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Prognostic models for the clinical management of malaria and its complications: a systematic review

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Abstract

 Objective: Malaria infection could result in severe disease with high mortality. Prognostic models and scores predicting severity of infection, complications and mortality could help clinicians prioritise patients. We conducted a systematic review to assess the various models that have been produced to predict disease severity and mortality of malaria.

Design: A systematic review

Methods: We searched the MEDLINE online databases for articles published up to 15th of February on models which used at least 2 points (or variables) of patient data.

Primary Outcomes: Prediction of disease severity; potential development of complications (including coma or cerebral malaria; shock; acidosis; severe anaemia; acute kidney injury; hypoglycaemia; respiratory failure and sepsis) and mortality in patients with malaria infection.

Results: A total of 537 articles were screened and 24 articles were retained describing 24 models/scores of interests. Three of the articles described models predicting complications of malaria (severe anaemia in children and development of sepsis); fifteen described original models predicting mortality in severe malaria; three described models predicting mortality in different contexts but adapted and validated to predict mortality in malaria; and three articles described models predicting severity of the disease.

For the models predicting mortality, all the models had neurologic dysfunction as a predictor; in children, half of the models contained hypoglycaemia and respiratory failure as a predictor meanwhile, six out of the nine models in adults had respiratory failure as a clinical predictor. Acidosis, renal failure and shock were also common predictors of mortality.

Conclusion: Evidence is lacking on the generalisability of most of these models due lack of external validation. Emphasis should be placed on external validation of existing models and publication of the findings of their use in clinical settings to guide clinicians on management options depending on the priorities of their patients.

Key words: malaria; prognostic model; prognostic score; mortality

Article Summary:

Strengths and limitations of this review:

This review is the first to comprehensively summarise the various prognostic models that have been produced to identify complications, severity and risk of mortality in patients with severe malaria.

The review covers prognostic models produced worldwide and for all the various malaria species.

The review reduced the risk of bias by using an independent review process for the screening of potential articles and the extraction of data.

Considering the wide variety of statistical methods used to generate and validate these models, there is the risk of heterogeneity in interpretation of the results.

Introduction

Malaria is a disease caused by infection with a protozoan parasite of the genus *Plasmodium*. The most relevant of these species is *Plasmodium falciparum* as it causes most deaths from the disease ¹. Another species of relevance is *Plasmodium vivax* which is predominantly found in Asia and has a wider distribution ². This parasitic infection can result in severe disease and is associated with a high mortality. In about 108 countries where the transmission of the disease still occurs, an estimated 429,000 people died in 2015 ³.

The incidence of malaria cases has decreased by 41% worldwide in the past ten years, with about 17 countries in Latin America and the Middle East reporting no new cases of malaria over this period ^{3 4}. There are however concerns that the fight against malaria might be slowed down by an overemphasis on prevention over treatment ⁵.

Treatment and clinical management of malaria is made difficult due to potential evolution of simple infections into life-threatening severe disease; the multi-organ affection of severe disease; the dilemma of when to admit to intensive care units (ICU) considering limited resources and the occurrence of concomitant sepsis infection with malaria ⁶ ⁷. Some of these issues can be addressed with the help of guidelines; scores or models that could help clinicians predict the occurrence of severe disease and complications in order to act appropriately.

We therefore conducted this review to systematically assess the various predictive models or scores available to guide clinicians in the management of severe malaria, whether these models have been validated and if there is any evidence that they are being successfully used in the clinical setting.

Methods

Institutional review board approval and informed consent were not required for this systematic review. We reported our findings according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Appendix 1).

Search strategy and selection criteria

We searched MEDLINE using a tailored search strategy (Appendix 2) to identify all the relevant titles and abstracts of studies (randomised control trials, cohort, cross-sectional and case-control studies)

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published in English from inception of the database up to the 15th of February 2019, that reported predictive/prognostic scores or models that could be used in the management of malaria. These included:

- Scores/models that predicted the severity of disease as this could guide clinicians decisions to admit for intensive care management or the use of parenteral treatment;
- Scores/models that predicted the potential development of complications (including coma or cerebral malaria; shock; acidosis; severe anaemia; acute kidney injury; hypoglycaemia; respiratory failure and sepsis);
- Scores/models that predicted mortality in patients with malaria infection.

The main keywords in the search strategy included: "prognostic model/score", "predictive model/score" and "predictive value of tests" coupled with "malaria", "plasmodium", "anti-malarials", "malaria falciparum", "malaria vivax" and "clinical malaria". Grey literature was obtained by identifying similar papers from the references of eligible papers.

We excluded any duplicate studies, editorials, systematic reviews, case studies, conference abstracts, unpublished studies and expert commentaries. For studies with more than one publication of findings, we selected the most recent publication.

We also excluded studies which contained models or scores that were aimed at the diagnosis of malaria as we intend to limit the scope of the study to only models that could be used to predict severity, mortality or risk of complications – that could guide clinicians in their management options.

Two independent reviewers (TN and BST) screened the titles and abstracts for compliance to the aforementioned inclusion and exclusion criteria and any conflicts were settled by mutual agreement. Articles considered to have data relevant to the topic were assessed in detail and the references cited in these publications were searched to identify further publications.

Data extraction

Data extraction sheets which were prepared prior to screening were used by the two independent reviewers to obtain the following details for inclusion into the final review: Last name of first author; date of publication; period of patient recruitment and/or follow-up; country of study; sample size; age group; type of predictive model; name of model; method of validation; diagnostic properties of model and evidence of external validation or use in clinical setting.

Definitions

By prognostic/predictive model, we mean a statistical tool which uses at least 2 points (or variables) of patient data to predict a specific clinical outcome ⁸. Prognostic models applied in clinical settings are usually used at the discretion of physicians for accurate future predictions based on characteristics

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gathered in the present ⁸⁹. The information found in prognostic models is usually specific to the patients' characteristics rather than the disease or treatment and includes: prediction of chance or the duration of survival; classification of patients into risk groups; and prediction of clinical events related to the treatment the patient is receiving ¹⁰.

For models that used the area under the curve (AUC) or c-statistic to assess discrimination, the following classification was used: 0.90 - 1 - excellent; 0.80 - 0.90 - good; 0.70 - 0.80 - fair; 0.60 - 0.70 - poor and $0.50 - 0.60 - \text{very poor discriminative properties}^{11}$.

Data synthesis and analysis

We assessed and discussed the selected studies qualitatively to describe the diagnostic properties of the models proposed in the study, their intended purpose and evidence of use of the model in other clinical settings.

We further divided the models into various categories: models used to predict a potential complication of severe malaria; models used to predict mortality as an outcome and models used to predict severity of malaria infection.

Assessment of methodological quality and risk of bias

The quality of studies and the risk of bias were assessed by the two independent reviewers using the Quality Assessment Tool for Observational Studies of the National Health Institute/National Heart, Lung, and Blood Institute (Appendix 3a and 3b). Any disagreements were handled by mutual agreement.

Patient and public involvement:

Patients and the public were not involved in the design and conduction of this review.

Results

A total of 537 articles were identified by the electronic search of the database and grey literature. The titles and abstracts of these articles were screened to retain 58 articles for full text review. These were then evaluated according to the inclusion criteria and 24 articles were identified describing 24 models/scores of interests; after eliminating 23 irrelevant articles, 9 articles which used only one variable to predict an outcome and two articles describing models in other languages (Figure 1). Three of the articles described models predicting complications of malaria ^{7 12 13}; fifteen described original models predicting mortality in severe malaria ¹⁴⁻²⁸; three described models predicting mortality in different contexts but adapted and validated to predict mortality in malaria ²⁹⁻³¹; and three articles described models predicting severity of the disease ³²⁻³⁴.

Using the Quality Assessment Tools for observational studies of the National Health Institute/National Heart, Lung, and Blood Institute; 22 of the articles were of "good quality" (score of 10 - 14 in quality assessment tool) $^{7 12 \ 14 \ 16 - 30 \ 32 - 35}$ while the other two were of "fair quality" (score of 7 - 9 in quality assessment tool) $^{13 \ 15}$ (Appendix 3a and 3b).

The general characteristics of the studies included in the review are summarised in Tables 1, 2 and 3.

Models predicting the risk of complications in malaria infection

Two models predicted the risk of developing severe anaemia in children admitted for severe malaria ¹² ¹³.

Webber *et al* ¹³ in 1997 conducted a study to predict the risk of severe anaemia (packed cell volume < 15%) in children with severe malaria in the Gambia using logistic regression analysis. This model was not validated, and the two predictors identified were pallor of the conjunctiva and pallor of the palms. Similarly, Brickley *et al* ¹² in 2017 conducted a study in Tanzania and produced a model in children aged 0 – 4 years using clinical data and biomarkers collected at birth; which was used to prognosticate the risk of these children developing severe anaemia if they were infected with malaria. Severe anaemia was described as a Hb concentration < 50g/dl and predictors in the model identified after Cox proportional hazards analysis were sex, gravidity, transmission season at delivery, and bed net possession. The model was internally validated using bootstrapping with a modest predictive ability (C-index of 0.77); and the authors postulated that this model could help identify a high-risk group of infants at birth who could be selected for targeted malaria intervention. There is no evidence from this review that both models have been externally validated and are being used in clinical settings.

In 2018, Njim *et al*⁷ described a prognostic model for clinical use to predict the risk of sepsis development amongst adult patients (> 16 years old) admitted for severe falciparum malaria in Southeast Asia. They used data from SEQUAMAT (South East Asian Quinine Artesunate Malaria Trial) – a large randomised control trial (RCT) conducted to determine the benefits of intravenous artesunate over quinine treatment for severe malaria. They used a multivariable logistic regression approach with internal validation using bootstrapping to generate a prognostic model with modest discriminative abilities (AUC: 0.789) with the following predictive variables: female sex, high blood urea nitrogen, high plasma anion gap, respiratory distress, shock on admission, high parasitaemia, coma and jaundice. The model has not been externally validated and there is no evidence of use in clinical settings.

Models predicting mortality in severe malaria

Models predicting mortality in paediatric severe malaria

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Ten articles described models that predicted mortality in paediatric severe malaria ¹⁴ ¹⁸⁻²¹ ²⁵ ²⁶ ²⁸⁻³⁰. Three articles described models which predicted mortality in paediatric patients with cerebral malaria ¹⁴ ¹⁹ ²⁵; two articles described models generated to assess mortality in different conditions that were validated for use in the present studies ²⁹ ³⁰; and five articles described original models predicting the risk of mortality in children with severe malaria ¹⁸ ²⁰ ²¹ ²⁶ ²⁸.

Models predicting mortality in paediatric cerebral malaria

Molyneux *et al* ²⁵ in 1989 conducted a study amongst 131 comatose Malawian children with severe malaria to determine the prognostic factors for death in these patients. The authors derived a "bedside prognostic index" with: blood glucose $\leq 2.2 \text{ mmol/L}$; parasitaemia > 106 ring forms/µL; white blood cell count > 15x10/L; age ≤ 3 years; coma score (modification of the Glasgow coma score) = 0; absent corneal reflexes; signs of decerebration and convulsions; as predictors of mortality with each predictor assigned a score of 1. Individuals with a score ≥ 4 were more likely to die. This score was calculated only using univariable analysis and internal and external validation were not done.

In 1997 in Gambia, Jaffar *et al* ¹⁹ performed a retrospective analysis on data obtained from a randomised control trial during which artemether was compared with quinine and a monoclonal antibody against tumour necrosis factor (TNF) compared with a placebo in patients with cerebral malaria. They used this data to identify predictors of mortality in cerebral malaria using a multivariable logistic regression model. A cold periphery, a coma score of either 0 or 1 (assessed using the Blantyre coma scale), and hypoglycaemia were found to be present at admission in 90% of the children who died. This model was not validated.

Conroy *et al* ¹⁴ in 2012 conducted a study amongst 155 children aged 8 months – 14 years in Malawi to determine predictors of mortality in cerebral malaria. They used a multivariable logistic regression model containing clinical parameters and biomarkers with a modest discriminative ability (C-index of 0.79) after internal validation; which contained the following variables: age, Blantyre coma score, respiratory distress, severe anaemia, angiopoietin-1, angiopoietin-2 and sTie-2 levels. The model was not externally validated.

Original models predicting mortality in paediatric severe malaria

Krishna *et al*²⁰ in 1994 conducted a study in the Gambia to predict mortality in children aged 8 months to 14 years. They used a multivariable logistic regression model internally validated using the Wald statistic to determine that the coma score (using the Blantyre coma scale), whole blood lactate/glucose ratio and TNF level were the best predictors of death.

In 1995, Marsh *et al*²¹ studied 1844 children in Kenya to determine predictors of life-threatening malaria (risk of death) using a multivariable logistic regression model without any validation. They

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determined that impaired consciousness (assessed using the Blantyre coma scale), hypoglycaemia, respiratory distress and jaundice could correctly predict 84.4% of deaths in the sample population.

In 2005, Newton *et al* ²⁶ conducted a study to assess the prognostic value of measures of acid/base balance in paediatric falciparum malaria. They examined 14,605 children in Malawi (Blantyre), Kenya (Kilifi) and Ghana (Kumasi) where they determined that deep breathing, Blantyre Coma Score of 2, inability to sit, and weight-for-age Z score were independent predictors of mortality in all the three sites. Discrimination of the model was performed by calculating the area under the receiver operating curve (AUROC). After addition of laboratory data to these models – hypoglycaemia, base excess and lactate concentrations, the c-statistics obtained were 0.88 (Blantyre), 0.87 (Kilifi) and 0.83 (Kumasi) denoting good discriminative properties of the models.

Helbok *et al* ¹⁸ in 2009 produced the the Lambarene Organ Dysfunction Score (LODS) which combined three variables: coma, prostration, and deep breathing to generate a model using multivariable logistic regression which predicted death in African children – Banjul (Gambia), Blantyre (Malawi), Kilifi (Kenya), Kumasi (Ghana), and Lambarene and Libreville (Gabon); who were admitted for severe falciparum malaria. Each component of the model was assigned a score of 1 and a LODS of 3 at admission had a 98% specificity and 25% sensitivity in predicting death. Meanwhile a LODS \geq 1 had a sensitivity of 85% and a specificity of 63%. The model had good discriminative properties with an AUC of 0.80 (95% CI: 0.79 – 0.82). In 2015, Conroy *et al* ²⁹ externally validated this model amongst 1589 Ugandan children. The model showed good discriminative properties with an AUC of 0.898.

Similarly, in 2012, von Seidlein *et al* ²⁸ conducted an analysis of data from a RCT carried out in several African countries (Gambia, Mozambique, Nigeria, Rwanda, Kenya, DRC, Tanzania, Ghana and Uganda) to generate a model for predicting mortality from severe falciparum malaria using multivariable logistic regression analysis and internally validated by AUROC analysis. After analysis of data from 5426 children, base deficit, impaired consciousness (assessed using the Blantyre Coma Score), convulsions, elevated blood urea, and underlying chronic illness were identified in the model to predict mortality with a good discriminative ability – AUROC: 0.85 (95% CI: 0.83 - 0.87).

Models predicting mortality validated for use in severe malaria in children

As described above, Conroy *et al*²⁹ externally validated the LODS model amongst 1589 Ugandan children. The authors further externally validated two other scores: the SICK (Signs of Inflammation in Children that Kill) score which was developed in India as a practical triage tool using variables related to the systemic inflammatory response syndrome, with data collected from 1,099 children in 2003 admitted for any paediatric illness ³⁶; and the PEDIA (Pediatric Early Death Index for Africa) score which was developed to predict early death amongst 8091 children in Kenya in 2003 admitted for paediatric illnesses ³⁷. The original SICK score containing the following variables: altered

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consciousness, temperature, heart rate, respiratory rate, systolic blood pressure, capillary refill time and age; had good discriminative properties with an AUC of 0.887³⁶. Externally validated against this cohort of 1589 children, the score maintained its good discriminative properties with an AUC of 0.846. Similarly, the PEDIA score which originally had excellent discriminative properties with an AUC of 0.93³⁷ had good discriminative properties (AUC: 0.896) when externally validated on the cohort of 1589 Ugandan children²⁹. The original PEDIA score contained Kwashiorkor, jaundice, subcostal indrawing, prostration (± seizures) and wasting as variables in the model. However, kwashiorkor was not included in the validation model as it was not measured amongst the Ugandan children.

In 2006, Gerardin *et al* ³⁰ validated the PRISM (Pediatric Risk of Mortality) model which was originally developed in 1988 by Pollack *et al* ³⁸ to reduce the number of physiologic variables required for paediatric intensive care unit death risk assessment. The model was developed from data of 1,227 patients with 105 deaths and contained 14 variables: systolic blood pressure, temperature, mental status, heart rate, dilatation of pupils, pH, total CO2, PCO2, arterial PaO2, serum glucose, potassium, urea, creatinine, white blood cells, prothrombin time, platelet count. The original score had excellent discriminative properties with an AUC of 0.92 ³⁸. Gerardin *et al* used a cohort of 311 Senegalese children admitted with severe malaria to externally validate this model. The model showed good discriminative properties in predicting death in children with severe malaria – AUC: 0.86 (95% CI: 0.81–0.90) ³⁰.

Models predicting mortality in adult severe malaria

There were eight articles assessing models that predicted mortality in adult severe malaria ^{15-17 22-24 26} ³⁵.

In 1995, Wilairatana *et al* ³⁵ used the APACHE II score (the acute physiology and chronic health evaluation system score commonly used in intensive care units) based on 12 physiologic variables - MAP, temperature, heart rate, respiratory rate, arterial pH, PaO2, haematocrit, WBC count, creatinine, sodium, potassium and Glasgow coma score to predict the risk of mortality in adult patients with cerebral malaria in Thailand. The score was able to predict mortality with a 95.8% accuracy.

Dondorp *et al* ¹⁵ in 2004 created a model using logistic regression with laboratory data form 268 patients in Vietnam to determine the risk of mortality in adult patients with severe malaria. This model had a good discriminative value with an AUROC of 0.81. The laboratory variables associcated with mortality in this cohort were: plasma lactate, plasma creatinine and a strong anion gap. On the other hand, in 2007, Mishra *et al* ²² created the MSA (Malaria score for adults) and the MPS (Malaria prediction score) from a cohort of 212 patients in India to predict mortality in severe malaria. The MSA was an upgrade of the MPI which required laboratory data and included a small proportion of children. The clinical variables included in the MSA were: severe anaemia, acute renal failure,

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respiratory distress and cerebral malaria and had a sensitivity of 89.9% and a specificity of 70.6%. This model was validated by Santos *et al* ³⁹ among 59 patients with imported severe malaria in Portugal and was shown to have good discriminative properties – AUROC: 0.84; 95% CI: 0.70 - 0.98.

Similarly, Hanson *et al* ¹⁶ produced the coma acidosis malaria (CAM) score after using a logistic regression analysis on data previously collected from the SEQUAMAT. The authors proposed the use of the presence of a coma and base deficit to calculate a five-point score to predict mortality. The score had good discriminative properties with an AUROC of 0.81 (95% CI: 0.77 - 0.84). The same author used data from several cohort studies and RCTs carried out in Bangladesh, India, Indonesia, Vietnam and Myanmar to predict 48-hour survival and survival to discharge in patients with severe malaria ¹⁷. The model containing the variables: shock, oligo-anuria, dysglycaemia, respiratory rate, Glasgow coma score and fever could correctly predict 48 hour-survival in 99.4% of the patients and survival to discharge in 96.9% of patients.

Mohapatra *et al* ²⁴ in 2009 carried out a cohort study of 2089 patients in 2009, where they produced the Malaria severity score (MSS) to predict mortality in adult patients with severe falciparum malaria in India. They assessed seven organ systems: neurologic, renal, haematologic, hepatic, respiratory, cardiovascular, and metabolic organ systems; assigning a maximum score of 0 - 3 for each organ system. The model had excellent discriminative propertiens with an AUROC of 0.9. The authors also developed the GCRBS (Glasgow coma scale, creatinine, respiratory rate, bilirubin and systolic BP) score in 2014 as an alternative to other scores like the APACHE II score which was considered cumbersome ²³. The score had a sensitivity of 85.3% and a specificity of 95.6% in predicting a fatal outcome in severe malaria.

In 2013 in Thailand, Newton *et al*²⁷ conducted a retrospective analysis of 988 records with severe falciparum malaria to produce the MPI (Malaria prognostic index) validated using ROC curve analysis and internal validation by data splitting. The MPI contained the following variables: Glasgow coma scale, parasitaemia, plasma lactate, serum bilirubin, pigmented parasites and treatment with ACT and had excellent discriminative properties with an AUROC of 0.97.

Models predicting the severity of malaria

 The Multi-organ dysfunction score (MODS) which is an index used in severely ill patients admitted in intensive care units to determine the severity of their disease irrespective of the diagnosis $^{32 40}$. The score evaluates ten organ systems: heart, blood vessel, blood, respiratory system, metabolism, gastrointestinal system, liver, kidney and urinary tract, immune system, and central nervous system – giving a score of 1 - 5 for each system depending on the level of dysfunction of the system, with a minimum score of 10 and a maximum score of 50 ³³. Helbok *et al* assessed the use of this score to predict severity in a small cohort (n = 22) of adult patients with uncomplicated falciparum malaria ³³

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and in adults with severe malaria (n = 29) ³² in Thailand. The score was not validated in both studies but the authors showed that higher scores were correlated with symptom severity and duration of hospitalisation. In 2006, the authors used a simplified version of the score - Simplified MODS (sMODS); in a cohort of 485 children in Gabon to predict the level of severity of the disease with respect to the amout of disability the children suffered into categories: ability to walk unaided and ability to sit unaided ³⁴. The authors obtained an AUC of 0.92 (95% CI, 0.89–0.95) in predicting inability to walk \geq 48 hours for children with sMODS \geq 16 and an AUC of 0.90 (95% CI, 0.87–0.93) in predicting inability to sit unaided.

Discussion:

In this review, we report on the various prognostic models and scores produced to predict complications, mortality and severity of malaria infection. We showed that there were three models produced to predict the risk of developing complications from malaria infection, twelve models that predict mortality from severe malaria in children, nine models that predict mortality from severe malaria in adults and three models that predict disease severity in malaria. Seventeen of these models were internally validated while only seven have been externally validated. There is no published evidence that any of these models are routinely used in clinical settings.

There have been several prognostic models generated in literature, some of which have made their way into daily clinical practice. Prognostic models are particularly useful in diseases with dire outcomes. An example is meningitis where accurate diagnosis of the causative organism and patient stratification could lead to appropriate treatment and initiation of adequate supportive measures. Models have been produced to accurately differentiate tuberculous meningitis from other forms of pyogenic meningoencephalitis ⁴¹, to predict unfavourable outcomes in adults admitted for bacterial meningitis ⁴² and to determine mortality in patients admitted with meningitis six weeks after follow-up in a resource-limited setting ⁴³. Other commonly recognised prognostic scores used routinely in clinical settings include the APGAR score which is used at birth to predict the development of future neurological complications in children.

The models identified in this review that were used to predict mortality in children with severe malaria have similar clinical predictors. All the models had neurologic dysfunction based on either the Glasgow coma score, impaired consciousness, altered mental status, convulsions, decerabration or coma as a predictor. Similarly, in adults, all the models predicting mortality also had neurologic dysfuction as a predictor. Microvascular obstruction in capillaries of the brain due to direct sequestration of red blood cells infected with the malaria parasite lead to tissue hypoxia ⁴⁴. The effects of this sequestration and its sequelae in the brain can be directly visualised in both adults and children as retinopathy ^{14 44-46}. This leads to varied results with increased intracranial pressure more pronounced in children than in adults

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⁴⁴. With the increased oxygen demand associated with brain hypoxia and raised intracranial pressure, coma and brain dysfunction become an important predictor of mortality.

In children, half of the models predicting mortality had hypoglycaemia as a predictor ^{19-21 25 26 30}. Hypoglycaemia is usually implicated as a complication of severe malaria infection. This association has been said to be multifactorial ⁴⁷. Proposed mechanisms for this association include: increased glucose use by the malaria parasites in the red blood cells, inhibition of gluconeogenesis by the cascade of cytokines released due to infection and prolonged starvation and fasting especially in severely ill children further compounds the problem ^{47 48}. Considering that glucose is the primary source for organs like the brain which is likely suffering from the above highlighted effects of microvascular obstruction and sequestration, depleted glucose sources could lead to neurologic dysfuction including seizures, deepening comas and hence death.

Half of the models in children predicting mortality had respiratory distress (including deep breathing and subcostal indrawing) as a predictor ^{14 18 21 26 29}. Meanwhile six out of the nine models in adults had respiratory failure as a clinical predictor of mortality ^{17 22 24 35}. The incidence of respiratory distress in severe malaria is quite common as it occurs in about 40% of children with severe falciparum malaria and in 25% of adults ⁴⁹. It results from acute respiratory distress syndrome (ARDS); metabolic acidosis; fluid overload possibly resulting from increased inflammatory related capillary permeability and endothelial damage ^{7 49}; and aspiration pneumonia which could lead to sepsis ⁷ – a common association with severe malaria. The high mortality rates (up to 87% in some cases) associated with respiratory failure like in ARDS ⁵⁰ could explain the prognostic significance of respiratory distress in predicting mortality in malaria infection.

Acidosis was also a prominent predictor of mortality in most of the models predicting mortality. It was present in three of the models predicting mortality in children ^{26 28 30} and five models predicting mortality in adults ^{15 16 24 27 35}. Acidosis usually results from underlying pathologies like respiratory distress, renal failure and shock. These three variables were also common variables in the models predicting mortality in both children and adults identified in this review. Renal failure expressed in these models either as acute renal failure, oligoanuria or estimates of the kidney function using serum urea and creatinine ^{15 17} ^{22-24 28 30 35}; is due to acute tubular necrosis that occurs in severe malaria infection as a direct result of microvascular obstruction of capillaries by infected red blood cells leading to the release of inflammatory cytokines like tumor necrosis factor ⁵¹. Similarly, shock expressed either as a function of the systolic blood pressure or cold peripheries in three models in children ^{19 29 30} and likewise in two models in adults ^{17 35} could result from peripheral vasodilation which may usually occur concomitantly with sepsis and is a marker of a poor prognosis ^{7 52 53}.

We found evidence of external validation in only seven of the models identified in this study ^{16 18 22 29} ³⁰. External validation is an important component as it determines the generalisability of the model and

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its potential use in different geographical regions ⁵⁴. As outlined above, most of the models have similar variables highlighting the fact that the predictors of complications, severity and mortality in malaria might be consistent across different settings. Emphasis could therefore be better placed in the validation of existing models and initiating their use in clinical settings to guide clinicians on prioritising patients and anticipating outcomes rather than the production of new models. Publication of the findings on the use of these models in clinical settings should also be encouraged to guide clinicians on which models work better in various settings.

Conclusion:

Models predicting severity and mortality of malaria infection identified in this review have similar predictors. Evidence is however lacking on the generalisability of most of these models due lack of external validation. Emphasis should therefore be placed on external validation of existing models and publication of the findings of their use in clinical settings to guide clinicians on management options depending on the priorities of their patients.

Abbreviations:

ICU: intensive care units; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; AUC: area under the curve; SEQUAMAT: South East Asian Quinine Artesunate Malaria Trial; RCT: randomised control trial; TNF: tumour necrosis factor; AUROC: area under the receiver operating curve; LODS:Lambarene Organ Dysfunction Score; SICK: Signs of Inflammation in Children that Kill; PEDIA: Pediatric Early Death Index for Africa; PRISM: Pediatric Risk of Mortality; APACHE: acute physiology and chronic health evaluation system; MSA: Malaria score for adults; MPS: Malaria prediction score; CAM: coma acidosis malaria; MSS: Malaria severity score; GCRBS: Glasgow coma scale, creatinine, respiratory rate, bilirubin and systolic BP; MODS: Multiorgan dysfunction score; sMODS: Simplified MODS

Declarations

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None

None

N	Authors	Year	Period of participant recruitmen t	Country	Type of study	Sampl e size	Statistics used	Name of mode l	Method internal of validation	Age profiles	Sex profiles	Outcome predicted uses	OVariables Sused	Diagnosti c properties
Co	mplications	s of mala	aria	1	1	1	1	1	1	I	1	relat		I
Sev	vere anaem	ia										ed	er	
1	Weber 13	199 7	July – December 1994	Gambia	Cohort	368	Logistic regression	None	None	Median age: 28 months (IQR: 14 – 48 months)	Female s – 49%	Paediatric developments of severex anaemia malaria (packed call volume a malaria (packed call volume <a href="https://www.example.com" www.example.com"="" www.example.com<br="">15%)	Pallor of conjunctiva and pallor of opalms	Sensitivit y of 80% and a specificity of 85%.
2	Brickle y ¹²	201 7	2002 - 2006	Tanzania	Cohort	880	Cox proportiona l hazards models	None	Bootsrappin g	0 – 4 years	Female s – 48.1%	Paediatria development of severa anaemia 50g/L) in falciparum malaria	Sex, gravidity, transmission season at delivery, and bed net possession	C-index - 0.63 (95% CI 0.54 - 0.71)
De	velopment	of sepsis		1	1		1	1			1	,	0	
3	Njim ⁷	201 8	June 2003 – May 2005	Bangladesh , India, Indonesia and Myanmar	Randomise d Control Trial	1187	Logistic regression	None	Bootsrappin g	17 – 87 years	Female - 24.3%	Developmen t of clinical sepsis in si adults with severe falciparunt malaria	Sex, blood urea nitrogen levels, plasma anion gap, distress, wishock on admission, parasitaemia coma and	AUC: 0.789. Sensitivit y – 70.0%; specificit – 69.4%

* not used in present model; BCS: Blantyre coma score; NC: not clear; NE: No evidence; ^a diagnostic properties of original model; IQR: interquatile range; RCT: randomised control trial; ACT: artemisinin combined therapy; DRC: Democratic Republic of the Congo; BUN: bood urea nitrogen; TNF: tissue necrotic factor

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`abl [,]	e 2: Sun	nmar	y of articl	es with m	odels predic	eting me	ortality in	BMJ O paediatric	pen c severe ma	alaria		by copyright, includ	/bmjopen-2019-03079			1
N	Authors	Yea r	Period of participan t recruitme nt	Country	Type of study	Sampl e size	Statistics used	Name of model	Method internal of validation	Age profile s	Sex profile s	Outcome predicte @	تن Ariables الاقط الاقط الاقط الاقط الاقط	Diagnostic properties	External validatio n	Use in clinica l setting s
Mort	ality			I		1	1	I				rela			1	1
1	Jaffar ¹⁹	199 7	1992 – 1994	Gambia	Retrospecti ve analysis of data from a randomised control trial	624	Logistic regression	None	None	1 – 9.5 years	Female s – 49%	Mortalited in paediatr c cerebral an	A Gold Mariphery,	Not done	None	NE
2	Molyneu x ²⁵	198 9	January 1987 – June 1988	Malawi	Cohort	131	Univariab le analysis	Bedside prognostic index	None	7 months – 10 years	Female s – 55.7%	Mortalit in data paediatra c erebralning, Al trai	Fillood Baucose, Harasitaemia, WBC count, are, coma spore, absent corneal reflexes, decerebration, convulsions	Positive predictive value – 83%, sensitivity – 66%	None	NE
3	Conroy 14	201 2	1997 – 2009	Malawi	Cohort	155	Logistic regression	None	Hosmer- Lemeshow goodness- of-fit test	8 months – 14 years	Female s – 54.4%	Mortalitis in g, and patients and with cerebral similar malaria lar techno	Age, Blantyre oma score, respiratory distress, sovere anaemia, aggiopoietin- ly aggiopoietin- 2 and sTie-2 lavels	C-index of 0.79 (95% CI 0.72 – 0.84)	None	NE
4	Krishna 20	199 4	1988 – 1989	Gambia	Cohort study	115	:Logistic regression	None	Wald statistic and ROC analysis	18 months – 12 years	NC	Mortalit 8 in r paediatr c severe malaria	Coma score, yhole blood lotate/glucos evatio, TNF level De p:	Wald statistic: coma score (4.5), lactate/gluco se ratio (8.36), TNF level (6.5)	None	NE

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5	Marsh ²¹	199 5	May 1989 - Novembe r 1991	Kenya	Cohort	1844	Logistic regression	None	None	Mean: 26 months	NC	Mortalitud in childrenng for with severe malaria u	Bepaired Consciousness , cospiratory Costress, hypoglycemia Stid jaundice	Predicted 92.2% of deaths	None	
6	Newton 26	200 5	January 2001 – December 2003	Malawi, Kenya and Ghana	Cohort	14605	Linear regression	None	AUROC	Mean age: 32 – 36 months	Female s - 53 - 55%	Mortalities in paediatrelated to c severe falciparted malaria ta	Igep Incething, Igep Incething, Igen Igen Igen Igen Igen Igen Igen Igen	C-statistic 0.83 – 0.88 in the three sites: Blantyre (0.88), Kilifi (0.87) and Kumasi (0.83)	None	
7	Gérardin ³⁰	200 6	October 1, 1997 – March 31, 1999	Senegal	Cohort	311	Logistic regression	PRISM (Pediatric Risk of Mortality) AUC: 0.92 ³⁸	Hosmer- Lemeshow chi-square test	Media n: 8 years (IQR: 5 – 11 years)	Female s - 40.5%	Mortality in children, Al training, and similar technolog	Section and the section of persons and the section of	AUROC for acute malaria: 0.89 (95% CI: 0.85 – 0.92) and 0.86 (95% CI: 0.81–0.90) for severe malaria	Yes	
8	Helbok ¹⁸	200 9	December 2000 – May 2005	Gambia, Malawi, Kenya, Ghana, and Gabon	Cohort	23890	Logistic regression	LODS (Lambaréné Organ Dysfunctio n Score)	Internal validation using Bonferroni correction	Mean: 30 – 38 months	Female s – 41% – 47%	Mortalit in children with severe falciparu m malaria	Coma, postration abil deep lacathing Departm	AUROC: 80 0.80 (0.79 – 0.82)	Yes	

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	9	von Seidlein 28	201 2	2005 - 2010	Gambia, Mozambiqu e, Nigeria, Rwanda, Kenya, DRC, Tanzania, Ghana, Uaanda	Retrospecti ve analysis	5426	Logistic regression	None	ROC analysis	Media n: 2.8 years (1.7, 4.3)	NC	, in Mortalit in din paediatring c severe t falcipart m malaria s re	See deficit, Sana, Sa	AUROC: 0.85 (95% Cl: 0.83 - 0.87)	None	NE
	10	Conroy 29	201 5	NC	Uganda	Cohort	1589	Logistic regression	SICK (Signs of Inflammati on in Children that Kill) ³⁶ – AUC ^a : 0.887 (sensitivity 84.1% specificity 82.2%)	Hosmer- Lemeshow goodnesso f- fit	NC	Female s – 54.3%	Mortalitied to text in malaria do text and data min	The result of th	AUROC - 0.846	Yes	NE
									LODS 55	Hosmer- Lemeshow goodnesso f- fit	NC	Female s – 54.3%	Mortali tç in Altrain malaria	Prostration, coma (BCS) and deep breathing	AUROC – 0.898	Yes	NE
									PEDIA ³⁷ – AUC ^a : 0.93 (95% CI 0.92 to 0.94)	Hosmer- Lemeshow goodnesso f- fit	NC	Female s - 54.3%	Mortaliting in malaria and Similar	Byashiokor*, Bundice, Subcostal illrawing, postration (Bseizures) and wasting	AUROC – 0.896	Yes	NE
F n	no CT ecr	t used in ': randon otic facto	prese nised or	nt model; control tri	BCS: Blant al; ACT: art	yre coma sc emisinin co	core; NG	C: not clea l therapy;]	r; NE: No e DRC: Demo	evidence; ^a ocratic Rep	diagnos	tic prop f the Co	ngo; BLogo	original mode V: By ood urea 4, 2025 at Dep	el; IQR: inte nitrogen; T	rquatile r NF: tissu	ange; e
ſ	`ab	le 3: Sur	nmar	y of artic	les with mo	dels predic	ting me	ortality in	adult seve	re malaria	a			artment GEZ-LTA			

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N	Authors	Yea	Period of	Country	Type of	Sampl	Statistics	Name of	Method	Age	Sex	,; in Outcom	9 9 0 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	Diagnostic	External	
		r	participant recruitmen t	country	study	e size	used	model	internal of validation	profile s	profiles	predicteding fo	Ased Ased On On	properties	validatio n	
Mo	rtality											or us	267			_
1	Wilairatan a ³⁵	199 5	July 1991 – May 1993	Thailand	Cohort	72	Univariabl e analysis	APACHE II score ⁵⁶	ROC analysis	Mean age: 29.9	Female s – 33.3%	Mortalia in adulter related patientsted to the cerebrator falcipart m malaext and data m	MAP, Gemperature, eart rate, espiratory te, arterial H, PaO ₂ , naematocrit, WBC count, reatinine, odium, aotassium and Clasgow aoma score	Predicted mortality with 95.8% accuracy	None	
2	Dondorp ¹⁵	200 4	NC	Vietnam	Cohort	268	Logistic regression	None	Hosmer- Lemesho w goodness- of-fit test	15 – 79 years	Female s – 19%	Mortali n in adulto with severe falciparta m malana	Flasma actate, alasma strong mion gap and alasma yreatinine	AUROC: 0.81	None	
3	Mishra ²²	200 7	NC	India	Cohort	212	Linear regression	MSA (Malaria score for adults)	Not done	NC	NC	Mortality in adulg with and severe discrete malaria	Severe enaemia, gcute renal espiratory distress, gerebral malaria	Sensitivity : 89.9%, specificity : 70.6%, positive predictive value: 94.1% with cut- off of 5/10	Yes ³⁹	
								MPS (Malaria prediction score)	Not done	NC	NC	Mortali Q in seve Q malaria e s	Age, serum creatinine tevel, t	NE	Yes ³⁹	

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4	Hanson ¹⁶	201 0	June 2003 – May 2005	Bangladesh , India, Indonesia and Myanmar	Retrospectiv e analysis of a randomised control trial	789	Logistic regression	CAM (coma acidosis malaria) score	Hosmer- Lemesho w goodness- of-fit	NC	NC	Mortalia in adulta with severe malaria	Soma and Scidosis (base Geficit On 20	AUROC: 0.81 (95% CI: 0.77 – 0.84)	Yes ⁵⁷	NE
5	Mohapatra ²⁴	200 9	January 200 – December 2004	India	Cohort study	2089	Logistic regression	MSS (Malaria severity score)	Hosmer- Lemesho w goodness- of-fit (internal validation by splitting data – 2089 vs 509)	18 – 71 years	Female - 34.6%	Mortalius in adultes patients related with severe falcipart and m malate text and da	Acurologic, Acural, Acural, Acural, Acural A	AUROC: 0.9	None	NE
6	Newton ²⁷	201 3	1986 – 2002	Thailand	Retrospectiv e analysis	988	Logistic regression	MPI (Malaria prognosti c index)	ROC curve analysis and internal validation by data splitting	15 – 74 years	Female s – 43%	Mortali ga • in adult m • severe ini falcipar ng m malaria Al training	Galasgow actate, serum actate, serum actate, serum alilrubin, barasites and areatment arith ACT	AUROC: 0.97	None	NE
7	Mohapatra ²³	201 4	NC	India	Cohort	112	NC	GCBRS (GCS, creatinine , respirator y rate, bilirubin and systolic BP) score	NC	Mean: 35.8 ± 15.1 years	Female s - 16.1	Mortali a in several falcipar si m mala b a ilar technolo	erebral malaria, renal ailure, respiratory sundice and ohock May	Sensitivity : 85.3%. Specificity : 95.6%	None	NE
8	Hanson ¹⁷	201 4	1996 – 2013	Bangladesh , India, Indonesia, Vietnam and Myanmar	Randomised control trials and cohort studies	1801	Logistic regression	None	Hosmer- Lemesho w goodness- of-fit	21 – 45	Female s - 24.4	48-hou fe surviva and survival to discharge in patients with severe malaria	Ahock, oligo- muria, Sysglycaemia, Sepiratory atte, Glasgow Doma Score pand absence af fever	PPV for 48 hour- survival: 99.4% (95% CI 97.8 – 99.9). PPV for survival to discharge: 96.9%	None	NE

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													19-030793 on 2 1, including for	(95% CI: 94.3 – 98.5)		
* no RC' nec Tat	ot used ir T: randoi rotic fact ble 4: Su Authors	n prese mised tor mma Year	ent model; control tria ry of articl Period of participant recruitment	BCS: Bla Il; ACT: a es with n	nodels Type of study	oma scor inin com predicti Sample size	ng sever	iot clear; NI erapy; DRC ity of mala	E: No evid : Democra ria infecti Method internal of validation	ence; ^a c atic Repu on Age profiles	liagnosti ublic of t Sex profiles	c properties o he Congo; BU Outcome predicted	Sectional mode Section and the section of the sect	Diagnostic	External validation	e B Use clir sett
Ser	verity of dis	ease											troi			
1	Helbok 33	2003	October 1, 2001 – January 30, 2002	Thailand	Cohort	22	NC	MODS (Multi- organ dysfunction score) ⁴⁰	None	16 – 41 years	Female - 41.8%	Severity of disease in adult patients with uncomplicated falciparum malaria	Ten organ Ten organ systems: (heart, blood vessel, blood vesse	None	None	NE
2	Helbok 32	2005	October 1, 2001 – July 30, 2002	Thailand	Cohort	29	Survival analysis	MODS ⁴⁰	None	Mean age: 27.1 (± 10.6)	Female – 27.6%	Severity of disease in adult patients with severe falciparum malaria	Ten-organ systems: (heart, blog, respiratory system, methoolism, gasmointestinal system, liver, kidtey and	None	None	NI

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ncc	Helbok ³⁴ ht used in C: rando rotic fac	2006 n prese mised tor	August 2003 – May 2005 ent model; control tria	Gabon BCS: Bla al; ACT:	Cohort antyre co artemisi	485	Survival analysis re; NC: n abined the	Simplified MODS ³³ ot clear; Ni erapy; DRC	ROC analysis E: No evic : Democr	4 months – 169 months	Females – 49%	Severity of disease and disability in children with severe falciparum malaria infection c properties of he Congo; B	STEREPrgan Ses Josephilie (heart, blogd vessel, blogd vess	AUC to predict prolonged disease (>48 hours unable to walk): 0.92 (95% CI, 0.89–0.95). el; IQR: int	None erquatile r TNF: tissu	range
													mjopen.bmj.com/ on May 14, 2025 ning, and similar technologies.			
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Figures Legends:

Figure 1: Flow chart showing reasons for exclusion of various studies from the review



Flow chart showing reasons for exclusion of various studies from the review

BMJ Open Appendix 1: PRISMA-P 2015 Checklist. From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petter 76 M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-**B**) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Section/topic	#	Checklist item	Inform	ation	Page
		inter en la companya de la comp	report	ed	(s)
		d to	Yes	No	-
ADMINISTRATIVE	INFORM				
Title					
Identification	1a	Identify the report as a systematic review			1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number at the Abstract			
Authors			-	- 1	
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide gyseal mailing			1
		address of corresponding author			
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review			14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, generative as such			
		and list changes; otherwise, state plan for documenting important protocol amendments			
Support	I	echi n	1	1	
Sources	5a	Indicate sources of financial or other support for the review			13
Sponsor	5b	Provide name for the review funder and/or sponsor			
Role of	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol			
sponsor/funder		at C			
INTRODUCTION			1	- 1	
Rationale	6	Describe the rationale for the review in the context of what is already known			3

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Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)		
METHODS				
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report that the study characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the study design.		
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study author trial registers, or other grey literature sources) with planned dates of coverage		-
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planed limits, such that it could be repeated		-
STUDY RECORDS	1			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the received		-
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)		-
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators		
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre- planned data assumptions and simplifications		1
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main additional outcomes, with rationale		1
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis		,
DATA	1		_1	
~	15a	Describe criteria under which study data will be quantitatively synthesized		Τ

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		15b	If data are appropriate for quantitative synthesis, describe planned summary measures, method soft handling			
			data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I ² , Kendall's tau)			
	-	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regession)			
	-	15d	If quantitative synthesis is not appropriate, describe the type of summary planned			5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selecting within studies)			
Confidence	e in evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)			5
Appendix 2 Searches	2: Search strat	tegy f	or Medline database		Num	ber of
	combination	IS			hits	
S1			"prognost* model" OR "predict* model" OR "Predictive Value of Tests"		203,7	28
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S5			"Malaria" OR "vivax malaria" OR "falciparum malaria" OR "cerebral malaria" OR	ria" OR	109,3	371
			"clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*			
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Appendix 5a and 5b: Assessment v	vas done using ti	le Quality Ass	essment 1001	for Obse	ervationa	I Studie			eann n	astitute/ina	ational
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Heart, Lung, and Blood Institute

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1	Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes simila	Yes	Yes	Yes	Yes
2	Was the study population clearly specified and defined?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes r tec	NC 9	Yes	Yes	Yes
3	Was the participation rate of eligible persons at least 50%?	NC	NC	Yes	NC	NC	No	NC	NC	NC hnold	May	NC	NC	Yes
4	Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes Gies	Yes 14, 2025 at Departm	Yes	Yes	Yes
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5	Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	Yes	No	No	No	No	No	ncluding	NC	NC	NC	No
5	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	for uses i	Yes	Yes	Yes	Ye								
7	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Erasmusho	Yes	Yes	Yes	Yes								
8	For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Yes	bgeschool . tt and data mining	Yes	Yes	Yes	Yes								
9	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	g, Al training	Yes	Yes	Yes	Yes								
10	Was the exposure(s) assessed more than once over time?	No	No	No	No	Yes	Yes	Yes	Yes	Yes	, and	Yes	No	NC	NC
11	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	similar tech	Yes	Yes	Yes	Yes								
12	Were the outcome assessors blinded to the exposure status of participants?	NC	No	NC	inologie	NC	NC	NC	NC						
13	Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	NC	Yes	Yes	Yes	Yes	Yes	2023 S.	Yes	Yes	Yes	Ye
14	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes		Yes	Yes	Yes	Yes								
	Quality rating														

Page	33	of	35
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*Not clear; Newton^a: Study carried out in 2005; Conroy^a: study carried out in 2012; Conroy^b: study carried out in 2012 for a study carried out in 2009 f

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1	Was the research question or objective in	Yes	Yes	Yes	Yes	Yes	Yes	Yes tec as	Yes	Yes	Yes	Yes
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11	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes Unding f	9-030 Yes on	Yes	Yes	NC
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14	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes ated to text	ber 2019.	Yes	Yes	Yes
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Prognostic models for the clinical management of malaria and its complications: a systematic review

Journal:	BMJ Open
Manuscript ID	bmjopen-2019-030793.R1
Article Type:	Original research
Date Submitted by the Author:	18-Sep-2019
Complete List of Authors:	Njim, Tsi; Regional Hospital Bamenda, Surgical Department Tanyitiku, Bayee; University of Bamenda
Primary Subject Heading :	Global health
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	malaria, prognostic model, prognostic score, mortality



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4	Prognostic models for the clinical management of malaria and its complications: a systematic
5	review
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7 8	Authors: Tsi Njim ¹ & Bayee Swiri Tanyitiku ²
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Abstract

Objective: Malaria infection could result in severe disease with high mortality. Prognostic models and scores predicting severity of infection, complications and mortality could help clinicians prioritise patients. We conducted a systematic review to assess the various models that have been produced to predict disease severity and mortality in patients infected with malaria.

Design: A systematic review.

Data sources: Medline, Global health and CINAHL were searched up to 04th of September 2019.

Eligibility criteria for selecting studies: Published articles on models which used at least 2 points (or variables) of patient data to predict disease severity; potential development of complications (including coma or cerebral malaria; shock; acidosis; severe anaemia; acute kidney injury; hypoglycaemia; respiratory failure and sepsis) and mortality in patients with malaria infection.

Data extraction and synthesis: Two independent reviewers extracted the data and assessed risk of bias using the Prediction model Risk Of Bias Assessment Tool (PROBAST).

Results: A total of 564 articles were screened and 24 articles were retained describing 24 models/scores of interests. Three of the articles described models predicting complications of malaria (severe anaemia in children and development of sepsis); fifteen described original models predicting mortality in severe malaria; three described models predicting mortality in different contexts but adapted and validated to predict mortality in malaria; and four articles described models predicting severity of the disease.

For the models predicting mortality, all the models had neurologic dysfunction as a predictor; in children, half of the models contained hypoglycaemia and respiratory failure as a predictor meanwhile, six out of the nine models in adults had respiratory failure as a clinical predictor. Acidosis, renal failure and shock were also common predictors of mortality.

Eighteen of the articles described models that could be applicable in real-life settings and all the articles had a high risk of bias due to lack of use of consistent and up-to-date methods of internal validation.

Conclusion: Evidence is lacking on the generalisability of most of these models due lack of external validation. Emphasis should be placed on external validation of existing models and publication of the findings of their use in clinical settings to guide clinicians on management options depending on the priorities of their patients.

Key words: malaria; prognostic model; prognostic score; mortality

Prospero registration number: CRD42019130673

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Article Summary:

Strengths and limitations of this review:

This review is the first to comprehensively summarise the various prognostic models that have been produced to identify complications, severity and risk of mortality in patients with severe malaria.

The review covers prognostic models produced worldwide and for all the various malaria species.

The review reduced the risk of bias by using an independent review process for the screening of potential articles and the extraction of data.

Considering the wide variety of statistical methods used to generate and validate these models, there is the risk of heterogeneity in interpretation of the results.

The search was carried out in only one language which could potentially exclude some relevant studies published in different languages.

Introduction

Malaria is a disease caused by infection with a protozoan parasite of the genus *Plasmodium*. The most relevant of these species is *Plasmodium falciparum* as it causes most deaths from the disease ¹. Another species of relevance is *Plasmodium vivax* which is predominantly found in Asia and has a wider distribution ². Malaria infection can result in severe disease and is associated with a high mortality. In about 108 countries where the transmission of the disease still occurs, an estimated 435,000 people died in 2017 ³⁴.

The incidence of malaria cases has decreased by 41% worldwide in the past ten years, with about 17 countries in Latin America and the Middle East reporting no new cases of malaria over this period ^{3 5}. There are however concerns that the fight against malaria might be slowed down by an overemphasis on prevention over treatment ⁶.

Treatment and clinical management of malaria is made difficult due to potential evolution of simple infections into life-threatening severe disease; the multi-organ affection of severe disease; the dilemma of when to admit to intensive care units (ICU) considering limited resources and the occurrence of concomitant sepsis infection with malaria ^{7 8}. Some of these issues can be addressed with the help of guidelines; scores or models that could help clinicians predict the occurrence of severe disease and complications in order to act appropriately.

We therefore conducted this review to systematically assess the various predictive models or scores available to guide clinicians in the management of severe malaria, whether these models have been validated and if there is any evidence that they are being successfully used in the clinical setting.

Methods

Institutional review board approval and informed consent were not required for this systematic review. We reported our findings according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Appendix 1).

Search strategy and selection criteria

We searched MEDLINE, CINAHL and Global Health databases using a tailored search strategy (Appendix 2) to identify all the relevant titles and abstracts of studies (randomised control trials, cohort, cross-sectional and case-control studies) published in English from inception of the database up to the 04th of September 2019, that reported predictive/prognostic scores or models that could be used in the management of malaria. These included:

- Scores/models that predicted the severity of disease as this could guide clinicians' decisions to admit for intensive care management or the use of parenteral treatment;
- Scores/models that predicted the potential development of complications (including coma or cerebral malaria; shock; acidosis; severe anaemia; acute kidney injury; hypoglycaemia; respiratory failure and sepsis);
- Scores/models that predicted mortality in patients with malaria infection.

The main keywords in the search strategy included: "prognostic model/score", "predictive model/score" and "predictive value of tests" coupled with "malaria", "plasmodium", "anti-malarials", "malaria falciparum", "malaria vivax" and "clinical malaria". We further canvassed the references of eligible papers to identify similar papers for review.

We excluded any duplicate studies, editorials, systematic reviews, case studies, conference abstracts, unpublished studies and expert commentaries. For studies with more than one publication of findings, we selected the most recent publication.

We also excluded studies which contained models or scores that were aimed at the diagnosis of malaria as we intend to limit the scope of the review to only models that could be used to predict severity, mortality or risk of complications – that could guide clinicians in their management options. Studies that used animal models to predict disease severity were also excluded.

Two independent reviewers (TN and BST) screened the titles and abstracts for compliance to the aforementioned inclusion and exclusion criteria and any conflicts were settled by mutual agreement. Articles considered to have data relevant to the topic were assessed in detail and the references cited in these publications were searched to identify further publications.

Data extraction

Data extraction sheets which were prepared prior to screening were used by the two independent reviewers to obtain the following details for inclusion into the final review: Last name of first author;

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date of publication; period of patient recruitment and/or follow-up; country of study; sample size; age group; type of predictive model; name of model; method of internal validation (calibration and discrimination); diagnostic properties of model and evidence of external validation or use in clinical settings.

Definitions

By prognostic/predictive model, we mean a statistical tool which uses at least 2 points (or variables) of patient data to predict a specific clinical outcome ⁹. Prognostic models applied in clinical settings are usually used at the discretion of physicians for accurate future predictions based on characteristics gathered in the present ^{9 10}. The information found in prognostic models is usually specific to the patients' characteristics rather than the disease or treatment and includes: prediction of chance or the duration of survival; classification of patients into risk groups; and prediction of clinical events related to the treatment the patient is receiving ¹¹.

For models that used the area under the curve (AUC) or c-statistic to assess discrimination, the following classification was used: 0.90 - 1 - excellent; 0.80 - 0.90 - good; 0.70 - 0.80 - fair; 0.60 - 0.70 - poor and $0.50 - 0.60 - \text{very poor discriminative properties}^{12}$.

Data synthesis and analysis

We assessed and discussed the selected studies qualitatively to describe the diagnostic properties of the models proposed in the study, their intended purpose and evidence of use of the model in other clinical settings.

We further divided the models into various categories: models used to predict a potential complication of severe malaria; models used to predict mortality as an outcome and models used to predict severity of malaria infection.

Assessment of risk of bias and applicability

The risk of bias and applicability of the models in the various studies were assessed by the two independent reviewers using the Prediction model Risk Of Bias Assessment Tool (PROBAST)^{13 14} (Appendix 3). Any disagreements were handled by mutual agreement.

Patient and public involvement:

Patients and the public were not involved in the design and conduction of this review.

Results

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A total of 564 articles were identified by the electronic search of the databases. The titles and abstracts of these articles were screened to retain 59 articles for full text review. These were then evaluated according to the inclusion criteria and 24 articles were identified describing 24 models/scores of interests; after eliminating 23 irrelevant articles, 9 articles which used only one variable to predict an outcome and two articles describing models in other languages (Figure 1). Two of the articles described models predicting complications of malaria ^{8 15}; fifteen described original models predicting mortality in severe malaria ¹⁶⁻³⁰; three described models predicting mortality in different contexts but adapted and validated to predict mortality in malaria ³¹⁻³³; and four articles described models predicting severity of the disease ³⁴⁻³⁷.

Using the PROBAST to assess risk of bias and applicability, none of the studies had a low risk of bias while six studies were not found to be applicable in real-life settings ¹⁵ ¹⁶ ²² ³⁴⁻³⁶ (Appendix 3).

The general characteristics of the studies included in the review are summarised in Tables 1, 2, 3 and 4.

Models predicting the risk of complications in malaria infection

Webber *et al* ¹⁵ in 1997 conducted a study to predict the risk of severe anaemia (packed cell volume < 15%) in children with severe malaria in the Gambia using logistic regression analysis. This model was not internally validated, and the two predictors identified were pallor of the conjunctiva and pallor of the palms. There is no evidence from this review that the model has been externally validated and is being used in clinical settings.

In 2018, Njim *et al* ⁸ described a prognostic model for clinical use to predict the risk of sepsis development amongst adult patients (> 16 years old) admitted for severe falciparum malaria in Southeast Asia. They used data from SEQUAMAT (South East Asian Quinine Artesunate Malaria Trial) – a large randomised control trial (RCT) conducted to determine the benefits of intravenous artesunate over quinine treatment for severe malaria. They used a multivariable logistic regression approach with internal validation using bootstrapping to generate a prognostic model with modest discriminative abilities [area under the curve (AUC): 0.789] containing the following predictive variables: female sex, high blood urea nitrogen, high plasma anion gap, respiratory distress, shock on admission, high parasitaemia, coma and jaundice. The model has not been externally validated and there is no evidence of use in clinical settings.

Models predicting mortality in severe malaria

Models predicting mortality in paediatric severe malaria

Ten articles described models that predicted mortality in paediatric severe malaria ^{16 20-23 27 28 30-32}. Three articles described models which predicted mortality in paediatric patients with cerebral malaria

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¹⁶ ²¹ ²⁷; two articles described models generated to assess mortality in different conditions that were validated for use in the present studies ³¹ ³²; and five articles described original models predicting the risk of mortality in children with severe malaria ²⁰ ²² ²³ ²⁸ ³⁰.

Models predicting mortality in paediatric cerebral malaria

Molyneux *et al* ²⁷ in 1989 conducted a study amongst 131 comatose Malawian children with severe cerebral malaria to determine the prognostic factors for death in these patients. The authors derived a "bedside prognostic index" with: blood glucose $\leq 2.2 \text{ mmol/L}$; parasitaemia > 106 ring forms/µL; white blood cell count > 15 x 10/L; age $\leq 3 \text{ years}$; coma score (modification of the Glasgow coma score) = 0; absent corneal reflexes; signs of decerebration and convulsions; as predictors of mortality with each predictor assigned a score of 1. Individuals with a score ≥ 4 were more likely to die. This score was calculated only using univariable analysis and internal and external validation were not done.

In 1997 in Gambia, Jaffar *et al*²¹ performed a retrospective analysis on data obtained from a randomised control trial during which artemether was compared with quinine and a monoclonal antibody against tumour necrosis factor (TNF) compared with a placebo in patients with cerebral malaria. They used this data to identify predictors of mortality in cerebral malaria using a multivariable logistic regression model. A cold periphery, a coma score of either 0 or 1 (assessed using the Blantyre coma scale measured on a scale of 0 - 5), and hypoglycaemia were found to be present at admission in 90% of the children who died. This model was not internally validated.

Conroy *et al* ¹⁶ in 2012 conducted a study amongst 155 children aged 8 months – 14 years in Malawi to determine predictors of mortality in cerebral malaria. They used a multivariable logistic regression model containing clinical parameters and biomarkers with a modest discriminative ability (C-index of 0.79) after internal validation; which contained the following variables: age, Blantyre coma score, respiratory distress, severe anaemia, angiopoietin-1, angiopoietin-2 and sTie-2 levels. The model was not externally validated.

Original models predicting mortality in paediatric severe malaria

Krishna *et al*²² in 1994 conducted a study in the Gambia to predict mortality in children aged 8 months to 14 years. They used a multivariable logistic regression model internally validated using the Wald statistic to determine that the coma score (using the Blantyre coma scale), whole blood lactate/glucose ratio and TNF level were the best predictors of death.

In 1995, Marsh *et al* ²³ studied 1844 children in Kenya to determine predictors of life-threatening malaria (risk of death) using a multivariable logistic regression model. They determined that impaired consciousness (assessed using the Blantyre coma scale), hypoglycaemia, respiratory distress and

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jaundice could correctly predict 84.4% of deaths in the sample population. The model was not validated internally or externally.

 In 2005, Newton *et al* ²⁸ conducted a study to assess the prognostic value of measures of acid/base balance in paediatric falciparum malaria. They examined 14,605 children in Malawi (Blantyre), Kenya (Kilifi) and Ghana (Kumasi); where they determined that deep breathing, Blantyre Coma Score, inability to sit, and weight-for-age Z score were independent predictors of mortality in all the three sites. Discrimination of the model was performed by calculating the area under the receiver operating curve (AUROC). After addition of laboratory data to these models – hypoglycaemia, base excess and lactate concentrations; the c-statistics obtained were 0.88 (Blantyre), 0.87 (Kilifi) and 0.83 (Kumasi) denoting good discriminative properties of the models.

Helbok *et al* ²⁰ in 2009 produced the the Lambarene Organ Dysfunction Score (LODS) which combined three variables: coma, prostration, and deep breathing to generate a model using multivariable logistic regression which predicted death in African children – Banjul (Gambia), Blantyre (Malawi), Kilifi (Kenya), Kumasi (Ghana), and Lambarene and Libreville (Gabon); who were admitted for severe falciparum malaria. Each component of the model was assigned a score of 1 and a LODS of 3 at admission had a 98% specificity and 25% sensitivity in predicting death. Meanwhile a LODS \geq 1 had a sensitivity of 85% and a specificity of 63%. The model had good discriminative properties with an AUC of 0.80 (95% CI: 0.79 – 0.82). In 2015, Conroy *et al* ³¹ externally validated this model amongst 1589 Ugandan children. The model showed good discriminative properties with an AUC of 0.898.

Similarly, in 2012, von Seidlein *et al* ³⁰ conducted an analysis of data from a RCT carried out in several African countries (Gambia, Mozambique, Nigeria, Rwanda, Kenya, DRC, Tanzania, Ghana and Uganda) to generate a model for predicting mortality from severe falciparum malaria using multivariable logistic regression analysis and internally validated by AUROC analysis. After analysis of data from 5426 children, base deficit, impaired consciousness (assessed using the Blantyre Coma Score), convulsions, elevated blood urea, and underlying chronic illness were identified in the model to predict mortality with a good discriminative ability – AUROC: 0.85 (95% CI: 0.83 - 0.87).

Existing Models validated for use in the prediction of mortality in severe malaria in children

As described above, Conroy *et al* ³¹ externally validated the LODS model amongst 1589 Ugandan children. The authors further externally validated two other scores: the SICK (Signs of Inflammation in Children that Kill) score which was developed in India as a practical triage tool using variables related to the systemic inflammatory response syndrome, with data collected from 1,099 children in 2003 admitted for any paediatric illness ³⁸; and the PEDIA (Pediatric Early Death Index for Africa) score which was developed to predict early death amongst 8091 children in Kenya in 2003 admitted for paediatric illnesses ³⁹. The original SICK score containing the following variables: altered

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consciousness, temperature, heart rate, respiratory rate, systolic blood pressure, capillary refill time and age; had good discriminative properties with an AUC of 0.887³⁸. Externally validated against this cohort of 1589 children, the score maintained its good discriminative properties with an AUC of 0.846. Similarly, the PEDIA score which originally had excellent discriminative properties with an AUC of 0.93³⁹ had good discriminative properties (AUC: 0.896) when externally validated on the cohort of 1589 Ugandan children³¹. The original PEDIA score contained Kwashiorkor, jaundice, subcostal indrawing, prostration (± seizures) and wasting as variables in the model. However, kwashiorkor was not included in the validation model as it was not measured amongst the Ugandan children.

In 2006, Gerardin *et al* ³² externally validated the PRISM (Pediatric Risk of Mortality) model which was originally developed in 1988 by Pollack *et al* ⁴⁰ to reduce the number of physiologic variables required for paediatric intensive care unit death risk assessment. The model was developed from data of 1,227 patients with 105 deaths and contained 14 variables: systolic blood pressure, temperature, mental status, heart rate, dilatation of pupils, pH, total CO2, PCO2, arterial PaO2, serum glucose, potassium, urea, creatinine, white blood cells, prothrombin time, platelet count. The original score had excellent discriminative properties with an AUC of 0.92 ⁴⁰. Gerardin *et al* used a cohort of 311 Senegalese children admitted with severe malaria to externally validate this model. The model showed good discriminative properties in predicting death in children with severe malaria – AUC: 0.86 (95% CI: 0.81-0.90) ³².

Models predicting mortality in adult severe malaria

There were eight articles assessing models that predicted mortality in adult severe malaria ^{17-19 24-26 28}
⁴¹.

In 1995, Wilairatana *et al* ⁴¹ used the APACHE II score (the acute physiology and chronic health evaluation system score commonly used in intensive care units) based on 12 physiologic variables – Mean arterial pressure (MAP), temperature, heart rate, respiratory rate, arterial pH, PaO2, haematocrit, WBC count, creatinine, sodium, potassium and Glasgow coma score to predict the risk of mortality in adult patients with cerebral malaria in Thailand. The score was able to predict mortality with a 95.8% accuracy. The original APACHE II model was produced in 1985 by Knaus *et al* ⁴², and clinical judgement and physiologic relationships were used to assign weightings for the various factors in the model.

Dondorp *et al* ¹⁷ in 2004 created a model using logistic regression with laboratory data form 268 patients in Vietnam to determine the risk of mortality in adult patients with severe malaria. This model had a good discriminative value with an AUROC of 0.81. The laboratory variables associcated with mortality in this cohort were: plasma lactate, plasma creatinine and a strong anion gap. On the other hand, in 2007, Mishra *et al* ²⁴ created the MSA (Malaria score for adults) and the MPS (Malaria

 prediction score) from a cohort of 212 patients in India to predict mortality in severe malaria. The MSA was an upgrade of the Malaria prognostic index (MPI) which required laboratory data and included a small proportion of children. The clinical variables included in the MSA were: severe anaemia, acute renal failure, respiratory distress and cerebral malaria and had a sensitivity of 89.9% and a specificity of 70.6%. This model was externally validated by Santos *et al* ⁴³ among 59 patients with imported severe malaria in Portugal and was shown to have good discriminative properties – AUROC: 0.84; 95% CI: 0.70 - 0.98.

Similarly, Hanson *et al* ¹⁸ produced the coma acidosis malaria (CAM) score after using a logistic regression analysis on data previously collected from the SEQUAMAT. The authors proposed the use of the presence of a coma and base deficit to calculate a five-point score to predict mortality. The score had good discriminative properties with an AUROC of 0.81 (95% CI: 0.77 - 0.84). The same author used data from several cohort studies and RCTs carried out in Bangladesh, India, Indonesia, Vietnam and Myanmar to predict 48-hour survival and survival to discharge in patients with severe malaria ¹⁹. The model containing the variables: shock, oligo-anuria, dysglycaemia, respiratory rate, Glasgow coma score and fever could correctly predict 48 hour-survival in 99.4% of the patients and survival to discharge in 96.9% of patients.

Mohapatra *et al* ²⁶ in 2009 carried out a cohort study of 2089 patients in 2009, where they produced the Malaria severity score (MSS) to predict mortality in adult patients with severe falciparum malaria in India. They assessed seven organ systems: neurologic, renal, haematologic, hepatic, respiratory, cardiovascular, and metabolic organ systems; assigning a maximum score of 0 - 3 for each organ system. The model had excellent discriminative propertiens with an AUROC of 0.9. The authors also developed the GCRBS (Glasgow coma scale, creatinine, respiratory rate, bilirubin and systolic BP) score in 2014 as an alternative to other scores like the APACHE II score which was considered cumbersome ²⁵. The score had a sensitivity of 85.3% and a specificity of 95.6% in predicting a fatal outcome in severe malaria.

In 2013 in Thailand, Newton *et al*²⁹ conducted a retrospective analysis of 988 records with severe falciparum malaria to produce the MPI (Malaria prognostic index) validated using ROC curve analysis and internal validation by data splitting. The MPI contained the following variables: Glasgow coma scale, parasitaemia, plasma lactate, serum bilirubin, pigmented parasites and treatment with ACT and had excellent discriminative properties with an AUROC of 0.97.

Models predicting the severity of malaria

The Multi-organ dysfunction score (MODS) which is an index used in severely ill patients admitted in intensive care units to determine the severity of their disease irrespective of the diagnosis ^{34 44}. The score evaluates ten organ systems: heart, blood vessel, blood, respiratory system, metabolism, gastrointestinal system, liver, kidney and urinary tract, immune system, and central nervous system –

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giving a score of 1-5 for each system depending on the level of dysfunction of the system, with a minimum score of 10 and a maximum score of 50 ³⁵. Helbok *et al* assessed the use of this score to predict severity in a small cohort (n = 22) of adult patients with uncomplicated falciparum malaria ³⁵ and in adults with severe malaria (n = 29) ³⁴ in Thailand. The score was not internally validated in both studies but the authors showed that higher scores were correlated with symptom severity and duration of hospitalisation. In 2006, the authors used a simplified version of the score - Simplified MODS (sMODS); in a cohort of 485 children in Gabon to predict the level of severity of the disease with respect to the amout of disability the children suffered into categories: ability to walk unaided and ability to sit unaided ³⁶. The authors obtained an AUC of 0.92 (95% CI: 0.89, 0.95) in predicting inability to walk \geq 48 hours for children with sMODS \geq 16 and an AUC of 0.90 (95% CI: 0.87, 0.93) in predicting inability to sit unaided (Table 4).

Grigg *et al* in 2018, used a multivariable logistic regression model to predict the severity of *Plasmodium knowlesi* malaria infection in a cohort of 481 participants in Malaysia. The authors showed that independent predictors of disease severity using the WHO 2014 research criteria ⁴⁵ were: increasing age, abdominal pain, shortness of breath, increasing parasite count, schizont proportion >10% and serum bicarbonate levels <18 mmol. The model was not internally or externally validated (Table 4).

Discussion:

In this review, we report on the various prognostic models and scores produced to predict complications, mortality and severity of malaria infection. We showed that there were two models produced to predict the risk of developing complications from malaria infection, twelve models that predict mortality from severe malaria in children, nine models that predict mortality from severe malaria in adults and four models that predict disease severity in malaria. Seventeen of these models were internally validated while only seven have been externally validated. There is no published evidence that any of these models are routinely used in clinical settings.

The models identified in this review that were used to predict mortality in children with severe malaria have similar clinical predictors. All the models had neurologic dysfunction based on either the Glasgow coma score, impaired consciousness, altered mental status, convulsions, decerabration or coma as a predictor. Similarly, in adults, all the models predicting mortality also had neurologic dysfuction as a predictor. Microvascular obstruction in capillaries of the brain due to direct sequestration of red blood cells infected with the malaria parasite could lead to tissue hypoxia ⁴⁶. The effects of this sequestration and its sequelae in the brain can be directly visualised in both adults and children as retinopathy ^{16 46-48}. This leads to varied results with increased intracranial pressure more pronounced in children than in

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adults ⁴⁶. With the increased oxygen demand associated with brain hypoxia and raised intracranial pressure, coma and brain dysfunction could therefore become an important predictor of mortality.

In children, half of the models predicting mortality had hypoglycaemia as a predictor ²¹⁻²³ ²⁷ ²⁸ ³². Hypoglycaemia is usually implicated as a complication of severe malaria infection. This association has been said to be multifactorial ⁴⁹. Proposed mechanisms for this association include: increased glucose use by the malaria parasites in the red blood cells, inhibition of gluconeogenesis by the cascade of cytokines released due to infection and prolonged starvation and fasting especially in severely ill children further compounds the problem ^{49 50}. Considering that glucose is the primary source for organs like the brain which is likely suffering from the above highlighted effects of microvascular obstruction and sequestration; depleted glucose sources could lead to neurologic dysfuction including seizures, deepening comas and hence death. As above, any factor that significantly affects neurologic dysfuction could be highly predictive of mortality or disease severity in patients.

Half of the models in children predicting mortality had respiratory distress (including deep breathing and subcostal indrawing) as a predictor ^{16 20 23 28 31}. Meanwhile six out of the nine models in adults had respiratory failure as a clinical predictor of mortality ^{19 24 26 41}. The incidence of respiratory distress in severe malaria is quite common as it occurs in about 40% of children with severe falciparum malaria and in 25% of adults ⁵¹. It results from acute respiratory distress syndrome (ARDS); metabolic acidosis; fluid overload possibly resulting from increased inflammatory related capillary permeability and endothelial damage ^{8 51}; and aspiration pneumonia which could lead to sepsis ⁸ – a common association with severe malaria. The high mortality rates (up to 87% in some cases) associated with respiratory failure like in ARDS ⁵² could explain the predictive significance of respiratory distress in predicting mortality in malaria infection. Respiratory failure usually leads to hypoxia and a high probability of acute mortality in patients.

Acidosis was also a prominent predictor of mortality in most of the models predicting mortality. It was present in three of the models predicting mortality in children ^{28 30 32} and five models predicting mortality in adults ^{17 18 26 29 41}. Acidosis usually results from underlying pathologies like respiratory distress, renal failure and shock. These three variables were also common variables in the models predicting mortality in both children and adults identified in this review. Renal failure expressed in these models either as acute renal failure, oligoanuria or estimates of the kidney function using serum urea and creatinine ^{17 19} ^{24-26 30 32 41}; is due to acute tubular necrosis that occurs in severe malaria infection as a direct result of microvascular obstruction of capillaries by infected red blood cells leading to the release of inflammatory cytokines like tumor necrosis factor ⁵³. Similarly, shock expressed either as a function of the systolic blood pressure or cold peripheries in three models in children ^{21 31 32} and likewise in two models in adults ^{19 41} could result from peripheral vasodilation which may usually occur concomitantly with sepsis and is a marker of a poor prognosis ^{8 54 55}.

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From the above, factors that were predictive of disease severity and mortality seemed to be consistent amongst these studies. The factors that should therefore be considered by physicians when faced with a patient with malaria infection should include: neurologic dysfunction (coma and seizures), acidosis, hypoglycaemia and respiratory distress (Figure 2). These factors seem to be highly predictive of mortality and disease severity in most of the articles that were included in the review and should therefore be included in any future studies attempting to predict these outcomes in malaria.

We found evidence of external validation in only seven of the models identified in this study ^{18 20 24 31} ³². External validation is an important component as it determines the generalisability of the model and its potential use in different geographical regions ⁵⁶. As outlined above, most of the models have similar variables highlighting the fact that the predictors of complications, severity and mortality in malaria might be consistent across different settings. Emphasis could therefore be better placed in the validation of existing models and initiating their use in clinical settings to guide clinicians on prioritising patients and anticipating outcomes. Publication of the findings on the use of these models in clincal settings should also be encouraged to guide clinicians on which models work better in various settings.

After assessment of the risk of bias of the various models, eighteen of the studies contained models that used variables that could be readily available and hence were applicable in real-life settings. However, all the models had a high risk of bias. This was primarily due to the lack of internal validation in several of the studies or the lack of use of up-to-date methods of validation. Caution should therefore be used when interpreting and using the results from the articles.

This review has some limitations. The search included only articles that were published in English. This could potentially lead to the exclusion of studies and models that could otherwise have been included in the review.

Conclusion:

Models predicting severity and mortality of malaria infection identified in this review have similar predictors. Evidence is however lacking on the generalisability of most of these models due lack of external validation. Emphasis should therefore be placed on external validation of existing models and publication of the findings of their use in clinical settings to guide clinicians on management options depending on the priorities of their patients.

Abbreviations:

APACHE: acute physiology and chronic health evaluation system; AUC: area under the curve; AUROC: area under the receiver operating curve; CAM: coma acidosis malaria; GCRBS: Glasgow coma scale, creatinine, respiratory rate, bilirubin and systolic BP; ICU: intensive care units; IQR: Interquatile range; LODS:Lambarene Organ Dysfunction Score; MODS: Multi-organ dysfunction score; MPI: Malaria Prognostic index; MPS: Malaria prediction score; MSA: Malaria score for adults; MSS: Malaria severity score; PEDIA: Pediatric Early Death Index for Africa; PRISM: Pediatric Risk of Mortality; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCT: randomised control trial; SEQUAMAT: South East Asian Quinine Artesunate Malaria Trial; SICK: Signs of Inflammation in Children that Kill; sMODS: Simplified MODS; TNF: tumour necrosis factor; WHO: World Health Organisation

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Consent for publication: Not applicable

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Authors' contributions: Conception: TN; independent reviews of papers: TN & BST; writing of initial draft: TN; manuscript revisions: TN & BST. Review only

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Table 1: Summary of articles with models predicting complications in severe malaria Ν Authors Year Period of Country Type of Sample Statistics Name Method Age participant study internal of profiles size used of recruitment model validation **Complications of malaria** Severe anaemia Weber 1997 July – Gambia Cohort 368 Logistic None None Median 15 age: 28 December regression 1994 months (IQR: 14 - 48 months) **Development of sepsis** 2 Njim⁸ 2018 June 2003 Bangladesh, Randomised 1187 Logistic None Bootsrapping 17 - 87Control – Mav India. regression vears 2005 Indonesia Trial and Myanmar * not used in present model; BCS: Blantyre coma score; NC: not clear; NE: No evidence; ^a diagnostic properties of original model, IQK. Interquation in RCT: randomised control trial; ACT: artemisinin combined therapy; DRC: Democratic Republic of the Congo; BUN: Blood urea nitrogen; TNF: tissue necrotic factor Table 2: Summary of articles with models predicting mortality in paediatric severe malaria * not used in present model; BCS: Blantyre coma score; NC: not clear; NE: No evidence; a diagnostic properties of original model; IQR: interquatile range; Ν Authors Yea Period of Country Type of Statistics Name of Method Sampl participan study used model internal of r e size validation recruitme nt

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1	Janar 21	7	1992 – 1994	Gamoia	ve analysis of data from a randomised control trial	624	regression	None	None	years	s – 49%	in g paediatrof c cerebral ses	by the second se	Not done	None	NE
2	Molyneu x ²⁷	198 9	January 1987 – June 1988	Malawi	Cohort	131	Univariab le analysis	Bedside prognostic index	None	7 months – 10 years	Female s – 55.7%	Mortalitise in paediatred to c cerebral to text malaria and da	In the second se	Positive predictive value – 83%, sensitivity – 66%	None	NE
3	Conroy ¹⁶	201 2	1997 – 2009	Malawi	Cohort	155	Logistic regression	None	Hosmer- Lemeshow goodness- of-fit test	8 months – 14 years	Female s – 54.4%	Mortalita in mining, Al training, ar malaria ltraining, ar	Age, Blantyre Age, B	C-index of 0.79 (95% CI 0.72 – 0.84)	None	NE
4	Krishna 22	199 4	1988 – 1989	Gambia	Cohort study	115	:Logistic regression	None	Wald statistic and ROC analysis	18 months – 12 years	NC	Mortalit a simi in simi paediatr mi c severea malaria techno	Goma score, Whole blood lactate/glucos atio, TNF level ON Ma	Wald statistic: coma score (4.5), lactate/gluco se ratio (8.36), TNF level (6.5)	None	NE
5	Marsh ²³	199 5	May 1989 – Novembe r 1991	Kenya	Cohort	1844	Logistic regression	None	None	Mean: 26 months	NC	Mortalit Q in c hildren. with severe malaria	Impaired consciousness spiratory destress, hypoglycemia , and jaundice	Predicted 92.2% of deaths	None	NE
6	Newton 28	200 5	January 2001 – December 2003	Malawi, Kenya and Ghana	Cohort	14605	Linear regression	None	AUROC	Mean age: 32 - 36 months	Female s - 53 - 55%	Mortality in paediatri c severe falciparu	Incep Breathing, Brantyre Grand Score, intability to st weight-	C-statistic 0.83 – 0.88 in the three sites: Blantyre (0.88), Kilifi	None	NE

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7	Gérardin ³²	200 6	October 1, 1997 – March 31, 1999	Senegal	Cohort	311	Logistic regression	PRISM (Pediatric Risk of Mortality) AUC: 0.92 40	Hosmer- Lemeshow chi-square test	Media n: 8 years (IQR: 5 – 11 years)	Female s – 40.5%	Mortalities in children elated with falciparud to text and data mining, Al tra	Systolic Systol	AUROC for acute malaria: 0.89 (95% CI: 0.85 – 0.92) and 0.86 (95% CI: 0.81– 0.90) for severe malaria	Yes	
8	Helbok 20	200 9	December 2000 – May 2005	Gambia, Malawi, Kenya, Ghana, and Gabon	Cohort	23890	Logistic regression	LODS (Lambaréné Organ Dysfunctio n Score)	Internal validation using Bonferroni correction	Mean: 30 – 38 months	Female s - 41% - 47%	Mortality in childrennd sin with severe falciparti m malaria	Gunt Gyma, Hostration and deep breathing	AUROC: 80 0.80 (0.79 – 0.82)	Yes	_
9	von Seidlein ³⁰	201 2	2005 - 2010	Gambia, Mozambiqu e, Nigeria, Rwanda, Kenya, DRC, Tanzania, Ghana, Uganda	Retrospecti ve analysis	5426	Logistic regression	None	ROC analysis	Media n: 2.8 years (1.7, 4.3)	NC	Mortalit in paediatro c severe falcipart m malaria	Base deficit, Mana, We Nulsions, BAN and chronic iBass 25 at	AUROC: 0.85 (95% CI: 0.83 - 0.87)	None	
1 0	Conroy 31	201 5	NC	Uganda	Cohort	1589	Logistic regression	SICK (Signs of Inflammati on in Children	Hosmer- Lemeshow goodnesso f- fit	NC	Female s – 54.3%	Mortality in malaria	Agtered Agenerature, Ageneratur	AUROC – 0.846	Yes	-

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							II score use clinical judgement and physiologic relationship s to assign weightings)					falcipa m mala for uses	Agematocrit, WBC count, Godium, Botassium and Clasgow Woma score			
2	Dondorp 17	200 4	NC	Vietnam	Cohort	268	Logistic regression	None	Hosmer- Lemesho w goodness- of-fit test	15 – 79 years	Female s – 19%	Mortality in adulted with d severe to falciparted m malaga	Blasma Bactate, Dlasma strong Conion gap and Colasma Creatinine	AUROC: 0.81	None	
3	Mishra ²⁴	200 7	NC	India	Cohort	212	Linear regression	MSA (Malaria score for adults)	Not done	NC	NC	Mortaliane in adulta data with data severe ata malaria mining, Al t	Gevere Maaemia, Jocute renal Aailure, Geospiratory Gerebral Malaria	Sensitivity : 89.9%, specificity : 70.6%, positive predictive value: 94.1% with cut- off of 5/10	Yes ⁴³	
								MPS (Malaria prediction score)	Not done	NC	NC	Mortalia in several malariage and similar te	Age, serum reatinine revel, aemoglobin revel, cerebral malaria, presence of a pregnancy, se of a prentilator	NE	Yes ⁴³	
4	Hanson ¹⁸	201 0	June 2003 – May 2005	Banglades h, India, Indonesia and Myanmar	Retrospectiv e analysis of a randomised control trial	789	Logistic regression	CAM (coma acidosis malaria) score	Hosmer- Lemesho W goodness- of-fit	NC	NC	Mortality in adulted with severe de malaria	Foma and Acidosis (base Fricit 14, 2	AUROC: 0.81 (95% CI: 0.77 – 0.84)	Yes ⁵⁹	
5	Mohapatra 26	200 9	January 200 – December 2004	India	Cohort study	2089	Logistic regression	MSS (Malaria severity score)	Hosmer- Lemesho W goodness- of-fit (internal validation by splitting	18 – 71 years	Female - 34.6%	Mortality in adult patients with severe falciparu m malaria	Seurologic, Tenal, Aaematologic, Depatic, Despiratory, ardiovascula m, and enetabolic Torgan systems	AUROC: 0.9	None	

								BMJ Op	en			1 by copyright, ir	/bmjopen-2019-(20
									data – 2089 vs 509)			ncluding for	030793 on 26			
6	Newton ²⁹	201 3	1986 – 2002	Thailand	Retrospectiv e analysis	988	Logistic regression	MPI (Malaria prognosti c index)	ROC curve analysis and internal validation by data splitting	15 – 74 years	Female s – 43%	Mortalusy in adults severe re falciparts m malate to text an	Filasgow Goma scale, Marasitaemia, Jalasma Marasite, serum Milirubin, Marasites and Graatment With ACT	AUROC: 0.97	None	NE
7	Mohapatra ²⁵	201 4	NC	India	Cohort	112	NC	GCBRS (GCS, creatinine , respirator y rate, bilirubin and systolic BP) score	NC	Mean: 35.8 ± 15.1 years	Female s – 16.1	Mortal A in seve falcipata m malatining, Al trait	Terebral Constantia, renal Constantia, renal Con	Sensitivity : 85.3%. Specificity : 95.6%	None	NE
8	Hanson ¹⁹	201 4	1996 – 2013	Banglades h, India, Indonesia, Vietnam and Myanmar	Randomised control trials and cohort studies	1801	Logistic regression	None	Hosmer- Lemesho W goodness- of-fit	21 - 45	Female s - 24.4	48-houng survivag and survivag to since and discharation patients, technologies,	A hock, oligo- onuria, eysglycaemia, respiratory ate, Glasgow Coma Score ond absence of fever on May 14, 2	PPV for 48 hour- survival: 99.4% (95% CI 97.8 – 99.9). PPV for survival to discharge: 96.9% (95% CI: 94.3 – 98.5)	None	NE

* not used in present model; BCS: Blantyre coma score; NC: not clear; NE: No evidence; a diagnostic properties of original model; IQR: interquatile range; RCT: randomised control trial; ACT: artemisinin combined therapy; DRC: Democratic Republic of the Congo; BUN: bood urea nitrogen; TNF: tissue necrotic factor Department GEZ-LTA

Table 4: Summary of articles with models predicting severity of malaria infection

3

								BM	J Open			1 by copyright,	/bmjopen-201§			21
N	Author s	Year	Period of participant recruitmen t	Country	Type of study	Sample size	Statistics used	Name of model	Method internal of validatio	Age profile s	Sex profiles	Outcome Cluding fo	Seriables used	Diagnosti c properties	External validatio n	Use in clinical setting s
Sev	erity of dis	sease				I	I				1	L L	6			
1	Helbok ³⁵	200 3	October 1, 2001 – January 30, 2002	Thailand	Cohor t	22	NC	MODS (Multi- organ dysfunctio n score) ⁴⁴	None	16 – 41 years	Female - 41.8%	Severity of Severity of severity of severity of adult patients adult patients and data mining,	The norgan sestems: The art, blood sestems: The art, blood, metabolism, fittabolism	None	None	NE
2	Helbok ³⁴	200 5	October 1, 2001 – July 30, 2002	Thailand	Cohor t	29	Survival analysis	MODS 44	None	Mean age: 27.1 (± 10.6)	Female 27.6%	Severity of disease in adult patients, and similar technologie malaria	The organ systems: (beart, blood wessel, blood, performation system, and system, liver, ledney and unary thet, immune system, and contral mervous system)	None	None	NE
3	Helbok 36	200 6	August 2003 – May 2005	Gabon	Cohor t	485	Survival analysis	Simplified MODS ³⁵	ROC analysis	4 months – 169 months	Female s – 49%	Severity of disease and disability in children with severe falciparum malaria infection	Non organ Systems: (Heart, blood vessel, blood, repiratory System, netabolism, systrointestina Pystem, liver,	AUC to predict prolonged disease (>48 hours unable to walk): 0.92 (95%)	None	NE

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								BM	J Open			d by copyright, ir	i/bmjopen-2019-(22
												cluding for use	Beiney and Beinary teect, immune Sestem, and Contral nervous Sestem)	CI, 0.89– 0.95).		
4	Grigg 37	201 8	October 2012 – April 2016	Malaysi a	Cohor t	481 patients with Plasmodiu m knowlesi	Logistic regressio n	None	None	33 years (IQR: 21 – 49)	Female - 43.2%	Severity of S related <i>Plasmodium</i> <i>knowlesi</i> infection using WHO 2014 researcher criteria ⁴⁵ and dat	Age >45, Age >4	None	None	NE

* not used in present model; BCS: Blantyre coma score; NC: not clear; NE: No evidence; * diagnostic properties of profismal model; IQR: interquatile range RCT: randomised control trial; ACT: artemisinin combined therapy; DRC: Democratic Republic of the Congo; BUSY. Bood urea nitrogen; TNF: tissue necrotic factor; WHO: World Health Organisation; IQR: Interquatile range * not used in present model; BCS: Blantyre coma score; NC: not clear; NE: No evidence; a diagnostic properties of original model; IQR: interquatile range;

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10.1016/S0140-6736(13)60024-0 [published Online First: 2013/08/21]
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Figures Legends:

Figure 1: Flow chart showing reasons for exclusion of various studies from the review

Review only

Figure 2: Predictive factors of disease severity and mortality in malaria infection

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seizures coma NEUROLOGIC DYSFUNCTION altered mental status renal MORTALITY DUE failure ACIDOSIS TO SEVERE MALARIA shock INFECTION acute RESPIRATORY respiratory DISTRESS distress syndrome HYPOGLYCAEMIA Predictive factors of disease severity and mortality in malaria infection For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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A	Appendix 1: PRISMA checkl	ist for sy	stematic reviews and meta-analysis.	
T	Sable 1		ng for 20	
	Section/topic	#	Checklist item	Repo on p
	TITLE			1
	Title	1	Identify the report as a systematic review, meta-analysis, or both.	
	ABSTRACT			
	Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; restricted to the synthes;	2
	INTRODUCTION		in from	
	Rationale	3	Describe the rationale for the review in the context of what is already known.	3
	Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
	METHODS			
	Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Webaddress), and, if available, provide registration information including registration number.	4
	Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report acteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational g	4
	Information sources	7	Describe all information sources (e.g., databases with dates of coverage, and study authors to identify additional studies) in the search and date last searched.	4
	Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
	Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5

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		Jht, inc. 019-03	1
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (in guding specification of whether this was done at the study or outcome level), and how this information is to be used in giny data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in meane).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, defined and combining results of studies,	5
		lo text	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evices (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the eview, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations.	6 -11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) signple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a ferrest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 45).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION		ep ep	
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main eutrome; consider their relevance to	11

	3	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at regimerative (e.g., incomplete identified research, reporting bias).	e retrieval of			
Conclusio	าร	26	Provide a general interpretation of the results in the context of other evider end implications for ful	ture research.			
FUNDING	3						
Funding		27	Describe sources of funding for the systematic review and other support (egginger burger) of data); role of systematic review.	f funders for the			
Fable 1a: S	Sources	Medlin	ne database				
Searches	Search	Sea	rch terms	Number of			
Startics	combinations			hits			
Startenes	combinations	"pro	bgnost* model" OR "predict* model" OR "Predictive Value of Tests"	hits 208,974			
S1 S2	combinations	"pro	ognost* model" OR "predict* model" OR "Predictive Value of Tests" gg odict* score" OR "prognos* score" gg	hits 208,974 3,884			
S1 S2 S3	combinations S1 OR S2	"pro	ognost* model" OR "predict* model" OR "Predictive Value of Tests" g odict* score" OR "prognos* score" d	hits 208,974 3,884 211,947			
S1 S2 S3 S4	combinations S1 OR S2	"pro "pre (MH Falc	beginset* model" OR "predict* model" OR "Predictive Value of Tests" edict* score" OR "prognos* score" H "Malaria+") OR (MH "Malaria, Vivax") OR (MH "Malaria, Cerebral") OR (MH "Malaria, eiparum+") OR (MH "Malaria, Avian")	hits 208,974 3,884 211,947 63,536			
S1 S2 S3 S4	combinations S1 OR S2	(MF Falc "Ma "clin	pgnost* model" OR "predict* model" OR "Predictive Value of Tests" edict* score" OR "prognos* score" H "Malaria+") OR (MH "Malaria, Vivax") OR (MH "Malaria, Cerebral") OR (MH "Malaria, Eiparum+") OR (MH "Malaria, Avian") daria" OR "vivax malaria" OR "falciparum malaria" OR "cerebral malaria" OR nical malaria" OR plasmodium OR antimalaria* OR anti-malaria*	hits 208,974 3,884 211,947 63,536 111,461			
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Sable 1b: S	Search strategy for	· CINAHL database	
Searches	Search	Search terms of a	Number o
	combinations		hits
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S2		"predict* score" OR "prognos* score"	1,041
S 3	S1 OR S2		50,217
S4		(MH "Malaria+")	7,468
		"Malaria" OR "vivay malaria" OR "falcinarum malaria" OR "cerebral malaria" OR "Bevere malaria" OR	10,945
S5		"clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*	
S5 S6	S4 OR S5	"clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*	10,945
S5 S6 S7	S4 OR S5 S3 AND S6	"clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*	10,945 52
S5 S6 S7 Fable 1c: S	S4 OR S5 S3 AND S6 Search strategy for	Global Health database	10,945 52
S5 S6 S7 Fable 1c: S Searches	S4 OR S5 S3 AND S6 Search strategy for Search combinations	Mataria OK Vivax mataria OK fatepartin mataria OK cerebrat mataria "clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria* ning Al training, and Global Health database Search terms	10,945 52 Number o hits
S5 S6 S7 Cable 1c: S Searches	S4 OR S5 S3 AND S6 Search strategy for Search combinations	Image: Search terms Search terms "prognost* model" OR "predict* model" OR "Predictive Value of Tests"	10,945 52 Number of hits 2,906
S5 S6 S7 Cable 1c: S Searches S1 S2	S4 OR S5 S3 AND S6 Search strategy for Search combinations	Walania OK Viva malana OK nacipatum malana OK eccora malana "clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria* mining, Al training, Al training, Al training, Book Global Health database "prognost* model" OR "predict* model" OR "Predictive Value of Tests" "predict* score" OR "prognos* score"	10,945 52 Number of hits 2,906 368
S5 S6 S7 Fable 1c: S Searches S1 S2 S3	S4 OR S5 S3 AND S6 Gearch strategy for Search combinations	Wataria OK viva malaria OK falciparum malaria OK ecceptaria malaria "clinical malaria" OR plasmodium OR antimalaria OR anti-malaria* "ining, and from training, and from on training, and f	10,945 52 Number of hits 2,906 368 2,906
S5 S6 S7 Fable 1c: S Searches S1 S2 S3 S4	S4 OR S5 S3 AND S6 Gearch strategy for Search combinations S1 OR S2	Malaria OK vivax malaria OK falciparum malaria OK celebral malaria "clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria* mining Malaria" OR plasmodium OR antimalaria* OR anti-malaria* Malaria" OR plasmodium OR antimalaria* OR anti-malaria* Malaria Global Health database Search terms "prognost* model" OR "predict* model" OR "Predictive Value of Tests" "predict* score" OR "prognos* score" "Malaria" OR "vivax malaria" OR "falciparum malaria" OR "cerebral malaria" OR "Severe malaria" OR "Malaria" OR plasmodium OR antimalaria* OR anti-malaria*	10,945 52 Number of hits 2,906 368 2,906 89,436

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Sluuv	Risk of bias				Applicability		i D	Overall	
~~~~)	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability
Conroy 2012	+	+	+	-	+	-	sn Ag	-	
Conroy 2015*	+	+	+	-	+	+	es þ	-	+
Dondorp	+	+	+	-	+	+	re	-	+
Gerardin*	+	+	+	-	+	+	at	-	+
Grigg	+	+	+	_	+	+	ed ed	-	+
Hanson 2010	+	+	+	-	+	+	to	-	+
Hanson 2014	+	+	+	-	+	+	19. te	-	+
Helbok 2003*	+	-	+	-	+	-		-	-
Helbok 2005*	+	-	+	-	+	-	9 NU D NU	-	-
Helbok 2006*	+	-	+	-	+	-		-	-
Helbok 2009	+	+	+	-	+	+	ad ata	-	+
Jaffar	+	+	+	-	+	+	n ed	-	+
Krishna	+	+	+		+	-	in fr	-	-
Marsh	+	+	+	-	+	+	ng m⊒c	-	+
Mishra	+	+	+	<u> </u>	+	+	, <u>1</u>	-	+
Mohapatra 2009	+	+	+	- " (	+	+	<mark>tp://t</mark>	-	+
Mohapatra 2014	+	+	+	-	+	+	ning	-	+
Molyneux	+	+	+	-	+	+	<u>ନ</u> କ	-	+
Newton 2005	+	+	+	-	+	+	b D	-	+
Newton 2013	+	+	+	-	+	+	, <mark>p</mark> j	-	+
Njim	+	+	+	-	+	+	nil: 6	-	+
von Seidlein	+	+	+	-	+	+	ar :	-	+
Webber	+	-	-	-	-	-	ol iec	-	-
Wilairatana*	+	+	+	-	+	+		-	+

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Р	PRISMA checklist for system	atic revi	ews and meta-analysis.	
	Section/topic	#	Checklist item	
	TITLE		ated ater	
-	Title	1	Identify the report as a systematic review, meta-analysis, or both.	
	ABSTRACT			
	Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; restrictions; conclusions and implications of key findings; systematic review registration number.	2
	INTRODUCTION		in from	
	Rationale	3	Describe the rationale for the review in the context of what is already known.	
	Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	;
	METHODS			
	Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Webaddress), and, if available, provide registration information including registration number.	•
	Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report acteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational g	•
	Information sources	7	Describe all information sources (e.g., databases with dates of coverage, sonsect with study authors to identify additional studies) in the search and date last searched.	•
	Search	8	Present full electronic search strategy for at least one database, including any imits used, such that it could be repeated.	4
	Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	

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Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (in guding specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in meane).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, be including measures of consistency (e.g., l ² ) for each meta-analysis.	5
		o text	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evider (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations.	6 -11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) signple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a ferrest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 45).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION		ep	
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main gutcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11

Page 37 of 37			BMJ Open C C D C	
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3 4 5	Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at received evel (e.g., incomplete retrieval of identified research, reporting bias).	13
6	Conclusions	26	Provide a general interpretation of the results in the context of other evider e, and implications for future research.	13
7 8	FUNDING		L C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C C S C C S C C S C C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C S C C C S C C S C C S C C S C C C S C C S C C S C C S C C C S C C S C C S C C S C C C S C C S C C S C C S C C C S C C C S C C C S C C C S C C C S C C C C C S C C C C C C C C C C C C C C C C C C C C	
9 10	Funding	27	Describe sources of funding for the systematic review and other support (each supply of data); role of funders for the systematic review.	14
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# Prognostic models for the clinical management of malaria and its complications: a systematic review

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<b>Primary Subject Heading</b> :	Global health
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	malaria, prognostic model, prognostic score, mortality



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5 4	Prognostic models for the clinical management of malaria and its complications: a systematic
5	review
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# Abstract

**Objective:** Malaria infection could result in severe disease with high mortality. Prognostic models and scores predicting severity of infection, complications and mortality could help clinicians prioritise patients. We conducted a systematic review to assess the various models that have been produced to predict disease severity and mortality in patients infected with malaria.

Design: A systematic review.

Data sources: Medline, Global health and CINAHL were searched up to 04th of September 2019.

**Eligibility criteria for selecting studies:** Published articles on models which used at least 2 points (or variables) of patient data to predict disease severity; potential development of complications (including coma or cerebral malaria; shock; acidosis; severe anaemia; acute kidney injury; hypoglycaemia; respiratory failure and sepsis) and mortality in patients with malaria infection.

**Data extraction and synthesis:** Two independent reviewers extracted the data and assessed risk of bias using the Prediction model Risk Of Bias Assessment Tool (PROBAST).

**Results:** A total of 564 articles were screened and 24 articles were retained which described 27 models/scores of interests. Two of the articles described models predicting complications of malaria (severe anaemia in children and development of sepsis); fifteen articles described original models predicting mortality in severe malaria; three articles described models predicting mortality in different contexts but adapted and validated to predict mortality in malaria; and four articles described models predicting severity of the disease.

For the models predicting mortality, all the models had neurologic dysfunction as a predictor; in children, half of the models contained hypoglycaemia and respiratory failure as a predictor meanwhile, six out of the nine models in adults had respiratory failure as a clinical predictor. Acidosis, renal failure and shock were also common predictors of mortality.

Eighteen of the articles described models that could be applicable in real-life settings and all the articles had a high risk of bias due to lack of use of consistent and up-to-date methods of internal validation.

**Conclusion:** Evidence is lacking on the generalisability of most of these models due lack of external validation. Emphasis should be placed on external validation of existing models and publication of the findings of their use in clinical settings to guide clinicians on management options depending on the priorities of their patients.

Key words: malaria; prognostic model; prognostic score; mortality

Prospero registration number: CRD42019130673

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#### Article Summary:

#### Strengths and limitations of this review:

This review is the first to comprehensively summarise the various prognostic models that have been produced to identify complications, severity and risk of mortality in patients with severe malaria.

The review covers prognostic models produced worldwide and for all the various malaria species.

The review reduced the risk of bias by using an independent review process for the screening of potential articles and the extraction of data.

Considering the wide variety of statistical methods used to generate and validate these models, there is the risk of heterogeneity in interpretation of the results.

The search was carried out in only one language which could potentially exclude some relevant studies published in different languages.

#### Introduction

Malaria is a disease caused by infection with a protozoan parasite of the genus *Plasmodium*. The most relevant of these species is *Plasmodium falciparum* as it causes most deaths from the disease ¹. Another species of relevance is *Plasmodium vivax* which is predominantly found in Asia and has a wider distribution ². Malaria infection can result in severe disease and is associated with a high mortality. In about 108 countries where the transmission of the disease still occurs, an estimated 435,000 people died in 2017 ³⁴.

The incidence of malaria cases has decreased by 41% worldwide in the past ten years, with about 17 countries in Latin America and the Middle East reporting no new cases of malaria over this period ^{3 5}. There are however concerns that the fight against malaria might be slowed down by an overemphasis on prevention over treatment ⁶.

Treatment and clinical management of malaria is made difficult due to potential evolution of simple infections into life-threatening severe disease; the multi-organ affection of severe disease; the dilemma of when to admit to intensive care units (ICU) considering limited resources and the occurrence of concomitant sepsis infection with malaria ^{7 8}. Some of these issues can be addressed with the help of guidelines; scores or models that could help clinicians predict the occurrence of severe disease and complications in order to act appropriately.

We therefore conducted this review to systematically assess the various predictive models or scores available to guide clinicians in the management of severe malaria, whether these models have been validated and if there is any evidence that they are being successfully used in the clinical setting.

#### Methods

Institutional review board approval and informed consent were not required for this systematic review. We reported our findings according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Appendix 1).

# Search strategy and selection criteria

We searched MEDLINE, CINAHL and Global Health databases using a tailored search strategy (Appendix 2) to identify all the relevant titles and abstracts of studies (randomised control trials, cohort, cross-sectional and case-control studies) published in English from inception of the database up to the 04th of September 2019, that reported predictive/prognostic scores or models that could be used in the management of malaria. These included:

- Scores/models that predicted the severity of disease as this could guide clinicians' decisions to admit for intensive care management or the use of parenteral treatment;
- Scores/models that predicted the potential development of complications (including coma or cerebral malaria; shock; acidosis; severe anaemia; acute kidney injury; hypoglycaemia; respiratory failure and sepsis);
- Scores/models that predicted mortality in patients with malaria infection.

The main keywords in the search strategy included: "prognostic model/score", "predictive model/score" and "predictive value of tests" coupled with "malaria", "plasmodium", "anti-malarials", "malaria falciparum", "malaria vivax" and "clinical malaria". We further canvassed the references of eligible papers to identify similar papers for review.

We excluded any duplicate studies, editorials, systematic reviews, case studies, conference abstracts, unpublished studies and expert commentaries. For studies with more than one publication of findings, we selected the most recent publication.

We also excluded studies which contained models or scores that were aimed at the diagnosis of malaria as we intend to limit the scope of the review to only models that could be used to predict severity, mortality or risk of complications – that could guide clinicians in their management options. Studies that used animal models to predict disease severity were also excluded.

Two independent reviewers (TN and BST) screened the titles and abstracts for compliance to the aforementioned inclusion and exclusion criteria and any conflicts were settled by mutual agreement. Articles considered to have data relevant to the topic were assessed in detail and the references cited in these publications were searched to identify further publications.

# **Data extraction**

Data extraction sheets which were prepared prior to screening were used by the two independent reviewers to obtain the following details for inclusion into the final review: Last name of first author;

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date of publication; period of patient recruitment and/or follow-up; country of study; sample size; age group; type of predictive model; name of model; method of internal validation (calibration and discrimination); diagnostic properties of model and evidence of external validation or use in clinical settings.

# Definitions

By prognostic/predictive model, we mean a statistical tool which uses at least 2 points (or variables) of patient data to predict a specific clinical outcome ⁹. Prognostic models applied in clinical settings are usually used at the discretion of physicians for accurate future predictions based on characteristics gathered in the present ^{9 10}. The information found in prognostic models is usually specific to the patients' characteristics rather than the disease or treatment and includes: prediction of chance or the duration of survival; classification of patients into risk groups; and prediction of clinical events related to the treatment the patient is receiving ¹¹.

For models that used the area under the curve (AUC) or c-statistic to assess discrimination, the following classification was used: 0.90 - 1 - excellent; 0.80 - 0.90 - good; 0.70 - 0.80 - fair; 0.60 - 0.70 - poor and  $0.50 - 0.60 - \text{very poor discriminative properties}^{12}$ .

#### Data synthesis and analysis

We assessed and discussed the selected studies qualitatively to describe the diagnostic properties of the models proposed in the study, their intended purpose and evidence of use of the model in other clinical settings.

We further divided the models into various categories: models used to predict a potential complication of severe malaria; models used to predict mortality as an outcome and models used to predict severity of malaria infection.

#### Assessment of risk of bias and applicability

The risk of bias and applicability of the models in the various studies were assessed by the two independent reviewers using the Prediction model Risk Of Bias Assessment Tool (PROBAST)^{13 14} (Appendix 3). Any disagreements were handled by mutual agreement.

#### Patient and public involvement:

Patients and the public were not involved in the design and conduction of this review.

#### Results

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A total of 564 articles were identified by the electronic search of the databases. The titles and abstracts of these articles were screened to retain 59 articles for full text review. These were then evaluated according to the inclusion criteria and 24 articles were identified describing 27 models/scores of interests; after eliminating 23 irrelevant articles, 9 articles which used only one variable to predict an outcome and two articles describing models in other languages (Figure 1).

Two of the articles described models predicting complications of malaria ^{8 15}; fifteen described original models predicting mortality in severe malaria ¹⁶⁻³⁰; three described models predicting mortality in different contexts but adapted and validated to predict mortality in malaria ³¹⁻³³; and four articles described models predicting severity of the disease ³⁴⁻³⁷. One of the articles described three models to predict mortality paediatric severe malaria ³¹, while another described two models to predict mortality in adult severe malaria ²⁴. The rest of the articles described one model each.

Using the PROBAST to assess risk of bias and applicability, none of the studies had a low risk of bias while six studies were not found to be applicable in real-life settings ¹⁵ ¹⁶ ²² ³⁴⁻³⁶ (Appendix 3).

The general characteristics of the studies included in the review are summarised in Tables 1, 2, 3 and 4.

#### Models predicting the risk of complications in malaria infection

Webber *et al* ¹⁵ in 1997 conducted a study to predict the risk of severe anaemia (packed cell volume < 15%) in children with severe malaria in the Gambia using logistic regression analysis. This model was not internally validated, and the two predictors identified were pallor of the conjunctiva and pallor of the palms. There is no evidence from this review that the model has been externally validated and is being used in clinical settings.

In 2018, Njim *et al* ⁸ described a prognostic model for clinical use to predict the risk of sepsis development amongst adult patients (> 16 years old) admitted for severe falciparum malaria in Southeast Asia. They used data from SEQUAMAT (South East Asian Quinine Artesunate Malaria Trial) – a large randomised control trial (RCT) conducted to determine the benefits of intravenous artesunate over quinine treatment for severe malaria. They used a multivariable logistic regression approach with internal validation using bootstrapping to generate a prognostic model with modest discriminative abilities [area under the curve (AUC): 0.789] containing the following predictive variables: female sex, high blood urea nitrogen, high plasma anion gap, respiratory distress, shock on admission, high parasitaemia, coma and jaundice. The model has not been externally validated and there is no evidence of use in clinical settings.

#### Models predicting mortality in severe malaria

Models predicting mortality in paediatric severe malaria

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Ten articles described models that predicted mortality in paediatric severe malaria ^{16 20-23 27 28 30-32}. Three articles described models which predicted mortality in paediatric patients with cerebral malaria ^{16 21 27}; two articles described models generated to assess mortality in different conditions that were validated for use in the present studies ^{31 32}; and five articles described original models predicting the risk of mortality in children with severe malaria ^{20 22 23 28 30}.

# Models predicting mortality in paediatric cerebral malaria

Molyneux *et al* ²⁷ in 1989 conducted a study amongst 131 comatose Malawian children with severe cerebral malaria to determine the prognostic factors for death in these patients. The authors derived a "bedside prognostic index" with: blood glucose  $\leq 2.2 \text{ mmol/L}$ ; parasitaemia  $> 106 \text{ ring forms/}\mu\text{L}$ ; white blood cell count > 15 x 10/L; age  $\leq 3 \text{ years}$ ; coma score (modification of the Glasgow coma score) = 0; absent corneal reflexes; signs of decerebration and convulsions; as predictors of mortality with each predictor assigned a score of 1. Individuals with a score  $\geq 4$  were more likely to die. This score was calculated only using univariable analysis and internal and external validation were not done.

In 1997 in Gambia, Jaffar *et al*²¹ performed a retrospective analysis on data obtained from a randomised control trial during which artemether was compared with quinine and a monoclonal antibody against tumour necrosis factor (TNF) compared with a placebo in patients with cerebral malaria. They used this data to identify predictors of mortality in cerebral malaria using a multivariable logistic regression model. A cold periphery, a coma score of either 0 or 1 (assessed using the Blantyre coma scale measured on a scale of 0 - 5), and hypoglycaemia were found to be present at admission in 90% of the children who died. This model was not internally validated.

Conroy *et al* ¹⁶ in 2012 conducted a study amongst 155 children aged 8 months – 14 years in Malawi to determine predictors of mortality in cerebral malaria. They used a multivariable logistic regression model containing clinical parameters and biomarkers with a modest discriminative ability (C-index of 0.79) after internal validation; which contained the following variables: age, Blantyre coma score, respiratory distress, severe anaemia, angiopoietin-1, angiopoietin-2 and sTie-2 levels. The model was not externally validated.

#### Original models predicting mortality in paediatric severe malaria

Krishna *et al*²² in 1994 conducted a study in the Gambia to predict mortality in children aged 8 months to 14 years. They used a multivariable logistic regression model internally validated using the Wald statistic to determine that the coma score (using the Blantyre coma scale), whole blood lactate/glucose ratio and TNF level were the best predictors of death.

In 1995, Marsh *et al* ²³ studied 1844 children in Kenya to determine predictors of life-threatening malaria (risk of death) using a multivariable logistic regression model. They determined that impaired

consciousness (assessed using the Blantyre coma scale), hypoglycaemia, respiratory distress and jaundice could correctly predict 84.4% of deaths in the sample population. The model was not validated internally or externally.

 In 2005, Newton *et al* ²⁸ conducted a study to assess the prognostic value of measures of acid/base balance in paediatric falciparum malaria. They examined 14,605 children in Malawi (Blantyre), Kenya (Kilifi) and Ghana (Kumasi); where they determined that deep breathing, Blantyre Coma Score, inability to sit, and weight-for-age Z score were independent predictors of mortality in all the three sites. Discrimination of the model was performed by calculating the area under the receiver operating curve (AUROC). After addition of laboratory data to these models – hypoglycaemia, base excess and lactate concentrations; the c-statistics obtained were 0.88 (Blantyre), 0.87 (Kilifi) and 0.83 (Kumasi) denoting good discriminative properties of the models.

Helbok *et al* ²⁰ in 2009 produced the the Lambarene Organ Dysfunction Score (LODS) which combined three variables: coma, prostration, and deep breathing to generate a model using multivariable logistic regression which predicted death in African children – Banjul (Gambia), Blantyre (Malawi), Kilifi (Kenya), Kumasi (Ghana), and Lambarene and Libreville (Gabon); who were admitted for severe falciparum malaria. Each component of the model was assigned a score of 1 and a LODS of 3 at admission had a 98% specificity and 25% sensitivity in predicting death. Meanwhile a LODS  $\geq$  1 had a sensitivity of 85% and a specificity of 63%. The model had good discriminative properties with an AUC of 0.80 (95% CI: 0.79 – 0.82). In 2015, Conroy *et al* ³¹ externally validated this model amongst 1589 Ugandan children. The model showed good discriminative properties with an AUC of 0.898.

Similarly, in 2012, von Seidlein *et al* ³⁰ conducted an analysis of data from a RCT carried out in several African countries (Gambia, Mozambique, Nigeria, Rwanda, Kenya, DRC, Tanzania, Ghana and Uganda) to generate a model for predicting mortality from severe falciparum malaria using multivariable logistic regression analysis and internally validated by AUROC analysis. After analysis of data from 5426 children, base deficit, impaired consciousness (assessed using the Blantyre Coma Score), convulsions, elevated blood urea, and underlying chronic illness were identified in the model to predict mortality with a good discriminative ability – AUROC: 0.85 (95% CI: 0.83 - 0.87).

# Existing Models validated for use in the prediction of mortality in severe malaria in children

As described above, Conroy *et al* ³¹ externally validated the LODS model amongst 1589 Ugandan children. The authors further externally validated two other scores: the SICK (Signs of Inflammation in Children that Kill) score which was developed in India as a practical triage tool using variables related to the systemic inflammatory response syndrome, with data collected from 1,099 children in 2003 admitted for any paediatric illness ³⁸; and the PEDIA (Pediatric Early Death Index for Africa) score which was developed to predict early death amongst 8091 children in Kenya in 2003 admitted

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for paediatric illnesses ³⁹. The original SICK score containing the following variables: altered consciousness, temperature, heart rate, respiratory rate, systolic blood pressure, capillary refill time and age; had good discriminative properties with an AUC of 0.887 ³⁸. Externally validated against this cohort of 1589 children, the score maintained its good discriminative properties with an AUC of 0.846. Similarly, the PEDIA score which originally had excellent discriminative properties with an AUC of 0.93 ³⁹ had good discriminative properties (AUC: 0.896) when externally validated on the cohort of 1589 Ugandan children ³¹. The original PEDIA score contained Kwashiorkor, jaundice, subcostal indrawing, prostration (± seizures) and wasting as variables in the model. However, kwashiorkor was not included in the validation model as it was not measured amongst the Ugandan children.

In 2006, Gerardin *et al* ³² externally validated the PRISM (Pediatric Risk of Mortality) model which was originally developed in 1988 by Pollack *et al* ⁴⁰ to reduce the number of physiologic variables required for paediatric intensive care unit death risk assessment. The model was developed from data of 1,227 patients with 105 deaths and contained 14 variables: systolic blood pressure, temperature, mental status, heart rate, dilatation of pupils, pH, total CO2, PCO2, arterial PaO2, serum glucose, potassium, urea, creatinine, white blood cells, prothrombin time, platelet count. The original score had excellent discriminative properties with an AUC of 0.92 ⁴⁰. Gerardin *et al* used a cohort of 311 Senegalese children admitted with severe malaria to externally validate this model. The model showed good discriminative properties in predicting death in children with severe malaria – AUC: 0.86 (95% CI: 0.81-0.90) ³².

## Models predicting mortality in adult severe malaria

There were eight articles assessing models that predicted mortality in adult severe malaria ^{17-19 24-26 28}
⁴¹.

In 1995, Wilairatana *et al* ⁴¹ used the APACHE II score (the acute physiology and chronic health evaluation system score commonly used in intensive care units) based on 12 physiologic variables – Mean arterial pressure (MAP), temperature, heart rate, respiratory rate, arterial pH, PaO2, haematocrit, WBC count, creatinine, sodium, potassium and Glasgow coma score to predict the risk of mortality in adult patients with cerebral malaria in Thailand. The score was able to predict mortality with a 95.8% accuracy. The original APACHE II model was produced in 1985 by Knaus *et al* ⁴², and clinical judgement and physiologic relationships were used to assign weightings for the various factors in the model.

Dondorp *et al* ¹⁷ in 2004 created a model using logistic regression with laboratory data form 268 patients in Vietnam to determine the risk of mortality in adult patients with severe malaria. This model had a good discriminative value with an AUROC of 0.81. The laboratory variables associated with mortality in this cohort were: plasma lactate, plasma creatinine and a strong anion gap. On the

other hand, in 2007, Mishra *et al* ²⁴ created the MSA (Malaria score for adults) and the MPS (Malaria prediction score) from a cohort of 212 patients in India to predict mortality in severe malaria. The MSA was an upgrade of the Malaria prognostic index (MPI) which required laboratory data and included a small proportion of children. The clinical variables included in the MSA were: severe anaemia, acute renal failure, respiratory distress and cerebral malaria and had a sensitivity of 89.9% and a specificity of 70.6%. This model was externally validated by Santos *et al* ⁴³ among 59 patients with imported severe malaria in Portugal and was shown to have good discriminative properties – AUROC: 0.84; 95% CI: 0.70 - 0.98.

Similarly, Hanson *et al* ¹⁸ produced the coma acidosis malaria (CAM) score after using a logistic regression analysis on data previously collected from the SEQUAMAT. The authors proposed the use of the presence of a coma and base deficit to calculate a five-point score to predict mortality. The score had good discriminative properties with an AUROC of 0.81 (95% CI: 0.77 - 0.84). The same author used data from several cohort studies and RCTs carried out in Bangladesh, India, Indonesia, Vietnam and Myanmar to predict 48-hour survival and survival to discharge in patients with severe malaria ¹⁹. The model containing the variables: shock, oligo-anuria, dysglycaemia, respiratory rate, Glasgow coma score and fever could correctly predict 48 hour-survival in 99.4% of the patients and survival to discharge in 96.9% of patients.

Mohapatra *et al* ²⁶ in 2009 carried out a cohort study of 2089 patients in 2009, where they produced the Malaria severity score (MSS) to predict mortality in adult patients with severe falciparum malaria in India. They assessed seven organ systems: neurologic, renal, haematologic, hepatic, respiratory, cardiovascular, and metabolic organ systems; assigning a maximum score of 0 - 3 for each organ system. The model had excellent discriminative propertiens with an AUROC of 0.9. The authors also developed the GCRBS (Glasgow coma scale, creatinine, respiratory rate, bilirubin and systolic BP) score in 2014 as an alternative to other scores like the APACHE II score which was considered cumbersome ²⁵. The score had a sensitivity of 85.3% and a specificity of 95.6% in predicting a fatal outcome in severe malaria.

In 2013 in Thailand, Newton *et al*²⁹ conducted a retrospective analysis of 988 records with severe falciparum malaria to produce the MPI (Malaria prognostic index) validated using ROC curve analysis and internal validation by data splitting. The MPI contained the following variables: Glasgow coma scale, parasitaemia, plasma lactate, serum bilirubin, pigmented parasites and treatment with ACT and had excellent discriminative properties with an AUROC of 0.97.

## Models predicting the severity of malaria

 The Multi-organ dysfunction score (MODS) which is an index used in severely ill patients admitted in intensive care units to determine the severity of their disease irrespective of the diagnosis ^{34 44}. The score evaluates ten organ systems: heart, blood vessel, blood, respiratory system, metabolism,

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gastrointestinal system, liver, kidney and urinary tract, immune system, and central nervous system giving a score of 1-5 for each system depending on the level of dysfunction of the system, with a minimum score of 10 and a maximum score of 50³⁵. Helbok *et al* assessed the use of this score to predict severity in a small cohort (n = 22) of adult patients with uncomplicated falciparum malaria ³⁵ and in adults with severe malaria  $(n = 29)^{34}$  in Thailand. The score was not internally validated in both studies but the authors showed that higher scores were correlated with symptom severity and duration of hospitalisation. In 2006, the authors used a simplified version of the score - Simplified MODS (sMODS); in a cohort of 485 children in Gabon to predict the level of severity of the disease with respect to the amout of disability the children suffered into categories: ability to walk unaided and ability to sit unaided ³⁶. The authors obtained an AUC of 0.92 (95% CI: 0.89, 0.95) in predicting inability to walk  $\geq$  48 hours for children with sMODS  $\geq$  16 and an AUC of 0.90 (95% CI: 0.87, 0.93) in predicting inability to sit unaided (Table 4).

Grigg *et al* in 2018, used a multivariable logistic regression model to predict the severity of Plasmodium knowlesi malaria infection in a cohort of 481 participants in Malaysia. The authors showed that independent predictors of disease severity using the WHO 2014 research criteria ⁴⁵ were: increasing age, abdominal pain, shortness of breath, increasing parasite count, schizont proportion >10% and serum bicarbonate levels <18 mmol. The model was not internally or externally validated (Table 4). N.C.

# **Discussion:**

In this review, we report on the various prognostic models and scores produced to predict complications, mortality and severity of malaria infection. We showed that there were two models produced to predict the risk of developing complications from malaria infection, twelve models that predict mortality from severe malaria in children, nine models that predict mortality from severe malaria in adults and four models that predict disease severity in malaria. Seventeen of these models were internally validated while only seven have been externally validated. There is no published evidence that any of these models are routinely used in clinical settings.

The models identified in this review that were used to predict mortality in children with severe malaria have similar clinical predictors. All the models had neurologic dysfunction based on either the Glasgow coma score, impaired consciousness, altered mental status, convulsions, decerabration or coma as a predictor. Similarly, in adults, all the models predicting mortality also had neurologic dysfuction as a predictor. Microvascular obstruction in capillaries of the brain due to direct sequestration of red blood cells infected with the malaria parasite could lead to tissue hypoxia ⁴⁶. The effects of this sequestration and its sequelae in the brain can be directly visualised in both adults and children as retinopathy ^{16 46-48}. This leads to varied results with increased intracranial pressure more pronounced in children than in

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adults ⁴⁶. With the increased oxygen demand associated with brain hypoxia and raised intracranial pressure, coma and brain dysfunction could therefore become an important predictor of mortality.

In children, half of the models predicting mortality had hypoglycaemia as a predictor ²¹⁻²³ ²⁷ ²⁸ ³². Hypoglycaemia is usually implicated as a complication of severe malaria infection. This association has been said to be multifactorial ⁴⁹. Proposed mechanisms for this association include: increased glucose use by the malaria parasites in the red blood cells, inhibition of gluconeogenesis by the cascade of cytokines released due to infection and prolonged starvation and fasting especially in severely ill children further compounds the problem ^{49 50}. Considering that glucose is the primary source for organs like the brain which is likely suffering from the above highlighted effects of microvascular obstruction and sequestration; depleted glucose sources could lead to neurologic dysfuction including seizures, deepening comas and hence death. As above, any factor that significantly affects neurologic dysfuction could be highly predictive of mortality or disease severity in patients.

Half of the models in children predicting mortality had respiratory distress (including deep breathing and subcostal indrawing) as a predictor ^{16 20 23 28 31}. Meanwhile six out of the nine models in adults had respiratory failure as a clinical predictor of mortality ^{19 24 26 41}. The incidence of respiratory distress in severe malaria is quite common as it occurs in about 40% of children with severe falciparum malaria and in 25% of adults ⁵¹. It results from acute respiratory distress syndrome (ARDS); metabolic acidosis; fluid overload possibly resulting from increased inflammatory related capillary permeability and endothelial damage ^{8 51}; and aspiration pneumonia which could lead to sepsis ⁸ – a common association with severe malaria. The high mortality rates (up to 87% in some cases) associated with respiratory failure like in ARDS ⁵² could explain the predictive significance of respiratory distress in predicting mortality in malaria infection. Respiratory failure usually leads to hypoxia and a high probability of acute mortality in patients.

Acidosis was also a prominent predictor of mortality in most of the models predicting mortality. It was present in three of the models predicting mortality in children ^{28 30 32} and five models predicting mortality in adults ^{17 18 26 29 41}. Acidosis usually results from underlying pathologies like respiratory distress, renal failure and shock. These three variables were also common variables in the models predicting mortality in both children and adults identified in this review. Renal failure expressed in these models either as acute renal failure, oligoanuria or estimates of the kidney function using serum urea and creatinine ^{17 19} ^{24-26 30 32 41}; is due to acute tubular necrosis that occurs in severe malaria infection as a direct result of microvascular obstruction of capillaries by infected red blood cells leading to the release of inflammatory cytokines like tumor necrosis factor ⁵³. Similarly, shock expressed either as a function of the systolic blood pressure or cold peripheries in three models in children ^{21 31 32} and likewise in two models in adults ^{19 41} could result from peripheral vasodilation which may usually occur concomitantly with sepsis and is a marker of a poor prognosis ^{8 54 55}.

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From the above, factors that were predictive of disease severity and mortality seemed to be consistent amongst these studies. The factors that should therefore be considered by physicians when faced with a patient with malaria infection should include: neurologic dysfunction (coma and seizures), acidosis, hypoglycaemia and respiratory distress (Figure 2). These factors seem to be highly predictive of mortality and disease severity in most of the articles that were included in the review and should therefore be included in any future studies attempting to predict these outcomes in malaria (Table 5).

We found evidence of external validation in only seven of the models identified in this study ^{18 20 24 31} ³². External validation is an important component as it determines the generalisability of the model and its potential use in different geographical regions ⁵⁶. As outlined above, most of the models have similar variables highlighting the fact that the predictors of complications, severity and mortality in malaria might be consistent across different settings. Emphasis could therefore be better placed in the validation of existing models and initiating their use in clinical settings to guide clinicians on prioritising patients and anticipating outcomes. Publication of the findings on the use of these models in clincal settings should also be encouraged to guide clinicians on which models work better in various settings.

After assessment of the risk of bias of the various models, eighteen of the studies contained models that used variables that could be readily available and hence were applicable in real-life settings. However, all the models had a high risk of bias. This was primarily due to the lack of internal validation in several of the studies or the lack of use of up-to-date methods of validation. Caution should therefore be used when interpreting and using the results from the articles.

This review has some limitations. The search included only articles that were published in English. This could potentially lead to the exclusion of studies and models that could otherwise have been included in the review.

# **Conclusion:**

Models predicting severity and mortality of malaria infection identified in this review have similar predictors. Evidence is however lacking on the generalisability of most of these models due lack of external validation. Emphasis should therefore be placed on external validation of existing models and publication of the findings of their use in clinical settings to guide clinicians on management options depending on the priorities of their patients.

# Abbreviations:

APACHE: acute physiology and chronic health evaluation system; AUC: area under the curve; AUROC: area under the receiver operating curve; CAM: coma acidosis malaria; GCRBS: Glasgow coma scale, creatinine, respiratory rate, bilirubin and systolic BP; ICU: intensive care units; IQR: Interquatile range; LODS:Lambarene Organ Dysfunction Score; MODS: Multi-organ dysfunction score; MPI: Malaria Prognostic index; MPS: Malaria prediction score; MSA: Malaria score for adults; MSS: Malaria severity score; PEDIA: Pediatric Early Death Index for Africa; PRISM: Pediatric Risk of Mortality; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCT: randomised control trial; SEQUAMAT: South East Asian Quinine Artesunate Malaria Trial; SICK: Signs of Inflammation in Children that Kill; sMODS: Simplified MODS; TNF: tumour necrosis factor; WHO: World Health Organisation

# **Declarations**

*Ethics approval and consent to participate:* Not applicable

Consent for publication: Not applicable

Availability of data and material: All data relevant to the study are included in the article or uploaded as supplementary information

*Competing interests*: The authors declare no competing interests

*Funding*: No external funding was used in carrying out this review.

Authors' contributions: Conception: TN; independent reviews of papers: TN & BST; writing of initial draft: TN; manuscript revisions: TN & BST. Review only

Acknowledgements: None.

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#### d by copyright, including for u Outcome predicted Table 1: Summary of articles with models predicting complications in severe malaria Ν Authors Year Period of Country Type of Sample Statistics Name Method Age Sex participant study internal of profiles profiles size used of recruitment model validation **Complications of malaria** Severe anaemia Paediatric to much and pallor of developments of good and pallor of anaemia it and pallor of ana Weber 1997 July – Gambia Cohort 368 Logistic None None Median Females 15 age: 28 - 49% December regression 1994 months (IQR: 14 - 48 months) **Development of sepsis** Development of clinical 2 Njim⁸ 2018 June 2003 Bangladesh, Randomised 1187 Logistic None Bootsrapping 17 - 87Female Control -24.3%– Mav India. regression vears sepsis in **≥** 2005 Indonesia Trial adults with an adults with an adults with an adults with an adult severe falciparunno g and Myanmar * not used in present model; BCS: Blantyre coma score; NC: not clear; NE: No evidence; ^a diagnostic properties of original model, IQK. Interquation in RCT: randomised control trial; ACT: artemisinin combined therapy; DRC: Democratic Republic of the Congo; BUN: Blood urea nitrogen; TNF: tissue necrotic factor Table 2: Summary of articles with models predicting mortality in paediatric severe malaria * not used in present model; BCS: Blantyre coma score; NC: not clear; NE: No evidence; a diagnostic properties of original model; IQR: interquatile range; Ν Authors Yea Period of Country Type of Statistics Name of Method Outcome Sampl Age Sex participan study used model internal of profile profile predicted r e size validation s s recruitme nt

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1	Jaffar ²¹	199 7	1992 – 1994	Gambia	Retrospecti ve analysis of data from a randomised control trial	624	Logistic regression	None	None	1 – 9.5 years	Female s – 49%	Mortaliting in paediatrof c uses malaria s	kan bar and a second se	Not done	None	NE
2	Molyneu x ²⁷	198 9	January 1987 – June 1988	Malawi	Cohort	131	Univariab le analysis	Bedside prognostic index	None	7 months – 10 years	Female s – 55.7%	Mortalit <b>F</b> in paediatred c cerebral to text malaria tand da	Hood Figures count, Sage count	Positive predictive value – 83%, sensitivity – 66%	None	NE
3	Conroy ¹⁶	201	1997 – 2009	Malawi	Cohort	155	Logistic regression	None	Hosmer- Lemeshow goodness- of-fit test	8 months – 14 years	Female s – 54.4%	Mortality in mining, Al training, an malaria	Age, Blantyre Age, B	C-index of 0.79 (95% CI 0.72 – 0.84)	None	NE
4	Krishna 22	199 4	1988 – 1989	Gambia	Cohort study	115	:Logistic regression	None	Wald statistic and ROC analysis	18 months – 12 years	NC	Mortalit <b>a similar</b> paediatr <b>milar</b> c severe malaria	Coma score, Valole blood listate/glucos enatio, TNF level on Ma	Wald statistic: coma score (4.5), lactate/gluco se ratio (8.36), TNF level (6.5)	None	NE
5	Marsh ²³	199 5	May 1989 – Novembe r 1991	Kenya	Cohort	1844	Logistic regression	None	None	Mean: 26 months	NC	Mortalit <b>g</b> in children. with severe malaria	Impaired consciousness , spiratory destress, hypoglycemia , and jaundice	Predicted 92.2% of deaths	None	NE
6	Newton 28	200 5	January 2001 – December 2003	Malawi, Kenya and Ghana	Cohort	14605	Linear regression	None	AUROC	Mean age: 32 - 36 months	Female s - 53 - 55%	Mortality in paediatri c severe falciparu	Incep Beathing, Bantyre Coma Score, imbility to Staweight-	C-statistic 0.83 – 0.88 in the three sites: Blantyre (0.88), Kilifi	None	NE

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												r, including malaria for u	fg-age Z schre, hypoglycaemi agbase excess avd lactate concentration	(0.87) and Kumasi (0.83)		
7	Gérardin ³²	200 6	October 1, 1997 – March 31, 1999	Senegal	Cohort	311	Logistic regression	PRISM (Pediatric Risk of Mortality) AUC: 0.92 40	Hosmer- Lemeshow chi-square test	Media n: 8 years (IQR: 5 – 11 years)	Female s – 40.5%	Mortalites related in childrened to text with falciparties of text malaria and data mining, Alt	Sestolic theod Testsure, thenperature, mental status, thental status,	AUROC for acute malaria: 0.89 (95% CI: 0.85 – 0.92) and 0.86 (95% CI: 0.81–0.90) for severe malaria	Yes	_
8	Helbok 20	200 9	December 2000 – May 2005	Gambia, Malawi, Kenya, Ghana, and Gabon	Cohort	23890	Logistic regression	LODS (Lambaréné Organ Dysfunctio n Score)	Internal validation using Bonferroni correction	Mean: 30 – 38 months	Female s - 41% - 47%	Mortality in childrend similar falciparular m	Goma, Hostration and deep becathing	AUROC: 80 0.80 (0.79 – 0.82)	Yes	
9	von Seidlein ³⁰	201 2	2005 - 2010	Gambia, Mozambiqu e, Nigeria, Rwanda, Kenya, DRC, Tanzania, Ghana, Uganda	Retrospecti ve analysis	5426	Logistic regression	None	ROC analysis	Media n: 2.8 years (1.7, 4.3)	NC	Mortalit in paediatroo c severed falcipart m malaria	Pase deficit, Tase d	AUROC: 0.85 (95% CI: 0.83 - 0.87)	None	
1 0	Conroy 31	201 5	NC	Uganda	Cohort	1589	Logistic regression	SICK (Signs of Inflammati on in Children	Hosmer- Lemeshow goodnesso f- fit	NC	Female s – 54.3%	Mortality in malaria	Attered Ansciousness Amperature, Insart rate, Inspiratory	AUROC – 0.846	Yes	_

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								that Kill) ³⁸ - AUC ^a : 0.887 (sensitivity 84.1% specificity 82.2%)				ncluding for use	ree, systolic hod pressure, copillary refill two and age			
					~			LODS 57	Hosmer- Lemeshow goodnesso f- fit	NC	Female s – 54.3%	Mortalit in malaria ted to	Postration, Tagma (BCS) Tagd deep Sbreathing	AUROC – 0.898	Yes	NE
					0		0	PEDIA ³⁹ – AUC ^a : 0.93 (95% CI 0.92 to 0.94)	Hosmer- Lemeshow goodnesso f- fit	NC	Female s – 54.3%	Mortalite in xt malaria and data	s kovashiokor*, jaundice, sobcostal childrawing, hopostration o(childrawing)	AUROC – 0.896	Yes	NE
	ot used in j Γ: random rotic factor	preser ised c r	it model; E ontrol trial	BCS: Blant ; ACT: art	yre coma so emisinin co	core; NC:	not clear; herapy; D	; NE: No e RC: Demo	vidence; ^a ocratic Rep	diagnos oublic of	tic prope	minor erties offer ngo; BUN Al tr	riginal mode	l; IQR: inte nitrogen; T	 rquatile r NF: tissue	ange e
nc C'	ot used in j Γ: random rotic facto	preser ised c r	tt model; E ontrol trial	BCS: Blant ; ACT: art	yre coma so emisinin co	core; NC:	not clear; herapy; D	; NE: No e RC: Demo	vidence; ^a ocratic Rep	diagnos	tic propo	minor erties off ago; BUA I training, and si	riginal mode ignal mode in blood urea	l; IQR: inte nitrogen; T	 rquatile r NF: tissu	ange e
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nc aC ect	ot used in j T: random rotic factor <b>ble 3: Sum</b> Authors	preser ised c r mary	y of article Period of participant recruitmen t	SCS: Blant ; ACT: art s with mo	yre coma so emisinin co dels predio	ting mor	rtality in a	NE: No e RC: Demo adult seven	vidence; ^a ocratic Rep re malaria Method internal of validation	diagnos public of Age profile s	tic propo	minorgy Al training, and similar technologies.	rignal mode rignal mode : the bood urea :	I; IQR: inte nitrogen; T Diagnostic properties	External validatio	Use clin sett
rab N Mo	ot used in j Γ: random rotic factor ole 3: Sum Authors	preser ised c r mary Yea	y of article Period of participant recruitmen t	CS: Blant ; ACT: art s with mo	yre coma so emisinin co dels predic Type of study	ting mor	rtality in a	NE: No e RC: Demo adult seven	vidence; ^a peratic Rep re malaria Method internal of validation	diagnos public of Age profile s	tic propo	minection of the second	rightanal mode rightanal mode : the second urea : the second urea	l; IQR: inte nitrogen; T Diagnostic properties	rquatile r NF: tissue External validatio n	Use clin sett s

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							II score use clinical judgement and physiologic relationship s to assign weightings)					in falcipa m mala for uses	Baematocrit, WBC count, Greatinine, Godium, Botassium and Clasgow Coma score			-
2	Dondorp 17	200 4	NC	Vietnam	Cohort	268	Logistic regression	None	Hosmer- Lemesho w goodness- of-fit test	15 – 79 years	Female s – 19%	Mortalie in adulted with <b>d</b> severe <b>to</b> falciparted m malaga	Basma Bactate, Plasma strong Conion gap and Basma Creatinine	AUROC: 0.81	None	
3	Mishra ²⁴	200 7	NC	India	Cohort	212	Linear regression	MSA (Malaria score for adults)	Not done	NC	NC	Mortalian escritori in adular data with data severe ata malaria mining, Al t	Gevere maaemia, focute renal ailure, eespiratory distress, formalaria http	Sensitivity : 89.9%, specificity : 70.6%, positive predictive value: 94.1% with cut- off of 5/10	Yes ⁴³	
								MPS (Malaria prediction score)	Not done	NC	NC	Mortalia in several malariage and similar te	Age, serum Freatinine Vevel, aemoglobin Fevel, cerebral Snalaria, Fresence of a Gregnancy, See of a Ventilator	NE	Yes ⁴³	
4	Hanson ¹⁸	201 0	June 2003 – May 2005	Banglades h, India, Indonesia and Myanmar	Retrospectiv e analysis of a randomised control trial	789	Logistic regression	CAM (coma acidosis malaria) score	Hosmer- Lemesho w goodness- of-fit	NC	NC	Mortality in adulted with severe de malaria	Foma and Acidosis (base Fricit 14, 2	AUROC: 0.81 (95% CI: 0.77 – 0.84)	Yes ⁵⁹	
5	Mohapatra ²⁶	200 9	January 200 – December 2004	India	Cohort study	2089	Logistic regression	MSS (Malaria severity score)	Hosmer- Lemesho w goodness- of-fit (internal validation by splitting	18 – 71 years	Female - 34.6%	Mortality in adult patients with severe falciparu m malaria	Seurologic, Tenal, Aaematologic, Depatic, Despiratory, ardiovascula m, and enetabolic Crgan systems	AUROC: 0.9	None	_

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								BMJ Op	en			d by copyright, i	i/bmjopen-2019			2
									data – 2089 vs 509)			including for	-030793 on 26			
6	Newton ²⁹	201 3	1986 – 2002	Thailand	Retrospectiv e analysis	988	Logistic regression	MPI (Malaria prognosti c index)	ROC curve analysis and internal validation by data splitting	15 – 74 years	Female s – 43%	Mortal in adults severe related to text an m malated to text an	Alasgow oma scale, arasitaemia, alasma actate, serum bilirubin, gigmented gransites and deatment with ACT	AUROC: 0.97	None	NE
7	Mohapatra ²⁵	201 4	NC	India	Cohort	112	NC	GCBRS (GCS, creatinine , respirator y rate, bilirubin and systolic BP) score	NC	Mean: 35.8 ± 15.1 years	Female s – 16.1	Mortalio in severation falcipata m malatining, Al trai	Terebral Analaria, renal Analaria, renal Aspiratory Tistress, Analdice and Anock	Sensitivity : 85.3%. Specificity : 95.6%	None	NE
8	Hanson ¹⁹	201 4	1996 - 2013	Banglades h, India, Indonesia, Vietnam and Myanmar	Randomised control trials and cohort studies	1801	Logistic regression	None	Hosmer- Lemesho w goodness- of-fit	21-45	Female s - 24.4	48-houns survivage and an survivage to sin dischar malaria severe hon malaria ogjess	Shock, oligo- onuria, wysglycaemia, respiratory ate, Glasgow Coma Score on dabsence on May 14, 20	PPV for 48 hour- survival: 99.4% (95% CI 97.8 – 99.9). PPV for survival to discharge: 96.9% (95% CI: 94.3 – 98.5)	None	NE

* not used in present model; BCS: Blantyre coma score; NC: not clear; NE: No evidence; ^a diagnostic properties of original model; IQR: interquatile range; RCT: randomised control trial; ACT: artemisinin combined therapy; DRC: Democratic Republic of the Congo; BUN: bood urea nitrogen; TNF: tissue necrotic factor Department GEZ-LTA

# Table 4: Summary of articles with models predicting severity of malaria infection

								BM	J Open			by copyright,	omjopen-2019			2
N	Author s	Year	Period of participant recruitmen t	Country	Type of study	Sample size	Statistics used	Name of model	Method internal of validatio	Age profile s	Sex profiles	Outcome Clud predicted ding fo	veriables used	Diagnosti c properties	External validatio n	Use in clinical setting s
Sev	erity of di	sease							11			, r	<u>26</u>			
1	Helbok 35	200 3	October 1, 2001 – January 30, 2002	Thailand	Cohor t	22	NC	MODS (Multi- organ dysfunctio n score) ⁴⁴	None	16 – 41 years	Female - 41.8%	Severity of Severity of a severity of a severity of adult patients adult patients and data mining, and data mining,	An organ Sestems: Effective Sestems: Effective Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Interatory Sestem, Sestem)	None	None	NE
2	Helbok ³⁴	200 5	October 1, 2001 – July 30, 2002	Thailand	Cohor t	29	Survival analysis	MODS 44	None	Mean age: 27.1 (± 10.6)	Female 27.6%	Severity of disease in adult patients, and similar technologi.	Fin organ systems: (Deart, blood, systems: (Deart, blood, system, blood, system, and system, liver, lefthey and unary they and unary they and unary they and unary they and unary they and unary they and unary they and unary they and unary they are and they are	None	None	NE
3	Helbok ³⁶	200 6	August 2003 – May 2005	Gabon	Cohor t	485	Survival analysis	Simplified MODS ³⁵	ROC analysis	4 months – 169 months	Female s – 49%	Severity of disease and disability in children with severe falciparum malaria infection	Ton organ Stems: (Heart, blood, vessel, blood, repiratory stem, metabolism, astrointestina Pystem, liver,	AUC to predict prolonged disease (>48 hours unable to walk): 0.92 (95%	None	NE

								BM	IJ Open				Vbmjopen-2019-0			2
4	Grigg	201	October	Malaysi	Cohor	481 patients	Logistic	None	None	33	Female	Severity of	kiney and ighney	CI, 0.89– 0.95).	None	NE
	37	8	2012 – April 2016	a	t	with Plasmodiu m knowlesi	regressio n			years (IQR: 21 – 49)	- 43.2%	Plasmodium Plasmodium knowlesi infection using WHO 2014 research criteria ⁴⁵	action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action action			

* not used in present model; BCS: Blantyre coma score; NC: not clear; NE: No evidence; • diagnostic properties or the model, BCS: Blantyre coma score; NC: not clear; NE: No evidence; • diagnostic properties or the model, BCS: Blantyre coma score; NC: not clear; NE: No evidence; • diagnostic properties or the model, BCS: Blantyre coma score; NC: not clear; NE: No evidence; • diagnostic properties or the model, BCS: Blantyre coma score; NC: not clear; NE: No evidence; • diagnostic properties or the model, BCS: Blantyre coma score; NC: not clear; NE: No evidence; • diagnostic properties or the model, BCS: Blantyre coma score; NC: not clear; NE: No evidence; • diagnostic properties or the model, BCS: Blantyre coma score; NC: not clear; DR: Democratic Republic of the Congo; BUSN: Bood urea nitrogen; TNF: tissue necrotic factor; WHO: World Health Organisation; IQR: Interquatile range not used in present model; BCS: Blantyre coma score; NC: not clear; NE: No evidence; a diagnostic properties of original model; IQR: interquatile range;

Findings of review	Research gaps	Potential for future	Other Dossible avenues
		research	simil co
Several models available to predict			Incorporation of produced models into artificial
various outcomes in severe malaria.			intelligence to help in the fast prediction of
Variables consistent in predicting disease	Models that take into	Studies with robust designs	risks a verse outcomes and suggestions of
severity, mortality and complications	consideration these major		treatment wind management modalities
include: neurologic dysfunction,	variables		25 at
respiratory distress and acidosis			

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1 2			ÿ	23 23
3	Most models have high risk of bias due to	Models without risk of bias	Internal validation and wide	
4 5	lack of use of up to date methods of	that use adequate statistical	external validation to help	
6	internal validation	methods of internal	integrate models into daily	for 26
7 8		validation	clinical practice	
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**Figures Legends:** 

Figure 1: Flow chart showing reasons for exclusion of various studies from the review

Revenues on the second

Figure 2: Predictive factors of disease severity and mortality in malaria infection



Flow chart showing reasons for exclusion of various studies from the review

**NEUROLOGIC DYSFUNCTION** 

ALTERED MENTAL STATUS

**RESPIRATORY DISTRESS** 

- ACUTE RESPIRATORY

DISTRESS SYNDROME

ACIDOSIS

MORTALITY DUE TO

SEVERE MALARIA

INFECTION

HYPOGYCAEMIA

зноск

RENAL

FAILURE

СОМА SEIZURES

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Predictive factors of disease severity and mortality in malaria infection

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Appendix 1: PRISMA check	list for sy	stematic reviews and meta-analysis.	
Fable 1		ing for 20	
Section/topic	#	Checklist item	Reported on page a
TITLE			1
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results, limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION		in from	
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to earticipants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS		ý, pe	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Webaddress), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report acteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational g	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, sons with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any imits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
		: GEZ-LTA	

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		BMJ Open BMJ	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (induding specification of whether this was done at the study or outcome level), and how this information is to be used in yony data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in meane).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, because of consistency (e.g., l ² ) for each meta-analysis.	5
		o text	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evice (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the Beview, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations.	6 -11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level as sessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) signple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a ferrest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 45).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION		D ep	
	24	Summarize the main findings including the strength of evidence for each main autome; consider their relevance to	11

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Linnations	5	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at redeweevel (e.g., incomplete identified research, reporting bias).	e retrieval of	13
Conclusio	ns	26	Provide a general interpretation of the results in the context of other evider end implications for fut	ture research.	13
FUNDING	3	I			
Funding		27	Describe sources of funding for the systematic review and other support (eap to be systematic review.	funders for the	14
Appendix 2 Electronic 2	2: Information sou s <i>ources</i> Search strategy for	rces Medlin	to text and data minimum database		
Searches	Search	Sea	rch terms	Number of	
	combinations		traini ini	hits	
S1	combinations	"pro	ognost* model" OR "predict* model" OR "Predictive Value of Tests"	<b>hits</b> 208,974	
S1 S2	combinations	"pro	bgnost* model" OR "predict* model" OR "Predictive Value of Tests" g	hits           208,974           3,884	
S1           S2           S3	combinations S1 OR S2	"pro	bgnost* model" OR "predict* model" OR "Predictive Value of Tests"  and codict* score" OR "prognos* score"  and codict* score (CR) (CR) (CR) (CR) (CR) (CR) (CR) (CR)	hits           208,974           3,884           211,947	
S1       S2       S3       S4	combinations S1 OR S2	"pro "pre (MH Falc	pgnost* model" OR "predict* model" OR "Predictive Value of Tests" edict* score" OR "prognos* score" H "Malaria+") OR (MH "Malaria, Vivax") OR (MH "Malaria, Cerebral") OR siparum+") OR (MH "Malaria, Avian")	hits           208,974           3,884           211,947           63,536	
S1       S2       S3       S4	combinations S1 OR S2	(MH Falc	pgnost* model" OR "predict* model" OR "Predictive Value of Tests" dict* score" OR "prognos* score" H "Malaria+") OR (MH "Malaria, Vivax") OR (MH "Malaria, Cerebral") OR iparum+") OR (MH "Malaria, Avian") daria" OR "vivax malaria" OR "falciparum malaria" OR "cerebral malaria" in the prognost of th	hits           208,974           3,884           211,947           63,536           111,461	
S1       S2       S3       S4       S5       S6	combinations S1 OR S2 S4 OR S5	(MH Falc "Dre	pgnost* model" OR "predict* model" OR "Predictive Value of Tests" dict* score" OR "prognos* score" H "Malaria+") OR (MH "Malaria, Vivax") OR (MH "Malaria, Cerebral") OR (MH "Malaria, tiparum+") OR (MH "Malaria, Avian") daria" OR "vivax malaria" OR "falciparum malaria" OR "cerebral malaria" hical malaria" OR plasmodium OR antimalaria* OR anti-malaria*	hits           208,974           3,884           211,947           63,536           111,461           111,510	

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Table 1b:	Search strategy for	r CINAHL database	019-03079; ht, includi	
Searche	Search combinations	Search terms	3 on 26 N	]
<b>S</b> 1		"prognost* model" OR "predict* model" OR "Predictive Value of Tests"	e over	
S2		"predict* score" OR "prognos* score"	n Erasi Erasi	
S3	S1 OR S2		2019 mush	:
S4		(MH "Malaria+")	ext a	,
07		"Malaria" OR "vivax malaria" OR "falciparum malaria" OR "cerebral malaria"	<b>A Severe malaria</b> " OR	
85		"clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*	ata r	
S5 S6	S4 OR S5	"clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*	aded from	
85 86 87	S4 OR S5 S3 AND S6	"clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*	aded from http://bm bol . ata mining, Al trainin	
S5 S6 S7 Table 1c: Searches	S4 OR S5 S3 AND S6 Search strategy for Search combinations	"clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*   • Global Health database   Search terms	aded from http://bmjopen.bmj.com/ bol . ata mining, Al training, and similar t	
S5 S6 S7 Table 1c: Searches	S4 OR S5   S3 AND S6   Search strategy for   Search combinations	"clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*   • Global Health database   • Search terms   "prognost* model" OR "predict* model" OR "Predictive Value of Tests"	aded from http://bmjopen.bmj.com/ on M bol . ata mining, Al training, and similar techn	
S5 S6 S7 Table 1c: Searches S1 S2	S4 OR S5 S3 AND S6 Search strategy for Search combinations	"clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*   • Global Health database   Search terms   "prognost* model" OR "predict* model" OR "Predictive Value of Tests"   "predict* score" OR "prognos* score"	aded from http://bmjopen.bmj.com/ on May 1. bol . ata mining, Al training, and similar technolog	
S5 S6 S7 Table 1c: Searches S1 S2 S3	S4 OR S5   S3 AND S6   Search strategy for   Search combinations   S1 OR S2	"clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*   • Global Health database   Search terms   "prognost* model" OR "predict* model" OR "Predictive Value of Tests"   "predict* score" OR "prognos* score"	aded from http://bmjopen.bmj.com/ on May 14, 20 bol . ata mining, Al training, and similar technologies.	
S5   S6   S7   Table 1c:   Searches   S1   S2   S3   S4	S4 OR S5   S3 AND S6   Search strategy for   Search combinations   S1 OR S2	"clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*   "clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria   Search terms   "prognost* model" OR "predict* model" OR "Predictive Value of Tests"   "predict* score" OR "prognos* score"   "Malaria" OR "vivax malaria" OR "falciparum malaria" OR "cerebral malaria"   "clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*	aded from http://bmjopen.bmj.com/ on May 14, 2020 ool . ata mining, Al training, and similar technologies. OR "at Dep	

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Study	Risk of bias				Applicability Q			Overall		
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcom	ROB	Applicability	
Conroy 2012	+	+	+	-	+	-	sn M g	-	-	
Conroy 2015*	+	+	+	-	+	+	es	-	+	
Dondorp	+	+	+	-	+	+	en   	-	+	
Gerardin [*]	+	+	+	-	+	+	nbe Era Iat	-	+	
Grigg	+	+	+	-	+	+	ed ed	-	+	
Hanson 2010	+	+	+	-	+	+	to	-	+	
Hanson 2014	+	+	+	-	+	+	9. sha	-	+	
Helbok 2003*	+	-	+	-	+	-		-	-	
Helbok 2005*	+	-	+	-	+	-	and See	-	-	
Helbok 2006*	+	-	+	-	+	-	p p bil	-	-	
Helbok 2009	+	+	+	-	+	+	ad	-	+	
Jaffar	+	+	+		+	+	ed ∙n	-	+	
Krishna	+	+	+	N L	+	-	fr.	-	-	
Marsh	+	+	+	-	+	+	o¢n	-	+	
Mishra	+	+	+	-	+	+	م , ا	-	+	
Mohapatra 2009	+	+	+	- ' (	+	+	tp://t vl trai	-	+	
Mohapatra 2014	+	+	+	-	Ť O .	+	ning.	-	+	
Molyneux	+	+	+	-	+	+	<u>ଥ</u> ୍ୟ	-	+	
Newton 2005	+	+	+	-	+	+	pu t	-	+	
Newton 2013	+	+	+	-	+	Ŧ	sir <mark>2</mark> i	-	+	
Njim	+	+	+	-	+	+	nii 6	-	+	
von Seidlein	+	+	+	-	+	+	ar ;	-	+	
Webber	+	-	-	-	-	-	QI tec	-	-	
Wilairatana [*]	+	+	+	-	+	+		-	+	

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PRISMA checklist for system	natic revi	iews and meta-analysis.	
Section/topic	#	Checklist item	Repor on pag
TITLE			1
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT	I		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION		in tron	
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to earticipants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS		ý, op a ee	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., vertical difference), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report had acteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational g	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, zonsct with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5

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Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (in guding specification of whether this was done at the study or outcome level), and how this information is to be used in guny data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in meane).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, been including measures of consistency (e.g., I ² ) for each meta-analysis.	5
		o text o	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evider (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the eview, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. astudy size, PICOS, follow-up period) and provide the citations.	6 -11
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		n-2019- /right, ii	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at reverse evel (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evider end implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (egginsed by the systematic review.	14
		Downloaded from http://bmjopen.bmj.com/ on May 14, 2025 at Department G geschool , Al training, Al training, and similar technologies.	