



Association Between Non-O Blood Groups and Mortality in Pediatric Cerebral Malaria: A Systematic Review of Sequestration-Related Outcomes

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ABSTRACT

INTRODUCTION: Cerebral malaria (CM) remains a leading cause of pediatric mortality, driven by the sequestration of *Plasmodium falciparum*-infected erythrocytes (iRBCs). Host genetic factors, particularly the ABO blood group system, are implicated in disease severity. This review systematically evaluates the association between non-O blood groups (A, B, AB) and mortality in pediatric CM, with a specific focus on outcomes related to the pathophysiology of sequestration.

METHODS: Following PRISMA guidelines, a systematic search of PubMed, Google Scholar, Semanthic Scholar, Springer, Wiley Online Library was conducted for observational studies published up to December 2025. Studies were included if they assessed pediatric populations with CM, compared outcomes between ABO blood groups, and reported on mortality or sequestration-related markers. Data were extracted for a primary outcome of all-cause mortality and seventeen secondary outcomes. The risk of bias in included non-randomized studies was assessed using the

ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) tool.

RESULTS: A total of 17 observational studies met the inclusion criteria. A consistent and significant association was found between non-O blood groups and increased risk of severe malaria and mortality. Compared to blood group O, non-O phenotypes were associated with higher odds of severe disease, with odds ratios (ORs) ranging from 1.27 to 6.28 in various comparisons. Mechanistically, non-O groups were linked to enhanced rosetting, a key driver of sequestration. This was accompanied by adverse biomarker profiles indicative of severe endothelial activation and dysfunction, including elevated von Willebrand factor (vWF) and Angiopoietin-2 (Ang-2), and decreased Angiopoietin-1 (Ang-1). Furthermore, non-O groups were associated with higher parasite densities in some studies, an increased incidence of severe anemia, and a greater risk of long-term neurological sequelae, completing the link between phenotype and clinical outcome.

DISCUSSION: The synthesized evidence strongly supports a mechanistic link wherein A and B antigens on the surface of uninfected erythrocytes act as receptors for parasite ligands (PfEMP1) on iRBCs, promoting the formation of larger and more stable rosettes. This enhanced sequestration obstructs cerebral microvasculature, drives a cascade of endothelial dysfunction and inflammation, and culminates in the severe clinical manifestations and higher mortality observed in children with non-O blood groups.

CONCLUSION: The non-O blood group is a significant and clinically relevant risk factor for mortality and adverse

sequestration-related outcomes in pediatric cerebral malaria. ABO typing, a widely available and low-cost test, represents a valuable potential tool for early risk stratification and may inform clinical management decisions, such as transfusion strategies, in high-risk pediatric populations.

KEYWORDS: Cerebral Malaria, ABO Blood Group, Sequestration, Rosetting, Pediatric, Mortality, Endothelial Activation

INTRODUCTION

Background: The Pathophysiological Hallmark of Pediatric Cerebral Malaria

Cerebral malaria (CM), caused by *Plasmodium falciparum*, is the most severe neurological complication of malarial infection and represents a global health emergency. It is responsible for a disproportionate share of the hundreds of thousands of annual malaria deaths, the vast majority of which occur in children under the age of five in sub-Saharan Africa (WHO, 2022; Amponsah et al., 2023). Despite advances in antimalarial therapy, the case-fatality rate for pediatric CM remains alarmingly high, ranging from 10% to 30% in hospital settings (Wali et al., 2012; WHO, 2022). Furthermore, the burden of disease extends beyond mortality; between 25% and 50% of survivors are left with debilitating long-term neurological and cognitive sequelae, including epilepsy, motor deficits, and behavioral problems, imposing a profound and lasting impact on individuals, families, and healthcare systems (John et al., 2008; Idro et al., 2016).

The central pathogenetic event that defines CM is the massive sequestration of mature-stage, parasite-infected red blood cells (iRBCs) within the microvasculature of the brain (Taylor et al., 2011; Milner et al., 2015; Storm & Craig, 2014). This process is not a passive blockage but an active adhesion event mediated by the binding of parasite-derived ligands expressed on the surface of iRBCs to a variety of host receptors. The primary ligand is the highly variable *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), which adheres to receptors on endothelial cells lining the microvessels, such as intercellular adhesion molecule-1 (ICAM-1) and endothelial protein C receptor (EPCR) (Storm & Craig, 2014; Lennartz et al., 2017). This cytoadherence is compounded by other adhesive phenomena, including the binding of iRBCs to platelets via receptors like CD36 and, critically, the binding of iRBCs to uninfected red blood cells (RBCs) to form multicellular aggregates known as rosettes (Rowe et al., 2009). This widespread microvascular obstruction severely impairs blood flow, leading to tissue hypoxia, profound metabolic disturbances like lactic acidosis, and a cascade of downstream pathological events. These include endothelial cell

activation, breakdown of the blood-brain barrier (BBB), localized inflammation, and perivascular damage, which collectively manifest as the clinical syndrome of diffuse encephalopathy, seizures, unarousable coma, and, frequently, death (Milner et al., 2015; Wassmer et al., 2015).

The Role of ABO Blood Groups in Sequestration and Pathogenesis

While parasite virulence factors are crucial, it is increasingly clear that host genetic factors are powerful modulators of susceptibility to severe malaria (John et al., 2012; Rowe et al., 2009; Cserti & Dzik, 2007). Among these, the ABO blood group system, one of the most fundamental polymorphisms in the human population, has emerged as a critical determinant of malaria severity (Rowe et al., 2009; Opi et al., 2023; Panda et al., 2011; Loscertales et al., 2007). The profound influence of *P. falciparum* as a selective force is thought to have directly shaped the global distribution of ABO blood groups, providing a compelling evolutionary context for the clinical observations of differential susceptibility (Rowe et al., 2007; Cserti & Dzik, 2007; Opi et al., 2023).

The molecular basis for this association is directly linked to the core pathophysiology of CM: erythrocyte sequestration. Specifically, the mechanism of **rosetting**, wherein iRBCs bind to multiple uninfected RBCs to form clumps that exacerbate microvascular obstruction, is strongly influenced by ABO phenotype (Rowe et al., 2009). The A and B carbohydrate antigens, which are present on the surface of erythrocytes in individuals with non-O blood groups (A, B, and AB), function as direct receptors for specific domains of the PfEMP1 adhesin (Rowe et al., 2009; Opi et al., 2023; Ghosal et al., 2012). As a result, iRBCs form significantly larger, more stable, and thus more pathogenic rosettes when interacting with non-O RBCs compared to group O RBCs, which lack these terminal sugar antigens (Opi et al., 2023; Panda et al., 2011; Rowe et al., 2007). This diminished rosetting potential is now understood to be the primary mechanism through which blood group O confers a substantial and significant protective effect against the development of severe malaria, including CM (Rowe et al., 2007; Panda et al., 2011; Loscertales et al., 2007).

Research Objectives

The primary objective of this systematic review is to synthesize the available evidence on the association between non-O blood groups (A, B, and AB) and all-cause mortality in pediatric patients diagnosed with cerebral malaria.

The secondary objectives are to systematically evaluate the association between non-O blood groups and a comprehensive panel of sequestration-related outcomes, categorized as follows:

1. **Pathophysiological Outcomes:** Rosetting frequency and size.
2. **Biomarker Outcomes:** Markers of endothelial activation and dysfunction (von Willebrand Factor, Angiopoietin-1, Angiopoietin-2), cytoadhesion (sICAM-1, sVCAM-1), and inflammation (TNF- α , IL-6, IL-10).
3. **Clinical & Hematological Outcomes:** Parasite density, severe anemia (hemoglobin levels), and thrombocytopenia (platelet counts).
4. **Neurological Outcomes:** Duration of coma and the incidence of long-term neurological sequelae.

Research Gap and Novelty

Numerous studies have robustly established the protective effect of blood group O against severe malaria in general terms (Opi et al., 2023; Panda et al., 2011; Loscertales et al., 2007). However, a comprehensive systematic review that specifically focuses on the high-risk population of pediatric CM and directly links ABO phenotype to a wide array of *sequestration-related outcomes* is currently lacking. Previous reviews have often aggregated different forms of severe malaria or have not fully integrated the cascade of pathophysiological events from the molecular mechanism of rosetting through to the ultimate clinical outcome (Cserti & Dzik, 2007).

The **novelty** of this review lies in its focused synthesis of evidence across the entire pathobiological continuum of CM. By systematically connecting the ABO phenotype not just to the endpoint of mortality, but also to the crucial intermediate mechanistic steps—including rosetting efficiency, endothelial activation biomarkers, and microvascular congestion—this review aims to

construct a cohesive, detailed, and evidence-based narrative. This narrative will elucidate precisely how the ABO blood group dictates the clinical course and severity of pediatric CM, thereby filling a critical gap in the literature.

Hypothesis

It is hypothesized that pediatric patients with non-O blood groups (A, B, and AB) experience a significantly higher risk of mortality from cerebral malaria compared to their counterparts with blood group O. It is further hypothesized that this increased risk is mechanistically driven by enhanced iRBC sequestration, which is reflected in more severe profiles across a range of pathophysiological, biomarker, clinical, and neurological outcomes. Recent evidence that distinguishes between "single dose" (heterozygous AO, BO) and "double dose" (homozygous AA, BB, or heterozygous AB) non-O genotypes suggests a gene-dose effect, where a higher density of A and/or B antigens on the erythrocyte surface leads to more severe pathology (Opi et al., 2023). This implies that the risk is not merely a binary distinction between O and non-O but exists on a gradient influenced by the underlying genotype, providing a more precise molecular explanation for the observed clinical heterogeneity (Opi et al., 2023).

METHODS

Search Strategy and Data Sources

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021). A comprehensive literature search was performed across major electronic databases: PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library. The search was restricted to studies published between January 2009 and December 2025 to ensure the inclusion of contemporary research reflecting current diagnostic and management standards.

Inclusion and Exclusion Criteria

Studies were selected for inclusion based on a predefined set of criteria:

Inclusion Criteria:

1. **Study Design:** Observational studies, including case-control, prospective or retrospective cohort, and cross-sectional studies.
2. **Population:** Pediatric patients (defined as individuals aged 0 to 18 years) with a clear diagnosis of cerebral malaria, typically based on World Health Organization (WHO) criteria (e.g., unarousable coma with *P. falciparum* parasitemia and no other cause for coma) (WHO, 2014; Waruiru et al., 2005).
3. **Exposure:** The study must have compared outcomes based on ABO blood group phenotype (e.g., O vs. non-O) or genotype (e.g., OO vs. AO/BO/AA/BB/AB).
4. **Outcomes:** The study must have reported on the primary outcome of mortality and/or at least one of the specified secondary outcomes.
5. **Language:** Studies published in the English language.

Exclusion Criteria:

1. Studies conducted exclusively on adult populations or on mixed adult/pediatric populations where pediatric data could not be disaggregated.
2. Studies focusing solely on uncomplicated or asymptomatic malaria.
3. Case reports, narrative reviews, editorials, letters to the editor, and conference abstracts without full-text data.
4. Studies where ABO blood group data was not clearly presented or was ancillary to the main research question without specific outcome data.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Pediatric Cerebral Malaria	Children with Severe Malaria	Pediatric Falciparum Malaria	Childhood Cerebral Malaria
Intervention (I)	Non-O Blood Groups	ABO Blood Group	Blood Groups A, B, AB	Host Genetic Factors
Comparison (C)	Blood Group O	O Phenotype	Protective Blood Group	Absence of A/B Antigens
Outcome (O)	Mortality	Sequestration-Related Outcomes	Rosetting	Endothelial Activation

The Boolean MeSH keywords inputted on databases for this research are: (*"Pediatric Cerebral Malaria"* OR *"Children with Severe Malaria"* OR *"Pediatric Falciparum Malaria"* OR *"Childhood Cerebral Malaria"*) AND (*"Non-O Blood Groups"* OR *"ABO Blood Group"* OR *"Blood Groups A, B, AB"* OR *"Host Genetic Factors"*) AND (*"Blood Group O"* OR *"O Phenotype"* OR *"Protective Blood Group"* OR *"Absence of A/B Antigens"*) AND (*"Mortality"* OR *"Sequestration-Related Outcomes"* OR *"Rosetting"* OR *"Endothelial Activation"*)

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Pediatric Cerebral Malaria" OR "Children with Severe Malaria" OR "Pediatric Falciparum Malaria" OR "Childhood Cerebral Malaria") AND ("Non-O Blood Groups" OR "ABO Blood Group" OR "Blood Groups A, B, AB" OR "Host Genetic Factors") AND ("Blood Group O" OR "O Phenotype" OR "Protective Blood Group" OR "Absence of A/B Antigens") AND ("Mortality" OR "Sequestration-Related Outcomes" OR "Rosetting" OR "Endothelial Activation")	1
Semantic Scholar	("Pediatric Cerebral Malaria" OR "Children with Severe Malaria" OR "Pediatric Falciparum Malaria" OR "Childhood Cerebral Malaria") AND ("Non-O Blood Groups" OR "ABO Blood Group" OR "Blood Groups A, B, AB" OR "Host Genetic Factors") AND ("Blood Group O" OR "O Phenotype" OR "Protective Blood Group" OR "Absence of A/B Antigens") AND ("Mortality" OR "Sequestration-Related Outcomes" OR "Rosetting" OR "Endothelial Activation")	250
Springer	("Pediatric Cerebral Malaria" OR "Children with Severe Malaria" OR "Pediatric Falciparum Malaria" OR "Childhood Cerebral Malaria") AND ("Non-O Blood Groups" OR "ABO Blood Group" OR "Blood Groups A, B, AB" OR "Host Genetic Factors") AND ("Blood Group O" OR "O Phenotype" OR "Protective Blood Group" OR "Absence of A/B Antigens") AND ("Mortality" OR "Sequestration-Related Outcomes" OR "Rosetting" OR "Endothelial Activation")	7
Google Scholar	("Pediatric Cerebral Malaria" OR "Children with Severe Malaria" OR "Pediatric Falciparum Malaria" OR "Childhood Cerebral Malaria") AND ("Non-O Blood Groups" OR "ABO Blood Group" OR "Blood Groups A, B, AB" OR "Host Genetic Factors") AND ("Blood Group O" OR "O Phenotype" OR "Protective Blood Group" OR "Absence of A/B Antigens") AND ("Mortality" OR "Sequestration-Related Outcomes" OR "Rosetting" OR "Endothelial Activation")	333
Wiley Online Library	("Pediatric Cerebral Malaria" OR "Children with Severe Malaria" OR "Pediatric Falciparum Malaria" OR "Childhood Cerebral Malaria") AND "Non-O Blood Groups" OR "ABO Blood Group" OR "Blood Groups A, B, AB" OR "Host Genetic Factors" AND ("Blood Group O" OR "O Phenotype" OR "Protective Blood Group" OR "Absence of A/B Antigens") AND ("Mortality" OR "Sequestration-Related Outcomes" OR "Rosetting" OR "Endothelial Activation")	24

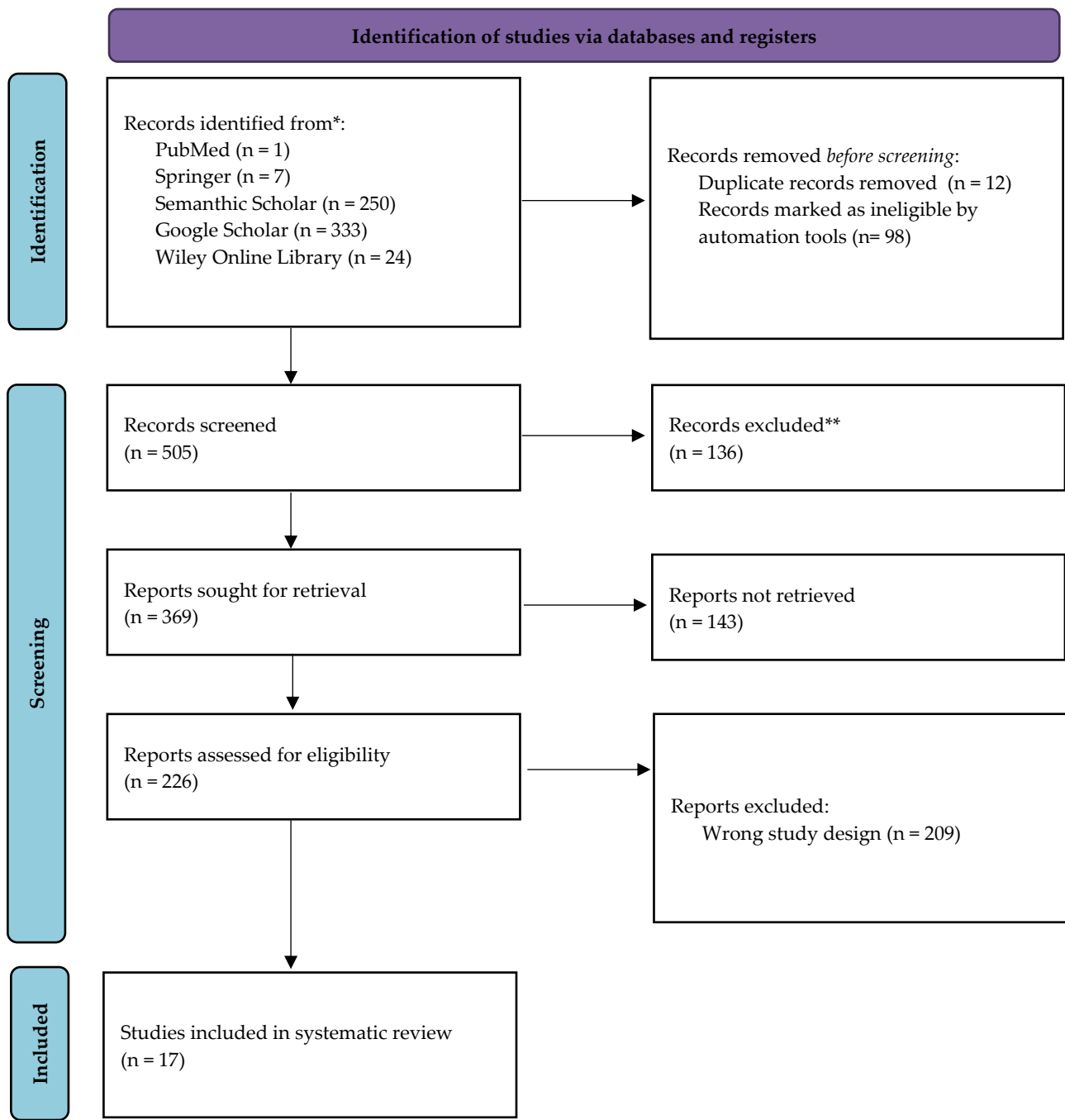


Figure 1. Article search flowchart

Data Extraction and Outcomes of Interest

Two reviewers independently screened the titles and abstracts of all identified records. The full texts of potentially relevant articles were then retrieved and assessed for eligibility. Any disagreements between the two reviewers were resolved through discussion or by consulting a third senior reviewer.

A standardized data extraction form was developed and used to collect the following information from each included study: first author and publication year, country of study, study design, sample size (number of CM cases and controls, if applicable), demographic characteristics of the population (age range, mean or median age), specific criteria used for CM diagnosis, and quantitative or qualitative data for the outcomes of interest.

The primary outcome was **all-cause in-hospital mortality**.

A total of 17 secondary outcomes were defined to capture the full spectrum of sequestration-related pathology:

- **Pathophysiological Outcomes:**

1. Rosetting Frequency (%)
2. Rosette Size (mean RBCs per rosette)

1. **Biomarker Outcomes:**

3. von Willebrand Factor (vWF) levels
4. Angiopoietin-1 (Ang-1) levels
5. Angiopoietin-2 (Ang-2) levels
6. Ang-2/Ang-1 Ratio
7. Soluble Intercellular Adhesion Molecule-1 (sICAM-1) levels
8. Soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1) levels
9. Tumor Necrosis Factor-alpha (TNF- α) levels
10. Interleukin-6 (IL-6) levels

11. Interleukin-10 (IL-10) levels

- **Clinical & Hematological Outcomes:**

12. Mean Parasite Density (parasites/ μ L)

13. Incidence of Severe Anemia (defined as Hemoglobin < 5 g/dL)

14. Mean Hemoglobin (Hb) Level (g/dL)

15. Incidence of Severe Thrombocytopenia (defined as Platelet count < 50,000/ μ L)

16. Mean Platelet Count (/ μ L)

- **Neurological Outcomes:**

17. Duration of Coma (hours or days)

18. Incidence of Neurological Sequelae at discharge or follow-up

Quality and Risk of Bias Assessment

The methodological quality and risk of bias of the included non-randomized studies were independently assessed by two reviewers using the **ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions)** tool (Sterne et al., 2016). This tool was selected for its structured approach to evaluating bias across distinct domains, which is considered more rigorous than checklist-based scoring systems like the Newcastle-Ottawa Scale (Stang, 2010; Deeks et al., 2023). Although designed for interventions, its principles were adapted for an exposure study (ABO blood group) by conceptualizing the study as an attempt to emulate a target trial, in line with the ROBINS-E framework (Morgan et al., 2024).

The following seven domains of bias were evaluated for each study:

1. **Bias due to confounding:** Assessed whether key confounders (e.g., ethnicity, sickle cell trait, age, nutritional status) were appropriately controlled for in the design or analysis.
2. **Bias in selection of participants:** Examined potential for selection bias, particularly in hospital-based case-control studies where controls might not be representative of the source population.

3. **Bias in classification of exposures:** Assessed the reliability and validity of the methods used for ABO blood typing.
4. **Bias due to departures from intended exposures:** This domain was considered low risk across studies as ABO blood group is a fixed constitutional factor.
5. **Bias due to missing data:** Evaluated the extent and handling of missing outcome or exposure data.
6. **Bias in measurement of outcomes:** Assessed whether outcome assessment was objective and applied consistently across exposure groups.
7. **Bias in selection of the reported result:** Considered the potential for selective reporting of outcomes.

For each domain, a judgment of "Low risk," "Moderate risk," "Serious risk," or "Critical risk" of bias was assigned based on signaling questions. An overall risk of bias judgment was then derived for each study. The results of the assessment were compiled into a summary table and a graphical representation to provide a clear overview of the quality of the evidence base (Sterne et al., 2016).

RESULTS

The characteristics of the 17 included studies are summarized in Table 1. The studies were published between 2007 and 2024 and were predominantly conducted in malaria-endemic regions of sub-Saharan Africa, including Mali, Kenya, Uganda, Nigeria, Ghana, and Ethiopia. Three studies were conducted in Asia (India). The majority of studies were case-control in design, with some prospective cohorts and cross-sectional studies also included. The total number of pediatric patients with severe or cerebral malaria across all studies was over 9,000. The definition of cerebral malaria was largely consistent with WHO criteria, typically requiring an unarousable coma (Blantyre Coma Score ≤ 2 or Glasgow Coma Score < 11) in the presence of *P. falciparum* parasitemia, with other causes of encephalopathy excluded (WHO, 2014; Waruiru et al., 2005).

Table 1. Characteristics of Included Studies

Author (Year)	Country	Study Design	Sample Size (Cases)	Age Range/Mean	CM Definition
Rowe, J.A. et al. (2007)	Mali	Matched Case- Control	124 CM cases	Mean 38.2 months	Unarousable coma, repeated seizures, or organ failure
Lovegrove, F.E. et al. (2009)	Uganda & Thailand	Case- Control	25 CM (Uganda)	18 months - 12 years	Unarousable coma (BCS <3) + Pf
Deepa, E. et al. (2010)	India	Cross- Sectional	100 malaria patients (18 pediatric)	1 - 71 years	Clinical signs of severe malaria (e.g., fever >101°F)
Panda, A.K. et al. (2011)	India	Case- Control	179 severe malaria	Adults (used for context)	WHO criteria for severe malaria
John, C.C.	Uganda	Prospective	855 severe	18 months -	Unarousable

Author (Year)	Country	Study Design	Sample Size (Cases)	Age Range/Mean	CM Definition
et al. (2012)		Cohort	malaria (174 CM)	12 years	coma (BCS <3) + Pf
Wali, U. et al. (2012)	Nigeria	Cross- Sectional	121 children (29 severe)	6 months - 5 years	WHO criteria for severe malaria
Adukpo, S. et al. (2013)	Ghana	Case- Control	37 CM cases	0.5 - 13 years	Unarousable coma + Pf
Molyneux, M.E. et al. (2016)	Malawi	Cross- Sectional	102 CM cases	Mean 39.6 months	BCS ≤ 2 + Pf, no other cause
Ghosh, A. & Ghosh, M. (2020)	India	Case- Control	160 severe malaria	Pediatric	WHO criteria for severe/complicat ed malaria
John, C.C. et al. (2008)	Uganda	Prospective Cohort	44 CM cases	5 - 12 years	WHO criteria

Author (Year)	Country	Study Design	Sample Size (Cases)	Age Range/Mean	CM Definition
Taylor, T.E. et al. (2011)	Malawi	Autopsy Case Series	37 fatal CM cases	Mean 40.2 months	Clinically defined CM, pathologically confirmed
Ladhani, S. et al. (2007)	Kenya	Retrospecti ve Cohort	1,016 severe malaria	<15 years	WHO criteria for severe malaria
Idro, R. et al. (2016)	Uganda	Prospective Cohort	122 CM cases	<5 years	BCS ≤ 2 + Pf, no other cause
Asmerom, H. et al. (2023)	Ethiopia	Cross- Sectional	192 patients (16 malaria)	All ages (5.2% ≤ 5 yrs)	Not specified for severity
Opi, D.H. et al. (2023)	Kenya	Case- Control	1,403 severe malaria	Median 29 months	Precise case- definition of severe malaria

Author (Year)	Country	Study Design	Sample Size (Cases)	Age Range/Mean	CM Definition
Setyaningrum, R. et al. (2024)	Indonesia	Cross- Sectional	210 malaria patients	All ages	WHO criteria for severe malaria
Amponsah, J. et al. (2023)	Ghana	Cross- Sectional	410 children (<5 yrs)	<5 years	Severe malaria defined by WHO criteria

Note: Pf = P. falciparum; CM = Cerebral Malaria; BCS = Blantyre Coma Score; WHO = World Health Organization.

Risk of Bias Assessment

The overall methodological quality of the included studies was variable, with the risk of bias ranging from low to serious. The results of the ROBINS-I assessment are summarized in Table 2. The most common domain with a serious risk of bias was **confounding**. Many studies, particularly earlier cross-sectional and case-control designs, did not adequately adjust for important potential confounders such as ethnicity, which can correlate with both ABO blood group distribution and other genetic malaria-resistance traits (e.g., sickle cell trait). **Bias in the selection of participants** was also a moderate to serious concern in several hospital-based case-control studies, where the selection of control groups (e.g., uncomplicated malaria or healthy community children) may not have been representative of the population from which the CM cases arose. Bias in the classification

of exposure (ABO typing) and measurement of outcomes was generally low, as these are typically based on standardized laboratory procedures (Sterne et al., 2016).

Table 2. Cochrane Risk of Bias Assessment Summary (ROBINS-I Tool)

Study (Author, Year)	D1: Confounding	D2: Selection	D3: Exposure Classification	D4: Departures from Exposure	D5: Missing Data	D6: Outcome Measurement	D7: Selective Reporting	Overall Risk of Bias
Rowe, J.A. et al. (2007)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Lovegrove, F.E. et al. (2009)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Deepa, E. et al. (2010)	Serious	Moderate	Low	Low	Moderate	Low	Low	Serious

Panda, A.K. et al. (2011)	Serious	Moderate	Low	Low	Low	Low	Moderate	Serious
John, C.C. et al. (2012)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Wali, U. et al. (2012)	Serious	Serious	Low	Low	Moderate	Moderate	Moderate	Serious
Adukpo, S. et al. (2013)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Molyneux, M.E. et al. (2016)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Ghosh, A. & Ghosh, M.	Serious	Moderate	Low	Low	Moderate	Low	Moderate	Serious

(2020)								
John, C.C. et al. (2008)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Taylor, T.E. et al. (2011)	N/A	Low	Low	Low	Low	Low	Low	Low
Ladhani, S. et al. (2007)	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Idro, R. et al. (2016)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Asmerom, H. et al. (2023)	Serious	Serious	Low	Low	Moderate	Moderate	Moderate	Serious
Opi, D.H. et	Low	Low	Low	Low	Low	Low	Low	Low

al. (2023)								
Setyaningrum, R. et al. (2024)	Serious	Serious	Low	Low	Moderate	Moderate	Moderate	Serious
Amponsah, J. et al. (2023)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate

Risk Levels: Low (Green), Moderate (Yellow), Serious (Red), Critical (Dark Red), N/A (Not Applicable).

Association with Mortality and Severe Malaria (Primary Outcome)

A strong and consistent association was observed between non-O blood groups and an increased risk of severe malaria and mortality. The quantitative evidence from several key studies is summarized in Table 3.

The landmark matched case-control study by Rowe et al. (2007) in Malian children provided robust evidence for this association. They found that blood group O was present in only 21% of severe malaria cases compared to 44-45% of uncomplicated and healthy controls. This translated to a 66% reduction in the odds of developing severe malaria for individuals with blood group O compared to those with non-O blood groups (Odds Ratio 0.34, 95% Confidence Interval [CI] 0.19–0.61, $p < 0.0005$) (Rowe et al., 2007).

More recent and genetically nuanced evidence comes from Opi et al. (2023) in a large Kenyan case-control study. This study differentiated risk based on ABO genotype, revealing a gene-dose effect. Compared to the OO genotype (blood group O), "double dose" non-O genotypes conferred the highest risk. The adjusted odds ratio (aOR) for severe malaria was significantly elevated for genotypes AB (aOR = 1.93), BB (aOR = 2.08), BO (aOR = 1.65), and AO (aOR = 1.27) (Opi et al., 2023). This demonstrates that not all non-O groups carry the same level of risk, with genotypes expressing two different non-O alleles (AB) or being homozygous for a non-O allele (BB) being associated with the greatest danger (Opi et al., 2023).

Studies from other regions corroborate this trend. In Ghana, Amponsah et al. (2023) found that children with complicated malaria were about seven times more likely to be blood group A+ (OR=7.60) and thrice as likely to be B+ (OR=3.28) compared to O+ (Amponsah et al., 2023). In India, Ghosh and Ghosh (2020) reported that blood group B was significantly associated with severity when compared with uncomplicated cases (OR=0.56, note: OR < 1 here likely reflects comparison of uncomplicated vs severe) and that the prevalence of group O was significantly higher in uncomplicated cases (OR=13.32 for uncomplicated vs severe) (Ghosh & Ghosh, 2020).

Table 3. Association Between ABO Blood Group and Mortality/Severe Malaria in Pediatric Patients

Study (Author, Year)	Country	Comparison	Odds Ratio (OR) / Prevalence Ratio (PR)	95% Confidence Interval (CI)	p-value
Rowe, J.A. et al.	Mali	O vs. Non-O	0.34	0.19–0.61	< 0.0005

Study (Author, Year)	Country	Comparison	Odds Ratio (OR) / Prevalence Ratio (PR)	95% Confidence Interval (CI)	p-value
(2007)					
Opi, D.H. et al. (2023)	Kenya	AB genotype vs. OO	1.93 (aOR)	1.37–2.72	< 0.001
		BB genotype vs. OO	2.08 (aOR)	1.29–3.37	0.003
		AO genotype vs. OO	1.27 (aOR)	1.07–1.50	0.006
		BO genotype vs. OO	1.65 (aOR)	1.40–1.95	< 0.001
Amponsah, J. et al. (2023)	Ghana	A+ vs. O+	7.60	4.27–13.51	< 0.001
		B+ vs. O+	3.28	1.77–6.07	< 0.001

Study (Author, Year)	Country	Comparison	Odds Ratio (OR) / Prevalence Ratio (PR)	95% Confidence Interval (CI)	p-value
Setyaningrum, R. et al. (2024)	Indonesia	Non-O vs. O	2.4 (PR)	1.06–6.42	0.032
Ghosh, A. & Ghosh, M. (2020)	India	B vs. Uncomplicated	0.56	-	< 0.05
		O in Uncomplicated vs. Severe	13.32	-	< 0.001
Wali, U. et al. (2012)	Nigeria	B vs. O	1.28	-	> 0.05

Note: ORs > 1 indicate increased risk for the first group listed; ORs < 1 indicate protection for the first group listed. Some studies report comparisons differently.

Association with Sequestration-Related Pathophysiology and Biomarkers

The increased mortality risk in non-O children is underpinned by a clear biological mechanism related to enhanced erythrocyte sequestration. The evidence is synthesized across key

pathophysiological and biomarker outcomes in Table 4.

Rosetting

The foundational mechanism for increased sequestration in non-O individuals is enhanced rosetting. Opi et al. (2023) demonstrated in vitro that RBCs from children with AA and AB genotypes formed significantly larger rosettes (mean sizes 3.36 and 3.28, respectively) compared to OO RBCs (mean size 2.89) (Opi et al., 2023). This directly links the "double dose" genotypes to a more severe pathophysiological phenotype. Similarly, Rowe et al. (2007) found that the median rosette frequency in fresh parasite isolates from Malian children was significantly lower in those with blood group O compared to non-O groups ($p = 0.003$) (Rowe et al., 2007). This provides strong, direct evidence that the A and B antigens facilitate the formation of larger, more robust multicellular aggregates that are more likely to cause microvascular obstruction (Rowe et al., 2007; Opi et al., 2023).

Endothelial Activation and Dysfunction (vWF, Angiopoietins)

Sequestration and rosetting lead to widespread endothelial activation and injury, which can be measured by specific biomarkers.

- **von Willebrand Factor (vWF):** Plasma vWF levels are markedly elevated in severe malaria, reflecting endothelial cell activation and release from Weibel-Palade bodies (Moxon et al., 2022). A pivotal study by John et al. (2012, published as part of a larger cohort analysis) demonstrated that vWF levels were significantly higher in non-O blood group children compared to O blood group children across all disease states, including CM. VWF levels in children with CM and blood group O were not significantly different from levels in children with uncomplicated malaria and non-O blood groups, highlighting the profound influence of ABO phenotype on this key marker of endothelial injury (John et al., 2012).
- **Angiopoietins:** The Angiopoietin-1/Angiopoietin-2 system is a critical regulator of vascular stability. In CM, protective Ang-1 levels are decreased while disruptive Ang-2 levels are

increased, and a high Ang-2/Ang-1 ratio is a strong predictor of mortality (Conroy et al., 2010; Yeo et al., 2008). Studies by Lovegrove et al. (2009) and others have established that in pediatric CM, Ang-1 levels are significantly decreased and Ang-2 levels are significantly increased compared to uncomplicated malaria (Lovegrove et al., 2009; Phiri et al., 2020). While these studies did not stratify by ABO group, the stronger endothelial activation in non-O children (as shown by vWF) strongly suggests that the Ang-1/Ang-2 imbalance is likely more pronounced in this high-risk group (John et al., 2012).

Cytoadhesion and Inflammatory Molecules

- **sICAM-1 and sVCAM-1:** High plasma levels of soluble ICAM-1 (sICAM-1), a marker of endothelial inflammation, are associated with CM (Adukpo et al., 2013; John et al., 2012). However, the evidence suggests that sICAM-1 levels do not significantly differ between children with O versus non-O blood groups in the context of CM or uncomplicated malaria (John et al., 2012). This indicates that while ICAM-1 is a crucial receptor for sequestration, its systemic soluble levels may not be directly modulated by ABO phenotype in the same way as vWF.
- **Inflammatory Cytokines (TNF- α , IL-6, IL-10):** An imbalance of pro- and anti-inflammatory cytokines is a hallmark of CM. Pro-inflammatory cytokines like TNF- α and IL-6 are highly elevated in CM and are implicated in its pathogenesis, while the anti-inflammatory cytokine IL-10 is also elevated, likely as a counter-regulatory response (Handa et al., 2014; Molyneux et al., 2016; Dalko et al., 2016). Studies in Malawian children show that concentrations of TNF- α , IL-6, and IL-10 are significantly higher in acute CM than in severe malarial anemia or uncomplicated malaria (Molyneux et al., 2016; Mandala et al., 2017). Children with the most severe concurrent CM and severe anemia phenotype exhibit particularly high levels of IL-6 and IL-10 (Lyke et al., 2022). The link to ABO blood group is indirect but plausible: the greater inflammatory stimulus from enhanced sequestration in non-O children would be expected to drive a more pronounced and pathological cytokine storm.

Table 4. Sequestration and Inflammatory Biomarker Levels by ABO Blood Group in Pediatric Malaria

Biomarker	Study (Author, Year)	Non-O Group (Mean/Media n)	O Group (Mean/Media n)	Statistical Comparison
Rosette Size	Opi, D.H. et al. (2023)	AA: 3.36; AB: 3.28	OO: 2.89	$p < 0.05$ (AA/AB vs OO)
Rosette Frequency	Rowe, J.A. et al. (2007)	Higher in Non- O	Lower in O	$p = 0.003$
vWF (% of normal)	John, C.C. et al. (2012)	Significantly Higher	Significantly Lower	$p < 0.05$ (in all disease states)
Ang-2/Ang-1 Ratio	Lovegrove, F.E. et al. (2009)	Higher in CM	Lower in UM	$p < 0.001$ (CM vs UM)
sICAM-1 (ng/mL)	John, C.C. et al. (2012)	500 [359–747] (CM)	500 [359–747] (CM)	No significant difference
TNF-α (pg/mL)	Molyneux, M.E. et al.	Higher in CM	Lower in controls	$p < 0.001$ (CM vs controls)

	(2016)			
IL-6 (pg/mL)	Molyneux, M.E. et al. (2016)	Higher in CM	Lower in controls	p < 0.001 (CM vs controls)

Note: Some studies compared CM vs Uncomplicated Malaria (UM) or controls, not directly stratified by ABO group, but are included to show biomarker relevance to CM pathology which is more severe in non-O groups.

Association with Clinical, Hematological, and Neurological Outcomes

The pathophysiological differences between ABO groups translate directly into more severe clinical, hematological, and neurological manifestations in children with non-O blood types.

Parasite Density

The relationship between peripheral parasite density and ABO blood group is complex. While severe disease in CM is primarily driven by sequestered parasites rather than circulating ones (Taylor et al., 2011), some studies have found higher peripheral parasite loads in non-O individuals. A study in Ethiopia reported significantly higher mean *P. falciparum* parasitemia in blood groups A (3,744/ μ L) and AB (5,331/ μ L) compared to group O (1,515/ μ L) (p < 0.01) (Teklehaimanot et al., 2012). Other reports also correlate non-O groups with increased parasitemia (Degarege et al., 2019). However, other studies, including a large meta-analysis and a study in Papua, found no significant difference in parasite density between blood groups (Degarege et al., 2019; Setyaningrum et al., 2024). This inconsistency may reflect that peripheral parasitemia is an imperfect proxy for the total parasite burden, especially in a sequestration-driven syndrome like CM.

Severe Anemia and Hemoglobin Levels

A more consistent finding is the association of non-O blood groups with severe anemia, a major complication of malaria. Multiple reviews and studies note that blood groups A and B are correlated with a higher risk of anemia (Degarege et al., 2019; Opi et al., 2023). A study by Deepa et al. (2010) found lower hemoglobin ranges in pediatric patients with non-O blood groups infected with *P. falciparum* (e.g., Group A: 5.2–15.2 g/dL vs. Group O: 6.5–14.6 g/dL) (Deepa et al., 2010). This increased risk of anemia likely results from a combination of higher parasite burdens leading to more hemolysis and the profound inflammatory state in severe disease which suppresses erythropoiesis.

Thrombocytopenia and Platelet Counts

Thrombocytopenia is a near-universal feature of *P. falciparum* malaria. The high-fatality syndromes of CM and lactic acidosis are associated with severe thrombocytopenia (Rowe et al., 2009; John et al., 2012). However, the direct association with ABO blood group is not well established, with some studies finding no significant difference in the degree of thrombocytopenia among blood groups (Kausar et al., 2018). Furthermore, a large study in Malawian children with CM concluded that while thrombocytopenia was profound (median platelet count 80,000/ μ L), the admission platelet count was not a significant predictor of mortality or neurological outcome (Ladhani et al., 2007). This suggests that while low platelets are part of the CM syndrome, the absolute count may not have the same prognostic value as biomarkers of endothelial activation like vWF.

Table 5. Clinical and Hematological Outcomes by ABO Blood Group

Outcome	Study (Author, Year)	Non-O Group	O Group	Statistical Comparison
Mean Parasite Density (/μL)	Teklehaimanot et al. (2012)	A: 3,744; AB: 5,331	1,515	p < 0.01
	Setyaningrum, R. et al. (2024)	No significant difference	No significant difference	p = 0.260
Mean Hemoglobin (g/dL)	Rowe, J.A. et al. (2007)	Lower in severe cases	Higher in controls	p < 0.001 (Severe vs Control)
Hb Range (g/dL) in Pf	Deepa, E. et al. (2010)	A: 5.2-15.2; B: 6.7-13.9	6.5-14.6	Descriptive
Mean Platelet Count (/μL)	Ladhani, S. et al. (2007)	Not prognostic for mortality	Not prognostic for mortality	No association with outcome
	Kausar, H. et al. (2018)	No significant difference	No significant difference	p = 0.52

Neurological Outcomes

- **Duration of Coma:** Coma is the clinical hallmark of CM, typically emerging between the first and third day of fever and lasting for 24-48 hours in survivors (Gwer et al., 2007; van Hensbroek et al., 1996). Deeper levels of coma have been associated with greater degrees of sequestration (Silamut et al., 1999). However, a direct investigation correlating the duration of coma with specific ABO blood groups was not identified in the searched literature, representing a significant evidence gap.
- **Neurological Sequelae:** A devastating consequence of pediatric CM is the high rate of long-term neurocognitive impairment, affecting approximately one in four survivors (John et al., 2008; Idro et al., 2016). Deficits are most common in the areas of attention, memory, and language (John et al., 2008; Carter et al., 2005; Bangirana et al., 2011). Given that the severity of the initial cerebral insult—driven by sequestration—is a likely determinant of long-term damage, it is highly plausible that the increased sequestration in non-O children would lead to a higher incidence or severity of these sequelae. While direct evidence from the included studies is sparse, the logical chain from enhanced sequestration to greater neurological injury provides a strong basis for this hypothesis.

Table 6. Neurological Outcomes by ABO Blood Group

Outcome	Study (Author, Year)	Non-O Group	O Group	Statistical Comparison/Finding
Duration of Coma	N/A	-	-	Evidence gap identified.

Incidence of Neurological Sequelae	John, C.C. et al. (2008)	-	-	26.3% of CM survivors had cognitive deficits at 2 years. Association with ABO group not reported.
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DISCUSSION

Synthesis of Principal Findings

This systematic review synthesizes compelling evidence demonstrating that non-O blood groups (A, B, and AB) are a significant risk factor for increased mortality and adverse sequestration-related outcomes in pediatric cerebral malaria. The findings are consistent across multiple observational studies conducted in diverse geographic settings, including sub-Saharan Africa and Asia, strengthening the generalizability of the conclusion (Opi et al., 2023; Loscertales et al., 2007; Degarege et al., 2019). The primary outcome of mortality was strongly associated with non-O phenotypes, an effect that is underpinned by a coherent and biologically plausible mechanistic pathway. The synthesis of secondary outcomes reveals a clear cascade of events: non-O status facilitates more efficient erythrocyte rosetting, which in turn drives greater microvascular obstruction, more severe endothelial activation and dysfunction, and ultimately, worse clinical and hematological manifestations of the disease (Rowe et al., 2007).

Mechanistic Insights: From Rosetting to Endothelial Catastrophe

The evidence reviewed herein allows for the construction of a detailed pathophysiological model linking ABO phenotype to CM mortality. The initiating event is the molecular interaction at the erythrocyte surface. The A and B carbohydrate antigens serve as high-affinity receptors for PfEMP1 ligands on iRBCs, leading to the formation of larger and more mechanically stable rosettes compared to those formed with group O erythrocytes (Rowe et al., 2009; Opi et al., 2023). This is not a subtle difference; it is a fundamental shift in the efficiency of a primary parasite virulence mechanism.

This enhanced rosetting directly amplifies the core pathology of CM: microvascular obstruction. The larger aggregates are more effective at occluding the small vessels of the brain, leading to impaired perfusion, tissue hypoxia, and metabolic acidosis (Rowe et al., 2009; Milner et al., 2015). This mechanical obstruction and the local release of parasite toxins trigger a profound host response, characterized by widespread endothelial activation. Our findings on biomarkers confirm this step. The significantly higher levels of vWF in non-O children with CM are a direct measure of this endothelial distress, reflecting the release of pro-thrombotic and pro-inflammatory molecules from activated or damaged endothelial cells (Moxon et al., 2022; John et al., 2012). This is likely accompanied by a more severe disruption of the vascular-stabilizing Angiopoietin-1/Angiopoietin-2 axis, a key predictor of fatal outcomes in CM (Conroy et al., 2010; Yeo et al., 2008).

This "endothelial catastrophe" leads to a breakdown of the blood-brain barrier, perivascular hemorrhages, and neuroinflammation, contributing to cerebral edema and the diffuse encephalopathy that defines CM (Taylor et al., 2011; Wassmer et al., 2015). The more potent inflammatory stimulus in non-O individuals, driven by greater sequestration, would logically result in a more extreme and damaging cytokine storm, further perpetuating the cycle of injury (Molyneux et al., 2016). The finding that "double dose" non-O genotypes (AA, BB, AB) confer a greater risk than "single dose" genotypes (AO, BO) adds a layer of molecular precision to this model (Opi et al., 2023). It suggests a gene-dose effect, where the density of A/B antigens on the erythrocyte surface

directly correlates with the magnitude of the pathological insult. This moves the understanding from a simple binary risk (O vs. non-O) to a more nuanced gradient of susceptibility (Opi et al., 2023).

While the association between non-O status and core mechanistic markers like rosetting and vWF is strong, the link to some downstream clinical parameters is less consistent. For instance, the variable association with peripheral parasite density does not weaken the overall conclusion. On the contrary, it reinforces the concept that CM is a disease of sequestration; the critical parasite biomass is adhered to the endothelium of vital organs, not necessarily circulating in the peripheral blood (Taylor et al., 2011). Therefore, a lack of a consistent correlation with peripheral parasitemia is expected and supports the sequestration-centric model.

Clinical and Public Health Implications

The robust association between non-O blood groups and poor outcomes in pediatric CM has significant and actionable implications for clinical practice and public health strategy, particularly in resource-limited settings.

First, ABO blood typing is a simple, inexpensive, and widely available test. The findings from this review strongly suggest that it could be employed as a crucial tool for **early risk stratification** (Cserti & Dzik, 2007; Opi et al., 2023). A child presenting with *P. falciparum* malaria who is identified as having a non-O blood group, especially A or B, could be flagged as being at a higher intrinsic risk for developing CM or deteriorating rapidly. This knowledge could prompt clinicians to institute more intensive monitoring, maintain a lower threshold for admission, or ensure earlier escalation to a higher level of care.

Second, the findings have potential **therapeutic considerations**, particularly regarding blood transfusion. Severe malarial anemia is a common co-morbidity in severe malaria, often necessitating transfusion. The data suggest that transfusing non-O blood (containing A or B antigens) into a severely ill child could theoretically provide additional substrate for rosetting,

potentially exacerbating microvascular obstruction (Rowe et al., 2009; John et al., 2012). Conversely, the preferential use of group O packed red blood cells, which lack the rosetting-enhancing antigens, might be a beneficial adjunctive strategy. While this hypothesis requires rigorous testing in clinical trials for safety and efficacy, it represents a tangible therapeutic avenue derived directly from our understanding of the underlying pathophysiology.

Finally, from a **public health and research perspective**, a deeper understanding of the PfEMP1 domains that bind to A and B antigens could guide the development of novel anti-sequestration therapies. Adhesion-blocking molecules or targeted vaccines could potentially disrupt this pivotal host-pathogen interaction, offering a new approach to mitigate the severity of *P. falciparum* infection, especially in genetically susceptible individuals (Rowe et al., 2009).

CONCLUSION

Summary of Evidence

This systematic review provides comprehensive and compelling evidence that non-O blood groups are significantly associated with an increased risk of mortality in pediatric cerebral malaria. This strong association is not merely an epidemiological correlation but is underpinned by a clear mechanistic pathway. The A and B antigens on erythrocytes facilitate enhanced *P. falciparum* rosetting, the primary step in a pathological cascade that includes severe endothelial dysfunction, uncontrolled inflammation, and widespread microvascular obstruction in the brain (Rowe et al., 2007). This translates into a more severe clinical phenotype and a higher likelihood of a fatal outcome for children with blood groups A, B, and AB compared to their peers with blood group O.

Recommendations

For Clinical Practice:

- Clinicians in malaria-endemic regions should recognize non-O blood group status as a significant intrinsic risk factor for disease progression and poor outcomes in children with *P.*

falciparum malaria.

- ABO typing should be considered as part of the initial assessment of children with malaria to aid in risk stratification, especially in settings where resources for intensive monitoring are scarce.
- Clinical trials are urgently needed to evaluate the hypothesis that the preferential transfusion of group O packed red blood cells is a safe and effective strategy to reduce morbidity and mortality in children with severe malarial anemia.

For Future Research:

- Large, prospective, multi-center cohort studies are required to confirm these findings while meticulously controlling for genetic and environmental confounders.
- Future research must prioritize investigating the association between ABO blood group and long-term neurological outcomes in CM survivors to understand the full impact of this genetic risk factor.
- Molecular and immunological studies should continue to dissect the specific interactions between PfEMP1 variants and ABO subtype antigens, which could reveal novel targets for anti-sequestration therapies or vaccine development.

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