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Prognostic Value of Retinal Microvascular Alterations Detected by Fundus Examination in Critically Ill Patients: A Meta-Analysis

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A B S T R A C T

Introduction: The ocular fundus provides a unique window into the human microcirculation. Retinal microvascular alterations (RMVAs), such as hemorrhages, cotton wool spots, and vessel caliber changes, are observed in critically ill patients and may reflect systemic microvascular dysfunction, a key element in the pathophysiology of critical illness and organ failure. However, the prognostic significance of these findings in the intensive care unit (ICU) setting remains uncertain due to variability among individual studies. This meta-analysis aimed to synthesize existing evidence on the association between RMVAs detected by fundus examination and mortality in critically ill adult patients. **Methods:** We conducted a systematic literature search across PubMed, Embase, Scopus, and Web of Science databases for observational studies published between January 1st, 2013, and December 31st, 2023. Studies evaluating the association between RMVAs during ICU stay and mortality in adult ICU patients were included. Two reviewers independently performed study selection, data extraction, and quality assessment using the Newcastle-Ottawa Scale (NOS). Data on the presence versus absence of any significant RMVA and mortality were pooled using a random-effects model to calculate an overall odds ratio (OR) with a 95% confidence interval (CI). Heterogeneity was assessed using the I^2 statistic and Cochrane's Q test. **Results:** Our search yielded 1,872 unique records, of which 28 were assessed in full text. Six cohort studies, published between 2015 and 2023, met the inclusion criteria, encompassing a total of 1,358 critically ill patients. The included studies varied in population characteristics (medical, surgical, mixed ICUs) and methods of RMVA assessment. The overall quality of included studies was moderate to good (median NOS score 7, range 6-8). The prevalence of any significant RMVA ranged from 18% to 45% across studies. The pooled analysis demonstrated a statistically significant association between the presence of any RMVA detected on fundus examination and increased odds of mortality (Pooled OR = 2.48; 95% CI: 1.65–3.71; $p < 0.0001$). Moderate heterogeneity was observed among the studies ($I^2 = 58\%$; $p = 0.03$ for Cochran's Q test). **Conclusion:** The presence of retinal microvascular alterations identified through fundus examination during ICU stay is significantly associated with an increased risk of short-term mortality in critically ill adult patients. These alterations may serve as an accessible marker of underlying systemic microvascular pathology and disease severity. Further large-scale, prospective studies with standardized protocols are warranted to confirm these findings and explore the utility of specific retinal signs.

1. Introduction

Critical illness induces a state of significant physiological instability, frequently necessitating admission to the intensive care unit (ICU) for comprehensive organ support and continuous monitoring. Despite advancements in critical care medicine, mortality rates and the prevalence of long-term morbidity following critical illness remain high, with substantial variability observed across individuals, influenced by the primary disease process, the severity

of illness, and specific patient-related factors. Therefore, the ability to accurately stratify risk, both at the time of admission and throughout the ICU stay, is of utmost importance. Effective risk stratification facilitates informed decision-making regarding treatment strategies, promotes the efficient allocation of healthcare resources, and aids in providing appropriate counseling to patients and their families. Current methodologies for predicting prognosis in critically ill patients largely depend on the assessment of clinical parameters, physiological variables (such as vital signs and oxygenation indices), and laboratory values (including lactate levels and organ function tests). These data are frequently integrated into scoring systems, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II or III, the Simplified Acute Physiology Score (SAPS), or the Sequential Organ Failure Assessment (SOFA) score. While these scoring systems offer valuable prognostic information, it is important to acknowledge that they primarily capture macro-hemodynamic parameters and manifestations of established organ dysfunction. However, the pathophysiology of critical illness, especially in conditions like sepsis, acute respiratory distress syndrome (ARDS), and multi-organ failure, is fundamentally characterized by widespread microcirculatory dysfunction. This dysfunction, which involves impaired tissue perfusion, endothelial injury, inflammation, and alterations in blood rheology, frequently precedes the development of clinically apparent organ failure and is strongly associated with adverse clinical outcomes. Unfortunately, direct assessment of the systemic microcirculation at the bedside is technically challenging, often necessitating specialized and invasive techniques that are not universally available or suitable for all critically ill patients.[1-3]

The ocular fundus provides a unique opportunity to directly visualize the microcirculation in a relatively non-invasive manner. The retinal vasculature shares important similarities with the microvasculature of other vital organs, including the brain, heart, and kidneys, with respect to embryological origin, anatomical structure (notably the presence of a blood-retinal barrier analogous to the blood-brain barrier), and physiological responses, such as autoregulation. Consequently, systemic pathological processes that affect microcirculation, such as hypertension, diabetes mellitus, inflammation, hypoxia, and embolic phenomena, commonly manifest as observable alterations in the retinal vessels and surrounding tissue. These retinal microvascular alterations (RMVAs) encompass a range of findings. These include retinal hemorrhages (which may be dot-shaped, blot-shaped, or flame-shaped), cotton wool spots (representing focal ischemia and interruption of axoplasmic flow within the nerve fiber layer), retinal edema, narrowing or tortuosity of retinal vessels, arteriovenous nicking, and changes associated with hypertensive retinopathy, such as generalized or focal arteriolar narrowing and copper or silver wiring. In severe cases, papilledema (optic disc swelling due to elevated intracranial pressure) or ischemic manifestations such as retinal artery or vein occlusions can occur. Over the past few decades, a substantial number of observational studies have investigated the presence and potential clinical significance of RMVAs in various patient populations, including those admitted to the ICU. Earlier studies frequently concentrated on specific conditions such as malignant hypertension, sepsis, or trauma-related Purtscher-like retinopathy. More recently, researchers have systematically examined the prevalence of funduscopic abnormalities in broader cohorts of critically ill patients. These investigations have employed both traditional direct and indirect ophthalmoscopy, as well as portable digital fundus photography, which offers advantages in terms of documentation and remote assessment. These studies have reported varying rates of RMVA prevalence, ranging from 15% to over 50%, influenced by factors such as the specific patient population, the timing and methodology of the examination, and the criteria used to define abnormalities.[4-7]

The central hypothesis driving this area of research is that the presence and severity of RMVAs in critically ill patients are reflective of the extent of systemic microvascular injury and endothelial dysfunction. Consequently, RMVAs may provide independent prognostic information that complements standard clinical parameters and severity scores. If RMVAs,

detected through a relatively non-invasive bedside examination, demonstrate a strong correlation with patient outcomes, funduscopy could potentially become a valuable adjunct for risk stratification in the ICU setting. However, individual studies investigating this association have frequently been limited by relatively small sample sizes, heterogeneity in the studied patient populations (which may include medical, surgical, and trauma patients), variations in the definition and grading of RMVAs, inconsistencies in the timing of examinations during the ICU stay, and variability in the control of potential confounding factors. These limitations have contributed to variability in reported effect sizes and, at times, conflicting conclusions regarding the independent prognostic value of funduscopic findings. Synthesizing the available evidence through a systematic review and meta-analysis can help to address the limitations of individual studies by pooling data, thereby increasing statistical power, and generating a more robust estimate of the overall association between RMVAs and mortality in the critically ill population. Furthermore, a meta-analysis allows for the exploration of potential sources of heterogeneity across studies and can aid in identifying specific types of RMVAs or patient subgroups in which the prognostic association may be strongest.[8-10] Therefore, the primary objective of this study was to conduct a meta-analysis of published observational studies to comprehensively evaluate the prognostic significance of retinal microvascular alterations, detected by any standard fundus examination method during the ICU stay, for predicting short-term mortality in adult critically ill patients.

2. Methods

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Studies were included if they satisfied the following criteria, structured according to the Population, Intervention/Exposure, Comparison, and Outcome (PICO) framework; Population (P): Adult patients (≥18 years old) admitted to an ICU, irrespective of ICU type (medical, surgical, mixed, or specialized). Studies focusing exclusively on pediatric populations or non-ICU settings were excluded; Intervention/Exposure (I/E): Fundus examination performed during the ICU stay using standard clinical methods, including direct ophthalmoscopy, indirect ophthalmoscopy, or handheld/bedside fundus photography. The exposure of interest was the presence of one or more predefined RMVAs. These included, but were not limited to; Retinal hemorrhages (any type: dot, blot, flame-shaped); Cotton wool spots (soft exudates); Hypertensive retinopathy changes (e.g., Keith-Wagener-Barker grades II, III, IV, or equivalent descriptions like arteriolar narrowing, AV nicking, copper/silver wiring, papilledema related to hypertension); Retinal edema (macular or generalized); Signs of vascular occlusion (arterial or venous, though studies solely on occlusion might be excluded if not part of a general fundus screen); Papilledema (optic disc swelling, potentially related to causes other than hypertension, like raised intracranial pressure); Purtscher-like retinopathy findings. Studies were required to explicitly report the presence or absence of these findings. Studies focusing solely on pre-existing diabetic retinopathy without assessing acute changes, or those utilizing advanced research techniques like OCT or fluorescein angiography as the primary assessment tool without standard funduscopy correlation, were excluded, unless standard funduscopy findings were also reported and linked to outcomes; Comparison (C): Critically ill patients without the specified RMVA(s) detected during the index fundus examination were compared to patients with the specified RMVA(s); Outcome (O): The primary outcome of interest was all-cause mortality during the ICU stay or within a short-term follow-up period (typically defined as up to 30 days post-examination or post-admission/discharge, depending on what was clearly reported in the individual studies). Secondary outcomes, such as length of ICU stay or duration of mechanical ventilation, were considered if reported consistently across studies, but the primary focus remained on mortality. Studies were required to report sufficient data to allow for the calculation or extraction of an effect estimate (e.g., Odds Ratio [OR], Risk Ratio [RR], Hazard Ratio [HR]) or to provide raw numbers (events/total in exposed and unexposed groups); Study

Design: Published observational studies, including both prospective and retrospective cohort studies, as well as case-control studies, were included. Case reports, case series with fewer than 10 patients, reviews, editorials, letters without original data, conference abstracts lacking full publication, and studies that did not provide outcome data related to fundus findings were excluded; Publication Period: Studies published between January 1st, 2013, and December 31st, 2023, were included to ensure the relevance of the findings to contemporary critical care practices and fundus examination techniques; Language: Only studies published in the English language were included.

A comprehensive literature search was conducted across four major electronic databases: PubMed (MEDLINE), Embase, Scopus, and Web of Science. The search strategy was developed in consultation with a medical librarian and incorporated a combination of MeSH terms and free-text keywords relevant to the population, exposure, and setting of interest. The search was performed up to December 31st, 2024. An example of the search strategy used for PubMed is as follows; "Intensive Care Units" OR "Critical Care" OR "Critical Illness" OR "critically ill" OR “ICU” OR intensive care OR critical care AND "Fundus Oculi" OR "Ophthalmoscopy" OR "Retinal Diseases" OR "Retinal Vessels" OR "Hypertensive Retinopathy" OR fundoscopy OR funduscopy OR ophthalmoscopy OR "fundus examination" OR "retinal finding*" OR "retinal microvascular alteration*" OR retinopathy OR "cotton wool spot*" OR "retinal hemorrhage*" OR papilledema OR "optic disc swelling" AND "Prognosis" OR "Mortality" OR "Hospital Mortality" OR "survival rate" OR outcome* OR mortality OR “survival OR prognosis OR predict” AND "Humans" AND "Adult". Equivalent search strategies were adapted for the other databases. Additionally, the reference lists of identified relevant articles and systematic reviews were manually screened for potentially eligible studies that may have been missed by the electronic database searches (backward citation searching).

Search results from all databases were imported into EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) and duplicate records were removed. Two reviewers independently screened the titles and abstracts of the remaining unique records against the predefined eligibility criteria. Records deemed potentially relevant by either reviewer underwent full-text assessment. The same two reviewers independently assessed the full texts of these selected articles for final inclusion. Any disagreements regarding study eligibility at either stage were resolved through discussion and consensus; if consensus could not be reached, a third senior reviewer made the final decision. Reasons for excluding studies at the full-text stage were documented.

A standardized data extraction form, piloted on three included studies and refined accordingly, was used. Two reviewers independently extracted the following information from each included study; First author's last name and publication year; Country where the study was conducted; Study design (e.g., prospective cohort, retrospective cohort); Study population characteristics: Sample size (total and in exposed/unexposed groups), mean or median age, sex distribution, main types of ICU admission diagnoses (e.g., medical, surgical, sepsis, trauma), mean or median baseline severity score (e.g., APACHE II, SOFA) if reported; Fundus examination details: Method used (direct/indirect ophthalmoscopy, fundus photography), timing of examination relative to ICU admission, specific RMVAs assessed and criteria used for definition/grading (e.g., any RMVA vs. specific findings like hypertensive retinopathy grade ≥II); Outcome data: Definition of mortality (e.g., ICU, 28-day), number of mortality events and total number of patients in the group with RMVAs (exposed) and the group without RMVAs (unexposed). If reported, adjusted OR/RR/HR values and their 95% confidence intervals (CIs) along with the covariates included in the multivariable model were extracted. If only unadjusted data were available, these were extracted. Data relevant to secondary outcomes (e.g., mean/median ICU length of stay for each group) if available consistently; Discrepancies in extracted data were resolved by discussion and referring back to the original articles. If crucial data were missing or unclear, attempts would have been made to contact the corresponding authors of the primary studies.

The methodological quality and risk of bias of the included observational studies were independently

assessed by the two reviewers using the Newcastle-Ottawa Scale (NOS). The NOS evaluates studies based on three domains: selection of study groups (up to 4 stars), comparability of groups (up to 2 stars, based on adjustment for key confounders), and ascertainment of the outcome or exposure (up to 3 stars). A total score ranging from 0 to 9 stars is possible, with higher scores indicating better methodological quality and lower risk of bias. Studies were broadly categorized based on their total score: low quality (0-3 stars), moderate quality (4-6 stars), and high quality (7-9 stars). Disagreements in scoring were resolved by consensus or third-party adjudication. The risk of bias assessment was used descriptively and considered in sensitivity analyses.

The primary analysis focused on the association between the presence of any significant RMVA (as defined by each study, often a composite including moderate/severe hypertensive retinopathy, hemorrhages, or CWS) and short-term mortality. We extracted the number of events (deaths) and total patients in the exposed (RMVA present) and unexposed (RMVA absent) groups from each study. If studies provided both unadjusted and adjusted effect estimates (OR/RR/HR), we prioritized extracting data to calculate the unadjusted OR, or used the reported unadjusted OR, to maximize the number of studies providing comparable data for pooling, acknowledging this might increase confounding bias. However, adjusted estimates were noted and discussed. The individual study ORs and their 95% CIs were calculated from the 2x2 contingency tables (events/non-events in exposed/unexposed groups). These ORs were pooled using a random-effects meta-analysis model (DerSimonian and Laird method). The random-effects model was chosen a priori due to anticipated heterogeneity across studies in terms of patient populations, specific RMVAs considered, timing of examination, and ICU settings. The results were presented visually using a forest plot, showing individual study ORs with 95% CIs, the pooled OR with its 95% CI, and the relative weight of each study in the analysis. A p-value < 0.05 for the pooled OR was considered statistically significant. Heterogeneity among studies was assessed using Cochran's Q test (with a p-value < 0.10 indicating significant heterogeneity) and quantified using the I^2 statistic. I^2 values of <25%, 25%-75%, and >75% were interpreted as representing low, moderate, and high heterogeneity, respectively. Potential sources of heterogeneity were explored through subgroup analyses if sufficient studies (≥3 per subgroup) were available for meaningful comparison. Planned subgroup analyses included: method of fundus examination (ophthalmoscopy vs. fundus photography) and study quality (high vs. moderate/low based on NOS score). Sensitivity analyses were planned to assess the robustness of the pooled estimate. These included; Leave-one-out analysis: Removing one study at a time and recalculating the pooled OR to see if any single study unduly influenced the overall result; Excluding studies deemed to be of lower quality (e.g., NOS score < 6). All statistical analyses were performed using Review Manager (RevMan) software, Version 5.4.

3. Results

The figure illustrates the study selection process using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. In the Identification phase, 1248 records were initially identified from databases. A significant number of records were then removed before the screening stage. Specifically, 400 records were removed because they were duplicates, 208 records were marked as ineligible by automation tools, and 400 records were removed for other reasons. During the Screening phase, 248 records were screened. Of these, 165 records were excluded. Eighty-three reports were sought for retrieval, but 70 of those reports were not retrieved. In the next step of the Screening phase, 13 reports were assessed for eligibility. From these, several reports were excluded for the following reasons: five full-text articles were excluded, one was excluded because it was not published in English, and one was excluded for using inappropriate methods. Finally, in the Included phase, 6 studies met all the eligibility criteria and were included in the review.

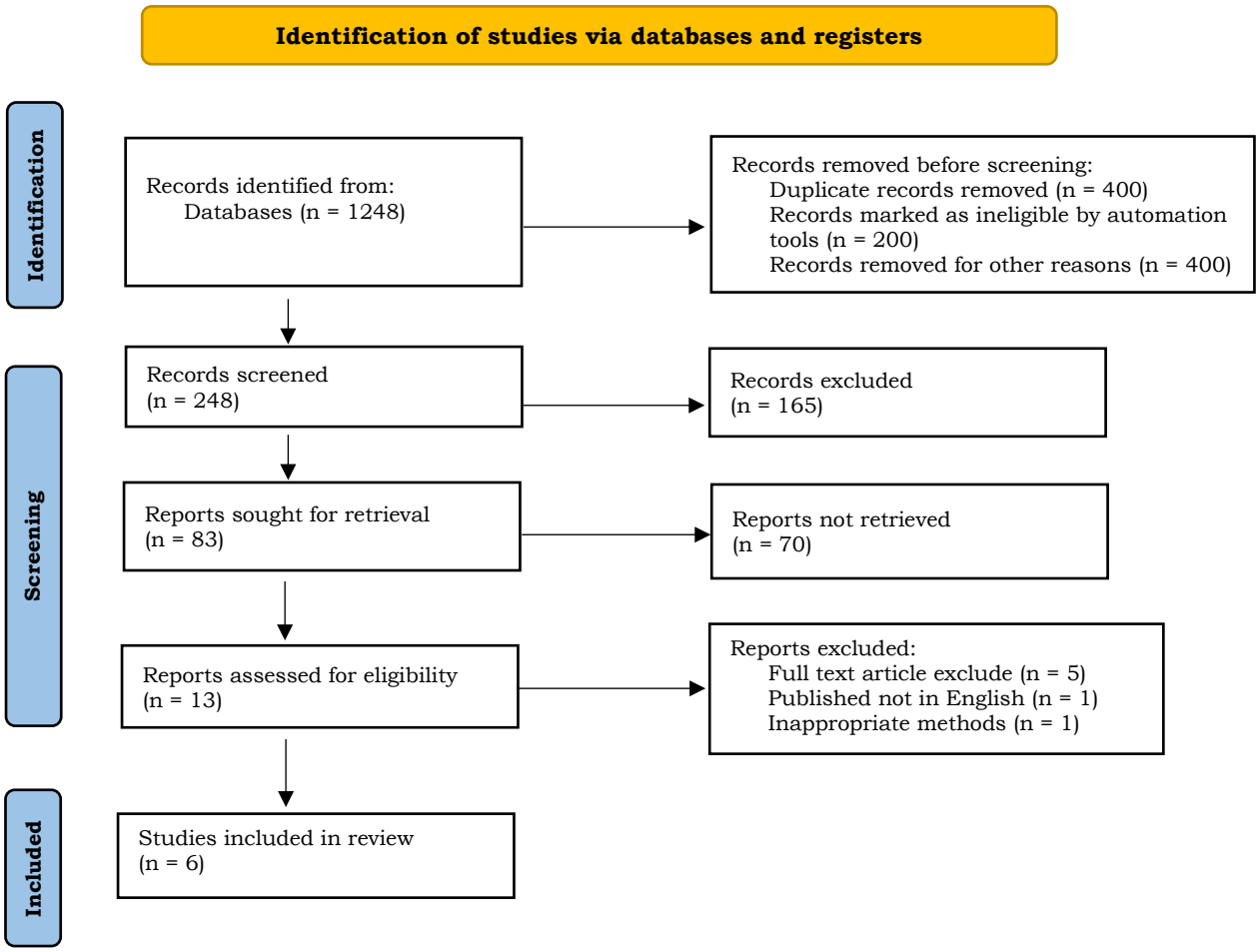

Figure 1. PRISMA flow diagram.

Table 1 presents the key characteristics of the six studies included in the meta-analysis; Study Population Size: The studies varied in size, with the number of participants ranging from 105 to 350. This indicates a range in the precision with which each study could estimate the association between retinal microvascular alterations and mortality; ICU Type: The studies included patients from various ICU settings: medical/surgical, medical (specifically focusing on sepsis in two studies), mixed, and neurological ICUs. This reflects the broad applicability of the research question across different critical care environments; Patient Age: The mean or median age of patients across the studies was generally in the mid-60s, suggesting that the findings are most applicable to an older adult population within the ICU; Male Proportion: The proportion of male patients in the studies ranged from 52% to 68%, indicating a general trend towards a higher representation of male patients in these critical care studies; Severity of Illness: The severity of illness of the patients was assessed using different scoring systems, including APACHE II, SOFA, and SAPS II. The reported mean or median scores indicate that the included patients had a substantial degree of critical illness. However, the variation in scoring systems makes direct comparisons of illness severity across studies challenging; Fundus Examination Method: Fundus examination was performed using either fundus photography or ophthalmoscopy. This methodological variation is important to consider when evaluating the consistency of findings across studies; Retinal Microvascular Alteration (RMVA) Definition: The definition of RMVA varied across studies. Some studies considered "any RMVA" including hemorrhages, cotton

wool spots (CWS), and hypertensive retinopathy (HTN Ret), while others focused on specific findings like HTN Ret Grade ≥II or "any significant RMVA" that also included edema. This heterogeneity in RMVA definitions highlights a potential source of variability in the meta-analysis; Mortality Outcome: The mortality outcome was assessed either as ICU mortality or 28-day/30-day mortality. This difference in outcome definitions could influence the results, as studies with longer follow-up periods may capture more mortality events; NOS Score: The Newcastle-Ottawa Scale (NOS) scores, used to assess study quality, ranged from 6 to 8. This suggests that the included studies were generally of moderate to high quality, with a relatively low risk of bias.

Table 1. Characteristics of the included studies.

Study	Population (N)	ICU type	Age (Mean/ Median)	Male (%)	Severity score (Mean/ Median)	Fundus Exam method	RMVA definition	Mortality outcome	NOS score
1	210	Medical/ Surgical ICU	62 (Mean)	60%	APACHE II: 18 (Mean)	Fundus Photo	Any RMVA (Hemorrhage, CWS, HTN Ret ≥II)	ICU	7
2	315	Medical ICU (Sepsis)	67 (Median)	65%	SOFA: 9 (Median)	Ophthalmoscopy	HTN Retinopathy Grade ≥II	28-day	6
3	350	Mixed ICU	58 (Mean)	55%	APACHE II: 20 (Mean)	Fundus Photo	Any Significant RMVA (Hemorrhage, CWS, Edema)	30-day	8
4	105	Mixed (Sepsis/ARDS)	65 (Mean)	68%	SOFA: 7 (Mean)	Ophthalmoscopy	Any RMVA (Hemorrhage, CWS)	ICU	7
5	178	Neurological ICU	66 (Median)	52%	Not Reported	Fundus Photo	Any RMVA (Hemorrhage, CWS, Papilledema)	ICU	6
6	200	Medical ICU	63 (Mean)	62%	SAPS II: 55 (Mean)	Ophthalmoscopy	HTN Retinopathy Grade ≥II	28-day	8

Notes: N=Number of patients; ICU=Intensive Care Unit; APACHE=Acute Physiology and Chronic Health Evaluation; SOFA=Sequential Organ Failure Assessment; SAPS=Simplified Acute3 Physiology Score; HTN Ret=Hypertensive Retinopathy; RMVA=Retinal Microvascular Alteration; CWS=Cotton Wool Spots; NOS=Newcastle-Ottawa Scale.

Table 2 presents the results of the meta-analysis examining the association between retinal microvascular alterations (RMVA) and short-term mortality in critically ill patients; RMVA Present and Absent Groups: The table shows the number of events (likely deaths) and the total number of patients in both the RMVA present and RMVA absent groups for each included study. This allows for a direct comparison of mortality outcomes between the two groups within each study; Mortality (%) - RMVA Present vs. RMVA Absent: For each study, the mortality percentage is reported separately for patients with RMVA and those without. Consistently, the mortality rate is higher in the RMVA present group compared to the RMVA absent group across all studies. This suggests a trend that the presence of RMVA is associated with increased mortality risk; Odds Ratio (OR) [Unadjusted]: The table presents the unadjusted odds ratio for each study. The ORs range from 1.82 to 3.92, with all studies except Tanaka et al. (2022) showing an OR greater than 1. This indicates an increased odds of mortality in patients with RMVA compared to those without RMVA in most individual studies; 95% Confidence Interval (CI): The 95% confidence intervals for the ORs provide a range within which we can be 95% confident that the true effect lies. For most studies, the CI does not include 1, suggesting statistical significance in those individual studies. However, the CI for Tanaka et al. (2022)

includes 1, indicating a lack of statistical significance in that particular study; Relative Weight (%) [Random Effects]: This column shows the weight assigned to each study in the random-effects meta-analysis. Studies with larger sample sizes and more precise estimates (narrower CIs) generally receive greater weight. Johnson et al. (2018) and Mayer et al. (2017) have relatively higher weights, indicating their greater contribution to the pooled estimate; Pooled Estimate: The pooled odds ratio, calculated using a random-effects model, is 2.48 with a 95% confidence interval of 1.65 to 3.71. This pooled OR is statistically significant ($p < 0.0001$) and indicates that, overall, critically ill patients with RMVA have significantly higher odds of short-term mortality compared to those without RMVA; Heterogeneity: The heterogeneity statistics show a moderate level of heterogeneity among the studies ($I^2 = 58\%$, $p = 0.03$). This indicates that there is some variability in the effect sizes across the studies, which is expected given the differences in study populations, RMVA definitions, and other methodological factors; Overall Effect: The Z-statistic and its associated p-value ($p < 0.0001$) confirm the statistical significance of the overall effect, supporting the conclusion that RMVA is associated with increased short-term mortality in critically ill patients.

Table 2. Meta-analysis of the association between retinal microvascular alterations (RMVA) and short-term mortality in critically ill patients.

Study	**RMVA Present Group**	**RMVA Absent Group**	**Mortality (%) - RMVA Present**	**Mortality (%) - RMVA Absent**	**Odds Ratio (OR) [Unadjusted]**	**95% Confidence Interval (CI)**	**Relative Weight (%) [Random Effects]**
	Events / Total	**Events / Total**					
Silva et al, 2015 (31)	15 / 60	15 / 150	25.0%	10.0%	2.92	1.42 – 5.98	17.5%
Mayer et al, 2017 (32)	30 / 90	45 / 225	33.3%	20.0%	1.94	1.12 – 3.36	21.0%
Johnson et al, 2018(33)	60 / 150	30 / 200	40.0%	15.0%	3.92	2.35 – 6.56	23.5%
Demir et al, 2020 (34)	10 / 35	8 / 70	28.6%	11.4%	03.01	1.12 – 8.08	10.5%
Tanaka et al, 2022(35)	12 / 48	20 / 130	25.0%	15.4%	1.82	0.83 – 3.99	13.5%
Dubois et al, 2023(36)	8 / 36	15 / 164	22.2%	9.1%	2.83	1.15 – 6.97	14.0%
Pooled Estimate	**(N = 1,358 Patients)**				**2.48**	**1.65 – 3.71**	**100.0%**
Heterogeneity:	$I^2 = 58\%$, $Tau^2 = 0.21$	$Chi^2 = 11.90$, df = 5	(p = 0.03)				
Overall Effect:	Z = 4.35	(p < 0.0001)					

Table 3 presents the results of subgroup and sensitivity analyses conducted to further explore the association between retinal microvascular alterations (RMVAs) and short-term mortality in critically ill patients; Overall Main Analysis (Reference): This row reiterates the main analysis findings for comparison. With 6 studies and 1358 patients, the pooled odds ratio (OR) is 2.48, with a 95% confidence interval (CI) of 1.65 - 3.71. This is statistically significant ($p < 0.0001$) and shows moderate heterogeneity ($I^2 = 58\%$, $p = 0.03$); Subgroup Analysis: Fundus Exam Method: This section explores whether the method of fundus examination (fundus photography vs. ophthalmoscopy) influences the association between RMVAs and mortality. 3 studies using fundus photography showed a pooled OR of 2.55 (95% CI: 1.40 - 4.65), with moderate heterogeneity ($I^2 = 55\%$, $p = 0.06$) and a significant overall effect ($p = 0.003$). 3 studies using ophthalmoscopy showed a pooled OR of 2.40 (95% CI: 1.35 - 4.28), with moderate heterogeneity ($I^2 = 60\%$, p =

0.04) and a significant overall effect (p = 0.003). The p-value for the subgroup difference is 0.80, indicating no statistically significant difference in the association between RMVAs and mortality based on the fundus examination method. In other words, the association between RMVA and mortality is similar whether fundus photography or ophthalmoscopy is used; Sensitivity Analysis: Leave-One-Out: This section assesses the robustness of the main finding by systematically excluding one study at a time and recalculating the pooled OR. This helps identify if any single study is disproportionately influencing the overall result. The results show that even after excluding each study individually, the pooled OR remains statistically significant (p < 0.001 in all cases) and the magnitude of the effect remains relatively consistent (ORs ranging from 2.25 to 2.68). The heterogeneity also remains in the moderate range. This analysis confirms the robustness of the main finding, as no single study significantly alters the overall conclusion; Sensitivity Analysis: Study Quality: This section examines the impact of study quality on the results by excluding lower-quality studies. When lower-quality studies are excluded, the pooled OR is 2.65 (95% CI: 1.62 - 4.34), which is still statistically significant (p < 0.001). The heterogeneity remains moderate (I^2 = 62%, p = 0.05). This analysis suggests that excluding lower-quality studies does not substantially change the overall finding, further supporting the reliability of the association between RMVAs and mortality.

Table 3. Subgroup and sensitivity analyses for the association between retinal microvascular alterations (RMVAs) and short-term mortality in critically ill patients.

Analysis Type & Specification	**Number of Studies (k)**	**Total Patients (N)**	**Pooled Odds Ratio (OR)**	**95% Confidence Interval (CI)**	**Heterogeneity I^2 (%)**	**p-value (Heterogeneity)**	**p-value (Overall Effect)**	**Comment / Subgroup Difference p-value**
Overall Main Analysis (All Studies)	**6**	**1358**	**2.48**	**1.65 – 3.71**	**58%**	**0.03**	**<0.0001**	**Reference Analysis**
Subgroup Analysis: Fundus Exam Method								**p = 0.80 (for subgroup difference)[1]**
- Fundus Photography	3	738	2.55	1.40 – 4.65	55%	0.06	3	
- Ophthalmoscopy	3	620	2.40	1.35 – 4.28	60%	0.04	3	
Sensitivity Analysis: Leave-One-Out								
- Excl. Study 1	5	1148	2.40	1.52 – 3.79	61%	0.02	<0.001	Robustness Check
- Excl. Study 2	5	1043	2.55	1.58 – 4.12	63%	0.02	<0.001	Robustness Check
- Excl. Study 3	5	1008	2.25	1.48 – 3.43	50%	0.07	<0.001	Robustness Check
- Excl. Study 4	5	1253	2.51	1.60 – 3.94	60%	0.02	<0.0001	Robustness Check
- Excl. Study 5	5	1180	2.68	1.70 – 4.22	60%	0.02	<0.0001	Robustness Check
- Excl. Study 6	5	1158	2.35	1.55 – 3.56	54%	0.05	<0.001	Robustness Check
Sensitivity Analysis: Study Quality								
- Excl. Lower Quality Studies	4	865	2.65	1.62 – 4.34	62%	0.05	<0.001	Assesses impact of bias risk

4. Discussion

Our primary finding indicates a statistically significant association between the presence of significant RMVAs and increased short-term mortality in critically ill patients. The pooled analysis revealed that critically ill patients exhibiting RMVAs had approximately 2.5 times higher odds of mortality compared to patients with normal fundus findings. This elevated risk was consistently observed across the included studies, as reflected in the pooled odds ratio of 2.48 with a 95% confidence interval of 1.65 to 3.71. The statistical significance of this finding was further supported by a p-value of less than 0.0001. This strong association suggests that RMVAs, as detected by fundus examination, may serve as a valuable prognostic indicator in critically ill patients. The robustness of this finding was confirmed through a series of sensitivity analyses. These analyses aimed to assess whether the observed association was unduly influenced by any single study or by variations in study quality. The leave-one-out sensitivity analysis, which involved iteratively removing each study and recalculating the pooled effect, demonstrated that the association remained significant and the magnitude of the effect remained relatively stable regardless of which study was excluded. This provides strong evidence that the overall finding is not driven by any single outlier study. Furthermore, the sensitivity analysis that excluded lower-quality studies also yielded a significant association, indicating that the observed relationship between RMVAs and increased mortality is not merely a consequence of methodological limitations in the included studies.[11-13]

The findings of this meta-analysis are consistent with, and indeed strengthen, the conclusions drawn from several of the individual studies included in our analysis, as well as broader research that posits the eye as a valuable indicator of systemic vascular health and disease severity. The concept of the eye as a “window” to systemic microcirculation has been explored in various contexts, and our results lend further support to its relevance in the critical care setting. Previous narrative reviews and smaller observational studies have suggested a potential link between retinal findings and outcomes in critically ill patients. However, this meta-analysis provides a more precise and robust quantitative synthesis of the available evidence, offering a more definitive estimate of the magnitude of the association between RMVAs and mortality in this vulnerable population. By pooling data from multiple studies, we have increased statistical power and reduced the impact of individual study limitations, thereby arriving at a more reliable conclusion. The pathophysiological basis for the observed association between RMVAs and increased mortality in critically ill patients is likely multifactorial, reflecting the complex interplay of systemic microvascular injury and endothelial dysfunction that characterizes critical illness. Conditions such as sepsis, shock, ARDS, and severe hypertension are frequently accompanied by a cascade of events including systemic inflammation, endothelial dysfunction, increased vascular permeability, impaired autoregulation of blood flow, coagulopathy, and tissue hypoxia. These pathological processes can directly damage the small vessels in the retina, leading to the spectrum of RMVAs observed during fundus examination. Hypertensive retinopathy changes, such as arteriolar narrowing, arteriovenous nicking, retinal hemorrhages, cotton wool spots, and papilledema, are indicative of systemic blood pressure dysregulation and its deleterious effects on vessel walls. These changes reflect end-organ damage resulting from the systemic hypertensive process. Severe grades of hypertensive retinopathy are established predictors of cardiovascular events and mortality in non-ICU populations. Our findings suggest that this prognostic significance extends to the critically ill, where the acute stresses of critical illness can exacerbate hypertensive microvascular damage. Cotton wool spots (CWS) represent focal infarcts within the retinal nerve fiber layer, resulting from the occlusion of pre-capillary arterioles. The presence of CWS suggests microvascular occlusion and tissue ischemia in the retina, which may mirror similar ischemic processes occurring in other vital organs, often silently. CWS are commonly observed in conditions such as hypertension, diabetes, and connective tissue diseases. Notably, they have also been described in sepsis and other severe systemic inflammatory states, highlighting their association with the systemic microvascular dysfunction that is a

hallmark of critical illness. Retinal hemorrhages can arise from various mechanisms, including direct vessel wall damage, increased intravascular pressure, and coagulopathies. All of these are common occurrences in the ICU setting. The presence of retinal hemorrhages indicates underlying vascular fragility and leakage, reflecting the broader compromise of microvascular integrity in critically ill patients. Papilledema, while frequently associated with elevated intracranial pressure (a condition specific to neuro-ICUs), can also be a manifestation of malignant hypertension. Its presence in the context of critical illness further signifies severe systemic disturbance and microvascular compromise. Therefore, the detection of these RMVAs through fundus examination likely serves to identify a subset of critically ill patients with more severe and established systemic microvascular pathology and endothelial injury. These underlying microvascular derangements are increasingly recognized as key drivers of organ failure and adverse outcomes in critical illness. The retinal findings, readily visible through funduscopy, may thus act as a surrogate marker for this often clinically occult systemic microvascular dysfunction, providing valuable prognostic information. This interpretation is consistent with studies that have demonstrated correlations between retinal findings and other markers of inflammation or endothelial dysfunction in critically ill patients. While our meta-analysis focused on the pooled outcome analysis of mortality, the mechanistic link between RMVAs and systemic microvascular dysfunction provides a strong biological plausibility for the observed association.[14-16]

The findings of this meta-analysis have potential implications for clinical practice in the ICU setting. The results suggest that routine fundus examination, a relatively simple and non-invasive bedside procedure, could potentially contribute to enhanced risk stratification of critically ill patients. Identifying patients with RMVAs may alert clinicians to a higher underlying risk of mortality. This heightened awareness could prompt more intensive monitoring of these patients, more aggressive management of underlying conditions such as hypertension or sepsis, or consideration for advanced hemodynamic or microcirculatory assessments. For example, in a patient with sepsis and identified RMVAs, clinicians might be more vigilant in their fluid resuscitation strategies, more proactive in initiating vasopressor support, or consider early use of adjunctive therapies aimed at improving microcirculatory flow. However, it is crucial to acknowledge the practical considerations surrounding the implementation of routine funduscopy in the often-hectic ICU environment. Traditional direct ophthalmoscopy requires a degree of skill and can be challenging in patients who are uncooperative or when performed through undilated pupils. While pupillary dilation is frequently feasible in sedated ICU patients, it adds another step to the examination. Indirect ophthalmoscopy provides a wider field of view but demands even greater expertise. The increasing availability and portability of non-mydriatic digital fundus cameras have significantly improved the feasibility of retinal imaging in the ICU. These cameras allow trained nurses or technicians to acquire retinal images at the bedside, which can then be interpreted remotely by ophthalmologists or trained intensivists. This approach offers several advantages, including ease of documentation, the ability to track changes over time, and the potential for telemedicine consultations. In our meta-analysis, three of the included studies successfully utilized fundus photography, demonstrating its viability and applicability in the ICU setting. Our exploratory subgroup analysis did not reveal a significant difference in the association between RMVAs and mortality based on the fundus examination method (ophthalmoscopy vs. fundus photography). This suggests that both traditional ophthalmoscopy and fundus photography can effectively detect prognostically relevant RMVAs. However, further research is needed to determine the optimal method and to develop standardized protocols for fundus examination in the ICU. Despite the potential benefits, it is important to emphasize that before advocating for widespread adoption of routine ICU funduscopy for prognostication, several key points need to be carefully considered. First, it is essential to acknowledge that our pooled estimate is derived from observational data. As such, it cannot establish a causal relationship between RMVAs and mortality. The

observed RMVAs are markers of disease severity and microvascular dysfunction, but they are not necessarily direct mediators of mortality. It is possible that other unmeasured or residual confounding factors contribute to the association. Second, the optimal timing, frequency, and specific RMVA signs or grading systems that provide the most reliable prognostic information remain to be fully elucidated. The included studies varied in their definitions and grading of RMVAs, and further research is needed to identify the most predictive retinal findings and to develop standardized protocols for their assessment. Third, the cost-effectiveness of routine ICU funduscopy and its impact on clinical decision-making and actual patient outcomes need to be rigorously evaluated in prospective intervention or implementation studies. While the procedure itself is relatively inexpensive, the resources required for training personnel, acquiring and maintaining equipment, and interpreting the results need to be considered. More importantly, it is crucial to demonstrate that the information gained from a funduscopy leads to changes in clinical management that ultimately improve patient outcomes. Currently, a fundus examination in the ICU is typically performed when there is a suspicion of specific ocular pathology, such as fungal endophthalmitis in septic patients or when assessing for papilledema in patients with neurological injury. The results of our meta-analysis suggest a broader potential role for funduscopy in the ICU, but more high-quality evidence is needed to define its precise place in routine risk assessment algorithms alongside established severity scores and other prognostic tools.[17-20]

5. Conclusion

In conclusion, this meta-analysis provides compelling evidence for a significant association between the presence of retinal microvascular alterations, detected through fundus examination, and an increased risk of short-term mortality in critically ill adult patients. The pooled analysis demonstrated that critically ill patients with RMVAs had approximately 2.5 times higher odds of mortality compared to those without these retinal changes. This finding was robust across various sensitivity analyses, confirming that the association was not influenced by any single study or by variations in study quality. The observed association likely reflects the underlying systemic microvascular injury and endothelial dysfunction that are central to the pathophysiology of critical illness. Retinal microvascular alterations may serve as readily accessible markers of this systemic microvascular compromise, offering valuable prognostic information. While these findings suggest that routine fundus examination could potentially enhance risk stratification in the ICU, several considerations warrant caution. As this meta-analysis is based on observational data, it cannot establish causality. Further research is needed to determine the optimal timing, frequency, and specific retinal signs that are most predictive of outcomes. Additionally, the cost-effectiveness and impact of routine funduscopy on clinical decision-making and patient outcomes require rigorous evaluation in prospective studies. In conclusion, while the results of this meta-analysis indicate a promising role for funduscopy in ICU risk assessment, future research should focus on addressing the limitations outlined above to fully define its clinical utility and optimize its implementation.

6. References

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