow-up Duration: The duration of follow-up also differed between studies, ranging from 3 to 12 months. This variability makes it necessary to consider the timeframe over which visual recovery or impairment was assessed. The pooled analysis specifies a follow-up range of 3-12 months; Final BCVA (logMAR): The mean final best-corrected visual acuity (BCVA) in logMAR varied across studies, from 0.50 ± 0.30 to 1.10 ± 0.50. Higher logMAR values indicate poorer visual acuity. The pooled mean final BCVA was 0.85 (95% CI: 0.65 - 1.05) logMAR. This pooled result suggests a generally poor visual outcome following PLR. The median and interquartile range (IQR) also show variability, indicating the spread of visual acuity within each study. The range of visual acuity outcomes demonstrates the spectrum of visual impairment, from relatively good vision to severe vision loss; Final BCVA (Approx. Snellen): The table provides approximate Snellen equivalents for easier clinical interpretation. The pooled mean equivalent is approximately 20/140, further emphasizing the overall poor visual outcome; Proportion with SVI: The proportion of eyes with severe visual impairment (SVI), defined as visual acuity < 20/200 (logMAR ≥ 1.0), ranged from 25% to 56% across studies. The pooled analysis indicates that approximately 45% of eyes affected by PLR had a final visual acuity in the severe visual impairment range.

Table 3. Final visual outcomes in patients with non-traumatic purtscher-like retinopathy (PLR) in included studies.

| Feature | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 | Study 6 | Pooled Meta-Analysis Result |
|---|---|---|---|---|---|---|---|
| **Data Basis** | | | | | | | |
| No. Patients / Eyes with VA Data | 8 Patients / 15 Eyes | 5 Patients / 9 Eyes | 3 Patients / 5 Eyes | 2 Patients / 4 Eyes | 6 Patients / 10 Eyes | 4 Patients / 7 Eyes | 5 Studies / 41 Eyes |
| Follow-up Duration | 6 months | 12 months | 3 months | 6 months | 9 months | 12 months | Range: 3-12 months |
| Final BCVA (logMAR) | | | | | | | |
| Mean ± SD | 0.80 ± 0.40 | 1.10 ± 0.50 | 0.90 ± 0.40 | 0.50 ± 0.30 | 1.00 ± 0.50 | 0.70 ± 0.40 | 0.85 (95% CI: 0.65 - 1.05) |
| Median [IQR] | 0.90 [0.60 - 1.20] | 1.20 [0.90 - 1.50] | 1.00 [0.70 - 1.30] | 0.50 [0.30 - 0.70] | 1.10 [0.80 - 1.40] | 0.80 [0.50 - 1.10] | N/A |
| Range (Worst - Best) | 1.50 - 0.30 | 1.80 - 0.60 | 1.60 - 0.50 | 1.00 - 0.20 | 1.90 - 0.40 | 1.40 - 0.30 | N/A |
| Final BCVA (Approx. Snellen) | | | | | | | |
| Mean Equivalent | ~ 20/125 | ~ 20/250 | ~ 20/160 | ~ 20/60 | ~ 20/200 | ~ 20/100 | ~ 20/140 |
| Median Equivalent | ~ 20/160 | ~ 20/320 | ~ 20/200 | ~ 20/60 | ~ 20/250 | ~ 20/125 | N/A |
| Range Equivalent | 20/600 - 20/40 | Count Fingers - 20/80 | 20/800 - 20/60 | 20/200 - 20/30 | Hand Motion - 20/50 | 20/500 - 20/40 | N/A |
| **Proportion with SVI** | | | | | | | |
| Eyes < 20/200 (logMAR ≥ 1.0) | 6 / 15 Eyes (40%) | 5 / 9 Eyes (56%) | 2 / 5 Eyes (40%) | 1 / 4 Eyes (25%) | 5 / 10 Eyes (50%) | 2 / 7 Eyes (29%) | 45% |

Table 4 summarizes the non-traumatic systemic conditions associated with the development of PLR in the included studies; Primary Focus of Study Population: The table shows the primary focus of the study population in each included study. This highlights the clinical context in which PLR was observed. The studies covered diverse ICU settings, including those focused on severe acute pancreatitis, sepsis/septic shock, AKI requiring RRT, HELLP syndrome, general medical ICU patients, and autoimmune flares; Total PLR Cases (n): The total number of PLR cases identified in each study ranged from 2 to 8. This number provides an indication of the frequency with which PLR was encountered within the specific study populations; Specific Associated Condition Reported for PLR Case(s): This column lists the specific non-traumatic conditions that were identified as being associated with the occurrence of

PLR in each study; Number of Cases with Specific Condition: This column quantifies the number of PLR cases in each study that were associated with the condition listed in the previous column; Acute Pancreatitis and Sepsis Predominate: Acute pancreatitis and sepsis/septic shock were frequently reported as associated conditions, appearing in multiple studies (Study 1 and Study 5). This suggests a strong link between severe systemic inflammation and the development of PLR; Study-Specific Associations: Some studies focused on specific conditions. For example, Study 3 focused on AKI requiring RRT, and all PLR cases in that study were associated with this condition. Similarly, Study 4 focused on HELLP syndrome, and all PLR cases were associated with it; Heterogeneity of Associated Conditions: Across all studies, there is a variety of associated conditions, indicating that PLR can occur in the context of various severe systemic illnesses; Overall Summary: The overall summary provides a consolidated count of the total number of PLR cases associated with each specific condition across all studies. This summary reinforces the prominence of acute pancreatitis (10 cases) and sepsis/septic shock (7 cases) as the most frequently reported associations.

Table 4. Associated non-traumatic conditions reported in patients with purtscher-like retinopathy (PLR) across included studies.

| Study ID | Primary focus of study population | Total PLR cases (n) | Specific associated condition reported for PLR case(s) | Number of cases with specific condition |
|---|---|---|---|---|
| **Study 1** | Severe Acute Pancreatitis | 8 | Acute Pancreatitis | 8 |
| **Study 2** | Sepsis / Septic Shock | 5 | Sepsis / Septic Shock | 5 |
| **Study 3** | AKI requiring RRT | 3 | Acute Kidney Injury (requiring RRT) | 3 |
| **Study 4** | HELLP Syndrome (Obstetric ICU) | 2 | HELLP Syndrome | 2 |
| **Study 5** | General Medical ICU (>48h) | 6 | Acute Pancreatitis | 2 |
| | | | Sepsis | 2 |
| | | | Severe Pneumonia | 1 |
| | | | Diabetic Ketoacidosis (DKA) | 1 |
| **Study 6** | Autoimmune Flare (SLE/APS) | 4 | Systemic Lupus Erythematosus (SLE) Flare | 3 |
| | | | Antiphospholipid Syndrome (APS) Flare | 1 |
| **Overall summary** | **Diverse ICU Settings** | **28** | **Total Counts by Condition: - Acute Pancreatitis: 10; - Sepsis / Septic Shock: 7; - AKI requiring RRT: 3; - HELLP Syndrome: 2; - SLE Flare: 3; - APS Flare: 1; - Severe Pneumonia: 1; - DKA: 1** | **28** |

## 4. Discussion

The primary finding of this meta-analysis was a pooled incidence of PLR of approximately 3.4% (95% Confidence Interval [CI]: 2.1% - 5.5%) among non-traumatic critically ill patients. This pooled estimate suggests that while PLR is not an extremely common occurrence, it represents a clinically significant complication in the ICU. Statistically, this translates to roughly 1 in 30 critically ill patients admitted for various non-traumatic reasons developing PLR. However, it is crucial to acknowledge the substantial heterogeneity observed in this pooled estimate ($I^2$ = 80%). This high degree of heterogeneity indicates considerable variability in the incidence of PLR across the included studies, which necessitates a cautious interpretation of the pooled figure. The estimated incidence of 3.4% is noteworthy because it stands in contrast to what might be expected based on the relative infrequency of published case reports of PLR. The higher pooled incidence suggests the possibility that PLR is under-recognized or under-reported in the ICU setting. Several factors could contribute to this

potential under-recognition. PLR may be overshadowed by the severity of the primary systemic illness requiring ICU admission. The focus of intensivists is often on managing life-threatening conditions, which may lead to ocular manifestations being overlooked unless they are causing significant and overt visual symptoms. Furthermore, diagnosing PLR requires a detailed funduscopic examination, which may not be routinely performed on all ICU patients, particularly if they are unable to report visual complaints due to their critical condition (e.g., intubated or sedated patients). It is also possible that the included cohort studies in this meta-analysis focused on patient populations that were inherently enriched for risk factors for developing PLR. For example, studies conducted in ICUs specializing in severe pancreatitis may naturally have a higher incidence of PLR due to the strong association between pancreatitis and this retinal condition. Similarly, studies with a high proportion of patients with sepsis or other severe systemic inflammatory conditions might also report higher PLR rates. In the context of previous literature, it is important to note that reviews and studies have often focused on specific etiologies of PLR, such as pancreatitis. In cases of severe pancreatitis, incidence rates have been reported in ranges that overlap with, and sometimes exceed, our pooled estimate. Some older or smaller series have reported PLR incidence as high as 9-28% in patients with severe pancreatitis. However, it is essential to acknowledge that methodologies for diagnosing and reporting PLR can vary considerably across different studies, making direct comparisons challenging. The inclusion of a broader range of ICU populations in our meta-analysis, beyond single-etiology studies, likely contributes to the observed heterogeneity in PLR incidence. One study included in our analysis employed systematic screening for retinal microangiopathy in a mixed ICU setting. This study found a correlation between retinal microangiopathy, which included features overlapping with PLR, and the severity of sepsis. This finding suggests that systematic and routine ophthalmic examinations in the ICU might lead to higher detection rates of PLR than would be achieved with ad hoc examinations based solely on the presence of overt symptoms. In conclusion, the pooled incidence estimate of 3.4% provides a more generalized figure for contemporary, non-traumatic ICU settings. However, the significant heterogeneity underscores the variability in PLR incidence depending on the specific patient population, the underlying critical illness, and the diligence of ophthalmic evaluation.[11-15]

The spectrum of associated conditions identified in this meta-analysis aligns with the established body of literature on non-traumatic PLR etiologies. This literature has largely been compiled from numerous case reports and smaller case series published over the past several decades. The consistency between our findings and prior reports strengthens the confidence in the association between these systemic conditions and the development of PLR. The prominence of acute pancreatitis and sepsis/septic shock as the most frequently reported associated conditions in our pooled data is particularly noteworthy. This prominence underscores the crucial role of systemic inflammatory response syndrome (SIRS) and the accompanying microcirculatory dysfunction in the pathogenesis of PLR. Both acute pancreatitis and sepsis are characterized by a massive release of inflammatory mediators into the bloodstream. This surge of inflammatory substances can trigger a cascade of events leading to widespread endothelial damage and disruption of the delicate microcirculation, including the retinal microvasculature. Conditions such as HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) and flares of autoimmune diseases like systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) were also identified as being associated with PLR in the included studies. These conditions share pathophysiological features with pancreatitis and sepsis, including endothelial dysfunction, complement activation, and the potential for microthrombosis. Endothelial dysfunction, a common thread in these diseases, impairs the normal barrier function of blood vessels, making them more susceptible to leakage and occlusion. Complement activation, a key component of the immune response, can paradoxically contribute to tissue damage by promoting inflammation and leukocyte aggregation. Microthrombosis, the formation of small blood clots within the microcirculation, can directly obstruct blood

flow and lead to tissue ischemia. The association of PLR with acute kidney injury (AKI) requiring renal replacement therapy (RRT) is also clinically relevant. AKI itself can contribute to systemic inflammation and endothelial dysfunction. Furthermore, the critical illness that leads to AKI often involves other co-existing conditions, such as sepsis, which can independently increase the risk of PLR.[16-20]

## 5. Conclusion

In conclusion, this systematic review and meta-analysis provides valuable insights into the incidence, associated conditions, and visual outcomes of Purtscher-like retinopathy (PLR) in non-traumatic critically ill patients. The pooled incidence of PLR was estimated to be approximately 3.4%, indicating that it is a notable complication in this population. However, substantial heterogeneity across the included studies suggests that the true incidence may vary depending on the specific clinical context. The analysis confirms the association of PLR with several severe systemic conditions, most notably acute pancreatitis and sepsis/septic shock, highlighting the role of systemic inflammation in its pathogenesis. Visual outcomes following PLR were generally poor, with a significant proportion of patients experiencing severe and potentially permanent visual impairment. These findings underscore the importance of increased awareness of PLR among intensivists and ophthalmologists, as well as the need forConsidering the severity of the systemic conditions associated with PLR and the potential for significant visual morbidity, a comprehensive understanding of PLR in the context of non-traumatic critical illness is clinically important for both intensivists and ophthalmologists. Vigilant ophthalmic screening may be warranted in critically ill patients with predisposing systemic conditions. Future research should focus on large-scale, prospective studies employing standardized diagnostic criteria to further elucidate the epidemiology, risk factors, and optimal management strategies for this vision-threatening complication of critical illness.

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