BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030793
Article Type:	Research
Date Submitted by the Author:	01-Apr-2019
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Keywords:	malaria, prognostic model, prognostic score, mortality

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)

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

gathered in the present [8 9]. 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 – 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

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 ≤ 2.2 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

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 ≥ 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

consciousness, temperature, heart rate, respiratory rate, systolic blood pressure, capillary refill time and age; had good discriminative properties with an AUC of 0.887 [36]. 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 [37] had good discriminative properties (AUC: 0.896) when externally validated on the cohort of 1589 Ugandan children [29]. 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 asscoicated 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,

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]

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 ≥ 48 hours for children with sMODS ≥ 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

[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

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 clincal 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: Multi-organ dysfunction score; sMODS: Simplified MODS

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

***Availability of data and material*:** Not applicable

***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.

Acknowledgements: None.

Table 1: Summary of articles with models predicting complications in severe malaria

N	Authors	Year	Period of participant recruitment	Country	Type of study	Sample size	Statistics used	Name of model	Method internal of validation	Age profiles	Sex profiles	Outcome predicted	Variables used	Diagnostic properties	External validation	Use in clinical settings
Complications of malaria																
Severe anaemia																
1	Weber [13]	1997	July – December 1994	Gambia	Cohort	368	Logistic regression	None	None	Median age: 28 months (IQR: 14 – 48 months)	Females – 49%	Paediatric development of severe anaemia in malaria (packed cell volume < 15%)	Pallor of conjunctiva and pallor of palms	Sensitivity of 80% and a specificity of 85%.	None	NE
2	Brickley [12]	2017	2002 - 2006	Tanzania	Cohort	880	Cox proportional hazards models	None	Bootsrapping	0 – 4 years	Females – 48.1%	Paediatric development of severe anaemia (Hb <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)	None	NE
Development of sepsis																
3	Njim [7]	2018	June 2003 – May 2005	Bangladesh, India, Indonesia and Myanmar	Randomised Control Trial	1187	Logistic regression	None	Bootsrapping	17 – 87 years	Female – 24.3%	Development of clinical sepsis in adults with severe falciparum malaria	Sex, blood urea nitrogen levels, plasma anion gap, respiratory distress, shock on admission, parasitaemia, coma and jaundice	AUC: 0.789. Sensitivity – 70.0%; specificity – 69.4%	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: blood urea nitrogen; TNF: tissue necrotic factor

Table 2: Summary of articles with models predicting mortality in paediatric severe malaria

N	Authors	Year	Period of participant recruitment	Country	Type of study	Sample size	Statistics used	Name of model	Method internal of validation	Age profiles	Sex profiles	Outcome predicted	Variables used	Diagnostic properties	External validation	Use in clinical settings
Mortality																
1	Jaffar [19]	1997	1992 – 1994	Gambia	Retrospective analysis of data from a randomised control trial	624	Logistic regression	None	None	1 – 9.5 years	Females – 49%	Mortality in paediatric cerebral malaria	Cold periphery, deep coma and hypoglycaemia	Not done	None	NE
2	Molyneux [25]	1989	January 1987 – June 1988	Malawi	Cohort	131	Univariable analysis	Bedside prognostic index	None	7 months – 10 years	Females – 55.7%	Mortality in paediatric cerebral malaria	Blood glucose, parasitaemia, WBC count, age, coma score, absent corneal reflexes, decerebration, convulsions	Positive predictive value – 83%, sensitivity – 66%	None	NE
3	Conroy [14]	2012	1997 – 2009	Malawi	Cohort	155	Logistic regression	None	Hosmer-Lemeshow goodness-of-fit test	8 months – 14 years	Females – 54.4%	Mortality in patients with cerebral malaria	Age, Blantyre coma score, respiratory distress, severe anaemia, angiopoietin-1, angiopoietin-2 and sTie-2 levels	C-index of 0.79 (95% CI 0.72 – 0.84)	None	NE
4	Krishna [20]	1994	1988 – 1989	Gambia	Cohort study	115	:Logistic regression	None	Wald statistic and ROC analysis	18 months – 12 years	NC	Mortality in paediatric severe malaria	Coma score, whole blood lactate/glucose ratio, TNF level	Wald statistic: coma score (4.5), lactate/glucose ratio (8.36), TNF level (6.5)	None	NE

5	Marsh [21]	1995	May 1989 – November 1991	Kenya	Cohort	1844	Logistic regression	None	None	Mean: 26 months	NC	Mortality in children with severe malaria	Impaired consciousness, respiratory distress, hypoglycemia and jaundice	Predicted 92.2% of deaths	None	NE
6	Newton [26]	2005	January 2001 – December 2003	Malawi, Kenya and Ghana	Cohort	14605	Linear regression	None	AUROC	Mean age: 32 – 36 months	Females – 53 – 55%	Mortality in paediatric severe falciparum malaria	Deep breathing, Blantyre Coma Score, inability to sit, weight-for-age Z score, hypoglycaemia, base excess and lactate concentration	C-statistic 0.83 – 0.88 in the three sites: Blantyre (0.88), Kilifi (0.87) and Kumasi (0.83)	None	NE
7	Gérardin [30]	2006	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	Median: 8 years (IQR: 5 – 11 years)	Females – 40.5%	Mortality in children with falciparum malaria	Systolic blood pressure, temperature, mental status, heart rate, dilatation of pupils, pH, total CO_2, PCO_2, arterial PaO_2, serum glucose, potassium, urea, creatinine, white blood cells, prothrombin time, platelet count	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	NE
8	Helbok [18]	2009	December 2000 – May 2005	Gambia, Malawi, Kenya, Ghana, and Gabon	Cohort	23890	Logistic regression	LODS (Lambaréné Organ Dysfunction Score)	Internal validation using Bonferroni correction	Mean: 30 – 38 months	Females – 41% – 47%	Mortality in children with severe falciparum malaria	Coma, prostration and deep breathing	AUROC: 80 0.80 (0.79 – 0.82)	Yes	NE

9	von Seidlein [28]	2012	2005 - 2010	Gambia, Mozambique, Nigeria, Rwanda, Kenya, DRC, Tanzania, Ghana, Uganda	Retrospective analysis	5426	Logistic regression	None	ROC analysis	Median: 2.8 years (1.7, 4.3)	NC	Mortality in paediatric severe falciparum malaria	Base deficit, Coma, convulsions, BUN and chronic illness	AUROC: 0.85 (95% CI: 0.83 - 0.87)	None	NE
10	Conroy [29]	2015	NC	Uganda	Cohort	1589	Logistic regression	SICK (Signs of Inflammation in Children that Kill) [36] – AUC[a]: 0.887 (sensitivity 84.1% specificity 82.2%)	Hosmer-Lemeshow goodness of-fit	NC	Females – 54.3%	Mortality in malaria	Altered consciousness temperature, heart rate, respiratory rate, systolic blood pressure, capillary refill time and age	AUROC – 0.846	Yes	NE
								LODS [55]	Hosmer-Lemeshow goodness of-fit	NC	Females – 54.3%	Mortality in 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 goodness of-fit	NC	Females – 54.3%	Mortality in malaria	Kwashiokor*, jaundice, subcostal indrawing, prostration (seizures) and wasting	AUROC – 0.896	Yes	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: blood urea nitrogen; TNF: tissue necrotic factor

Table 3: Summary of articles with models predicting mortality in adult severe malaria

N	Authors	Year	Period of participant recruitment	Country	Type of study	Sample size	Statistics used	Name of model	Method internal of validation	Age profiles	Sex profiles	Outcome predicted	Variables used	Diagnostic properties	External validation	Use in clinical settings
Mortality																
1	Wilairatana [35]	1995	July 1991 – May 1993	Thailand	Cohort	72	Univariable analysis	APACHE II score [56]	ROC analysis	Mean age: 29.9	Females – 33.3%	Mortality in adult patients with cerebral falciparum malaria	MAP, temperature, heart rate, respiratory rate, arterial pH, PaO_2, haematocrit, WBC count, creatinine, sodium, potassium and Glasgow coma score	Predicted mortality with 95.8% accuracy	None	NE
2	Dondorp [15]	2004	NC	Vietnam	Cohort	268	Logistic regression	None	Hosmer-Lemeshow goodness-of-fit test	15 – 79 years	Females – 19%	Mortality in adults with severe falciparum malaria	Plasma lactate, plasma strong anion gap and plasma creatinine	AUROC: 0.81	None	NE
3	Mishra [22]	2007	NC	India	Cohort	212	Linear regression	MSA (Malaria score for adults)	Not done	NC	NC	Mortality in adults with severe malaria	Severe anaemia, acute renal failure, respiratory distress, cerebral malaria	Sensitivity: 89.9%, specificity: 70.6%, positive predictive value: 94.1% with cut-off of 5/10	Yes [39]	NE
								MPS (Malaria prediction score)	Not done	NC	NC	Mortality in severe malarias	Age, serum creatinine level, haemoglobin level, cerebral malaria, presence of a pregnancy, use of a ventilator	NE	Yes [39]	NE

4	Hanson [16]	2010	June 2003 – May 2005	Bangladesh, India, Indonesia and Myanmar	Retrospective analysis of a randomised control trial	789	Logistic regression	CAM (coma acidosis malaria) score	Hosmer-Lemeshow goodness-of-fit	NC	NC	Mortality in adults with severe malaria	Coma and acidosis (base deficit	AUROC: 0.81 (95% CI: 0.77 – 0.84)	Yes [57]	NE
5	Mohapatra [24]	2009	January 200 – December 2004	India	Cohort study	2089	Logistic regression	MSS (Malaria severity score)	Hosmer-Lemeshow goodness-of-fit (internal validation by splitting data – 2089 vs 509)	18 – 71 years	Female – 34.6%	Mortality in adult patients with severe falciparum malaria	Neurologic, renal, haematologic, hepatic, respiratory, cardiovascular and metabolic organ systems	AUROC: 0.9	None	NE
6	Newton [27]	2013	1986 – 2002	Thailand	Retrospective analysis	988	Logistic regression	MPI (Malaria prognostic index)	ROC curve analysis and internal validation by data splitting	15 – 74 years	Females – 43%	Mortality in adult severe falciparum malaria	Glasgow coma scale, parasitaemia, plasma lactate, serum bilirubin, pigmented parasites and treatment with ACT	AUROC: 0.97	None	NE
7	Mohapatra [23]	2014	NC	India	Cohort	112	NC	GCBRS (GCS, creatinine, respiratory rate, bilirubin and systolic BP) score	NC	Mean: 35.8 ± 15.1 years	Females – 16.1	Mortality in severe falciparum malaria	Cerebral malaria, renal failure, respiratory distress, jaundice and shock	Sensitivity: 85.3%. Specificity: 95.6%	None	NE
8	Hanson [17]	2014	1996 – 2013	Bangladesh, India, Indonesia, Vietnam and Myanmar	Randomised control trials and cohort studies	1801	Logistic regression	None	Hosmer-Lemeshow goodness-of-fit	21 – 45	Females – 24.4	48-hour survival and survival to discharge in patients with severe malaria	Shock, oligo-anuria, hypoglycaemia, respiratory rate, Glasgow Coma Score and absence of fever	PPV for 48 hour-survival: 99.4% (95% CI 97.8 – 99.9). PPV for survival to discharge: 96.9%	None	NE

													(95% CI: 94.3 – 98.5)		

* 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: blood urea nitrogen; TNF: tissue necrotic factor

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

N	Authors	Year	Period of participant recruitment	Country	Type of study	Sample size	Statistics used	Name of model	Method internal of validation	Age profiles	Sex profiles	Outcome predicted	Variables used	Diagnostic properties	External validation	Use in clinical settings
Severity of disease																
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 systems: (heart, blood vessel, blood, respiratory system, metabolism, gastrointestinal system, liver, kidney and urinary tract, immune system, and central nervous system)	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, blood vessel, blood, respiratory system, metabolism, gastrointestinal system, liver, kidney and urinary	None	None	NE

													tract, immune system, and central nervous system)			
3	Helbok [34]	2006	August 2003 – May 2005	Gabon	Cohort	485	Survival analysis	Simplified MODS [33]	ROC analysis	4 months – 169 months	Females – 49%	Severity of disease and disability in children with severe falciparum malaria infection	Ten organ systems: (heart, blood vessel, blood, respiratory system, metabolism, gastrointestinal system, liver, kidney and urinary tract, immune system, and central nervous system)	AUC to predict prolonged disease (>48 hours unable to walk): 0.92 (95% CI, 0.89–0.95).	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: blood urea nitrogen; TNF: tissue necrotic factor

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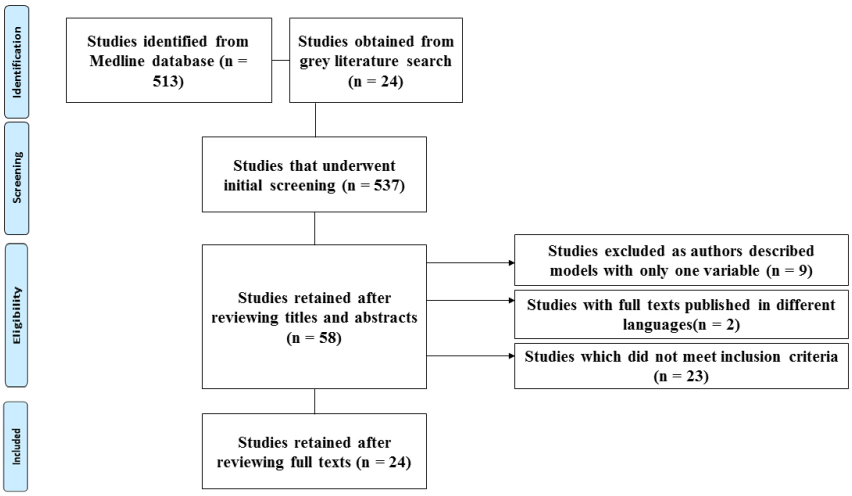
Figures Legends:

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

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

Section/topic	#	Checklist item	Information reported		Page (s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
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 in the Abstract	☐	☒	
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1
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, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
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 sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	3

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	3
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	3
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	App
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	4
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)	☒	☐	4
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	☒	☐	4
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	☒	☐	4
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	4
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	☒	☐	4
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☒	

	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of 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-regression)	☐	☒	
	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, selective reporting within studies)	☐	☒	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	5

Information sources

Electronic sources

Appendix 2: Search strategy for Medline database

Searches	**Search combinations**	**Search terms**	**Number of hits**
S1		"prognost* model" OR "predict* model" OR "Predictive Value of Tests"	203,728
S2		"predict* score" OR "prognos* score"	3,655
S3	S1 OR S2		206,531
S4		(MH "Malaria+") OR (MH "Malaria, Vivax") OR (MH "Malaria, Cerebral") OR (MH "Malaria, Falciparum+") OR (MH "Malaria, Avian")	62,414
S5		"Malaria" OR "vivax malaria" OR "falciparum malaria" OR "cerebral malaria" OR "severe malaria" OR "clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*	109,371

S6	S4 OR S5		664,548
S7	S3 AND S6		513

Appendix 3a and 3b: Assessment was done using the Quality Assessment Tool for Observational Studies of the National Health Institute/National Heart, Lung, and Blood Institute

	Criteria	Brickley	Webber	Njim	Conroy[a]	Molyneux	Marsh	Krishna	Jaffar	Newton[a]	Helbok[a]	von Seidlein	Conroy[b]	Gerardin
1	Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Was the study population clearly specified and defined?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NC	Yes	Yes	Yes
3	Was the participation rate of eligible persons at least 50%?	NC	NC	Yes	NC	NC	No	NC	NC	NC	NC	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	Yes	Yes	Yes	Yes

5	Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	Yes	No	No	No	No	No	NC	NC	NC	No
6	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	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	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10	Was the exposure(s) assessed more than once over time?	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	NC	NC
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	Yes	Yes	Yes	Yes	Yes	Yes
12	Were the outcome assessors blinded to the exposure status of participants?	NC	No	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
13	Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	NC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
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	Yes	Yes	Yes	Yes	Yes	Yes
	Quality rating													

	Rater #1 TN	Good	Fair	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
	Rater #2 OA	Good	Fair	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good

*Not clear; Newton[a]: Study carried out in 2005; Conroy[a]: study carried out in 2012; Conroy[b]: study carried out in 2015; Helbok[a]: study carried out in 2009

	Criteria	**Wilairatana**	**Dondorp**	**Mishra**	**Hanson[a]**	**Hanson[b]**	**Mohapatra[a]**	**Mohapatra[b]**	**Newton[b]**	**Helbok[b]**	**Helbok[c]**	**Helbok[d]**
1	Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Was the study population clearly specified and defined?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Was the participation rate of eligible persons at least 50%?	NC	NC	NC	Yes	Yes	Yes	NC	NC	Yes	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	Yes	Yes
5	Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	No	No	No	No	No	No	No	No
6	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	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	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10	Was the exposure(s) assessed more than once over time?	Yes	No	No	Yes	Yes	Yes	Yes	NC	Yes	Yes	No

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	Yes	Yes	Yes	NC
12	Were the outcome assessors blinded to the exposure status of participants?	NC	No	NC	NC	NC	NC	NC	NC	NC	NC	NC
13	Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
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	Yes	Yes	Yes	Yes
	Quality rating											
	Rater #1 TN	Good	Fair	Good	Good	Good	Good	Good	Good	Good	Good	Good
	Rater #2 OA	Good	Fair	Good	Good	Good	Good	Good	Good	Good	Good	Good

Hanson[a]: Study carried out in 2010; Hanson[b]; study carried out in 2014; Mohapatra[a]: study carried out in 2009; Mohapatra[b]: study carried out in 2014; Helbok[b]: study carried out in 2003; Helbok[c]: study carried out in 2006; Helbok[d]: study carried out in 2005

BMJ Open

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

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 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

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 [3 4].

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;

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 – 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

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

[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 ≤ 2.2 mmol/L; parasitaemia > 106 ring forms/μL; white blood cell count > 15 x 10/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* [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 ≥ 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

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 asscoicated 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 –

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 ≥ 48 hours for children with sMODS ≥ 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

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].

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

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.

Acknowledgements: None.

Table 1: Summary of articles with models predicting complications in severe malaria

N	Authors	Year	Period of participant recruitment	Country	Type of study	Sample size	Statistics used	Name of model	Method internal of validation	Age profiles	Sex profiles	Outcome predicted	Variables used	Diagnostic properties	External validation	Use in clinical settings
Complications of malaria																
Severe anaemia																
1	Weber [15]	1997	July – December 1994	Gambia	Cohort	368	Logistic regression	None	None	Median age: 28 months (IQR: 14 – 48 months)	Females – 49%	Paediatric development of severe anaemia in malaria (packed cell volume < 15%)	Pallor of conjunctiva and pallor of palms	Sensitivity of 80% and a specificity of 85%.	None	NE
Development of sepsis																
2	Njim [8]	2018	June 2003 – May 2005	Bangladesh, India, Indonesia and Myanmar	Randomised Control Trial	1187	Logistic regression	None	Bootsrapping	17 – 87 years	Female – 24.3%	Development of clinical sepsis in adults with severe falciparum malaria	Sex, blood urea nitrogen levels, plasma anion gap, respiratory distress, shock on admission, parasitaemia, coma and jaundice	AUC: 0.789. Sensitivity – 70.0%; specificity – 69.4%	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: blood urea nitrogen; TNF: tissue necrotic factor

Table 2: Summary of articles with models predicting mortality in paediatric severe malaria

N	Authors	Year	Period of participant recruitment	Country	Type of study	Sample size	Statistics used	Name of model	Method internal of validation	Age profiles	Sex profiles	Outcome predicted	Variables used	Diagnostic properties	External validation	Use in clinical settings

Mortality															
1	Jaffar [21]	1997	1992 – 1994	Gambia	Retrospective analysis of data from a randomised control trial	624	Logistic regression	None	None	1 – 9.5 years	Females – 49%	Mortality in paediatric cerebral malaria	Cold periphery, deep coma and hypoglycaemia	Not done	None	NE
2	Molyneux [27]	1989	January 1987 – June 1988	Malawi	Cohort	131	Univariable analysis	Bedside prognostic index	None	7 months – 10 years	Females – 55.7%	Mortality in paediatric cerebral malaria	Blood glucose, parasitaemia, WBC count, age, coma score, absent corneal reflexes, decerebration, convulsions	Positive predictive value – 83%, sensitivity – 66%	None	NE
3	Conroy [16]	2012	1997 – 2009	Malawi	Cohort	155	Logistic regression	None	Hosmer-Lemeshow goodness-of-fit test	8 months – 14 years	Females – 54.4%	Mortality in patients with cerebral malaria	Age, Blantyre coma score, respiratory distress, severe anaemia, angiopoietin-1, angiopoietin-2 and sTie-2 levels	C-index of 0.79 (95% CI 0.72 – 0.84)	None	NE
4	Krishna [22]	1994	1988 – 1989	Gambia	Cohort study	115	:Logistic regression	None	Wald statistic and ROC analysis	18 months – 12 years	NC	Mortality in paediatric severe malaria	Coma score, whole blood lactate/glucose ratio, TNF level	Wald statistic: coma score (4.5), lactate/glucose ratio (8.36), TNF level (6.5)	None	NE
5	Marsh [23]	1995	May 1989 – November 1991	Kenya	Cohort	1844	Logistic regression	None	None	Mean: 26 months	NC	Mortality in children with severe malaria	Impaired consciousness, respiratory distress, hypoglycemia and jaundice	Predicted 92.2% of deaths	None	NE
6	Newton [28]	2005	January 2001 – December 2003	Malawi, Kenya and Ghana	Cohort	14605	Linear regression	None	AUROC	Mean age: 32 – 36 months	Females – 53 – 55%	Mortality in paediatric severe falciparu	Deep breathing, Blantyre Coma Score, inability to sit, weight-	C-statistic 0.83 – 0.88 in the three sites: Blantyre (0.88), Kilifi	None	NE

												m malaria	for-age Z score, hypoglycaemia, base excess and lactate concentration	(0.87) and Kumasi (0.83)		
7	Gérardin [32]	2006	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	Median: 8 years (IQR: 5 – 11 years)	Females – 40.5%	Mortality in children with falciparum malaria	Systolic blood pressure, temperature, mental status, heart rate, dilatation of pupils, pH, arterial CO_2, arterial O_2, serum glucose, potassium, urea, creatinine, white blood cells, prothrombin time, platelet count	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	NE
8	Helbok [20]	2009	December 2000 – May 2005	Gambia, Malawi, Kenya, Ghana, and Gabon	Cohort	23890	Logistic regression	LODS (Lambaréné Organ Dysfunction Score)	Internal validation using Bonferroni correction	Mean: 30 – 38 months	Females – 41% – 47%	Mortality in children with severe falciparum malaria	Coma, prostration and deep breathing	AUROC: 80 0.80 (0.79 – 0.82)	Yes	NE
9	von Seidlein [30]	2012	2005 - 2010	Gambia, Mozambique, Nigeria, Rwanda, Kenya, DRC, Tanzania, Ghana, Uganda	Retrospective analysis	5426	Logistic regression	None	ROC analysis	Median: 2.8 years (1.7, 4.3)	NC	Mortality in paediatric severe falciparum malaria	Base deficit, Coma, convulsions, BUN and chronic illness	AUROC: 0.85 (95% CI: 0.83 - 0.87)	None	NE
10	Conroy [31]	2015	NC	Uganda	Cohort	1589	Logistic regression	SICK (Signs of Inflammation in Children	Hosmer-Lemeshow goodness of-fit	NC	Females – 54.3%	Mortality in malaria	Altered consciousness temperature, heart rate, respiratory	AUROC – 0.846	Yes	NE

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								that Kill) [38] – AUC[a]: 0.887 (sensitivity 84.1% specificity 82.2%)					rate, systolic blood pressure, capillary refill time and age			
								LODS [57]	Hosmer-Lemeshow goodness of-fit	NC	Females – 54.3%	Mortality in malaria	Prostration, coma (BCS) and deep breathing	AUROC – 0.898	Yes	NE
								PEDIA [39] – AUC[a]: 0.93 (95% CI 0.92 to 0.94)	Hosmer-Lemeshow goodness of-fit	NC	Females – 54.3%	Mortality in malaria	Kwashiokor*, jaundice, subcostal indrawing, prostration (seizures) and wasting	AUROC – 0.896	Yes	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: blood urea nitrogen; TNF: tissue necrotic factor

Table 3: Summary of articles with models predicting mortality in adult severe malaria

N	Authors	Year	Period of participant recruitment	Country	Type of study	Sample size	Statistics used	Name of model	Method internal of validation	Age profiles	Sex profiles	Outcome predicted	Variables used	Diagnostic properties	External validation	Use in clinical settings
Mortality																
1	Wilairatana [41]	1995	July 1991 – May 1993	Thailand	Cohort	72	Validation of APACHE II model (Original APACHE	APACHE II score [58]	ROC analysis	Mean age: 29.9	Females – 33.3%	Mortality in adult patients with cerebral	MAP, temperature, heart rate, respiratory rate, arterial pH, PaO_2,	Predicted mortality with 95.8% accuracy	None	NE

							II score use clinical judgement and physiologic relationships to assign weightings)					falciparum malaria	haematocrit, WBC count, creatinine, sodium, potassium and Glasgow coma score			
2	Dondorp [17]	2004	NC	Vietnam	Cohort	268	Logistic regression	None	Hosmer-Lemeshow goodness-of-fit test	15 – 79 years	Females – 19%	Mortality in adults with severe falciparum malaria	Plasma lactate, plasma strong anion gap and plasma creatinine	AUROC: 0.81	None	NE
3	Mishra [24]	2007	NC	India	Cohort	212	Linear regression	MSA (Malaria score for adults)	Not done	NC	NC	Mortality in adults with severe malaria	Severe anaemia, acute renal failure, respiratory distress, cerebral malaria	Sensitivity: 89.9%, specificity: 70.6%, positive predictive value: 94.1% with cut-off of 5/10	Yes [43]	NE
								MPS (Malaria prediction score)	Not done	NC	NC	Mortality in severe malaria	Age, serum creatinine level, haemoglobin level, cerebral malaria, presence of a pregnancy, use of a ventilator	NE	Yes [43]	NE
4	Hanson [18]	2010	June 2003 – May 2005	Bangladesh, India, Indonesia and Myanmar	Retrospective analysis of a randomised control trial	789	Logistic regression	CAM (coma acidosis malaria) score	Hosmer-Lemeshow goodness-of-fit	NC	NC	Mortality in adults with severe malaria	Coma and acidosis (base deficit	AUROC: 0.81 (95% CI: 0.77 – 0.84)	Yes [59]	NE
5	Mohapatra [26]	2009	January 200 – December 2004	India	Cohort study	2089	Logistic regression	MSS (Malaria severity score)	Hosmer-Lemeshow goodness-of-fit (internal validation by splitting	18 – 71 years	Female – 34.6%	Mortality in adult patients with severe falciparum malaria	Neurologic, renal, haematologic, hepatic, respiratory, cardiovascular, and metabolic organ systems	AUROC: 0.9	None	NE

									data – 2089 vs 509)							
6	Newton [29]	2013	1986 – 2002	Thailand	Retrospective analysis	988	Logistic regression	MPI (Malaria prognostic index)	ROC curve analysis and internal validation by data splitting	15 – 74 years	Females – 43%	Mortality in adult severe falciparum malaria	Glasgow coma scale, parasitaemia, plasma lactate, serum bilirubin, pigmented parasites and treatment with ACT	AUROC: 0.97	None	NE
7	Mohapatra [25]	2014	NC	India	Cohort	112	NC	GCBRS (GCS, creatinine, respiratory rate, bilirubin and systolic BP) score	NC	Mean: 35.8 ± 15.1 years	Females – 16.1	Mortality in severe falciparum malaria	Cerebral malaria, renal failure, respiratory distress, jaundice and shock	Sensitivity: 85.3%. Specificity: 95.6%	None	NE
8	Hanson [19]	2014	1996 – 2013	Bangladesh, India, Indonesia, Vietnam and Myanmar	Randomised control trials and cohort studies	1801	Logistic regression	None	Hosmer-Lemeshow goodness-of-fit	21 – 45	Females – 24.4	48-hour survival and survival to discharge in patients with severe malaria	Shock, oligo-anuria, hypoglycaemia, respiratory rate, Glasgow Coma Score and absence of fever	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: blood urea nitrogen; TNF: tissue necrotic factor

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

N	Authors	Year	Period of participant recruitment	Country	Type of study	Sample size	Statistics used	Name of model	Method internal of validation	Age profiles	Sex profiles	Outcome predicted	Variables used	Diagnostic properties	External validation	Use in clinical settings
Severity of disease																
1	Helbok [35]	2003	October 1, 2001 – January 30, 2002	Thailand	Cohort	22	NC	MODS (Multi-organ dysfunction score) [44]	None	16 – 41 years	Female – 41.8%	Severity of disease in adult patients with uncomplicated falciparum malaria	Seven organ systems: (heart, blood vessel, blood, respiratory system, metabolism, gastrointestinal system, liver, kidney and urinary tract, immune system, and central nervous system)	None	None	NE
2	Helbok [34]	2005	October 1, 2001 – July 30, 2002	Thailand	Cohort	29	Survival analysis	MODS [44]	None	Mean age: 27.1 (± 10.6)	Female – 27.6%	Severity of disease in adult patients with severe falciparum malaria	Seven organ systems: (heart, blood vessel, blood, respiratory system, metabolism, gastrointestinal system, liver, kidney and urinary tract, immune system, and central nervous system)	None	None	NE
3	Helbok [36]	2006	August 2003 – May 2005	Gabon	Cohort	485	Survival analysis	Simplified MODS [35]	ROC analysis	4 months – 169 months	Females – 49%	Severity of disease and disability in children with severe falciparum malaria infection	Seven organ systems: (heart, blood vessel, blood, respiratory system, metabolism, gastrointestinal system, liver,	AUC to predict prolonged disease (>48 hours unable to walk): 0.92 (95%	None	NE

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												kidney and urinary tract, immune system, and central nervous system)	CI, 0.89–0.95).		
4	Grigg [37]	2018	October 2012 – April 2016	Malaysia	Cohort	481 patients with *Plasmodium knowlesi*	Logistic regression	None	None	33 years (IQR: 21 – 49)	Female – 43.2%	Severity of *Plasmodium knowlesi* infection using WHO 2014 research criteria [45]	Age >45, abdominal pain, shortness of breath, increased parasite count, schizont proportion >10%, bicarbonate <8 mmol	None	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: blood urea nitrogen; TNF: tissue necrotic factor; WHO: World Health Organisation; IQR: Interquatile range

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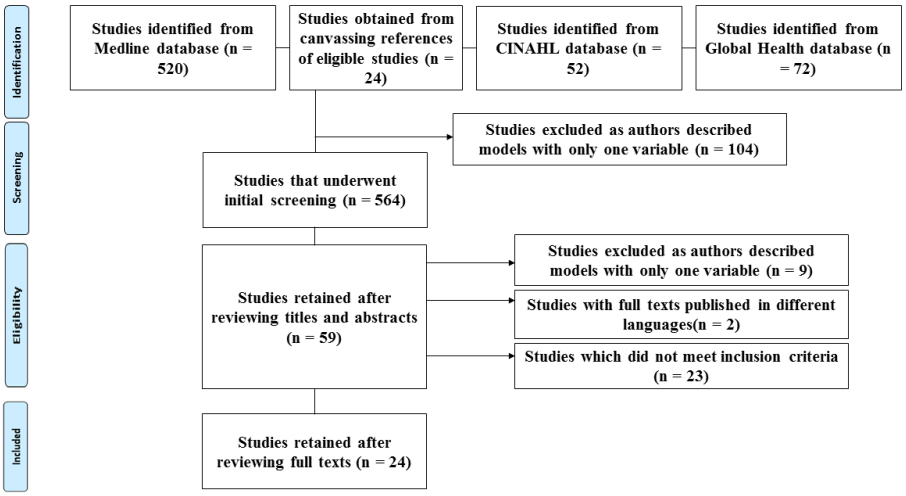
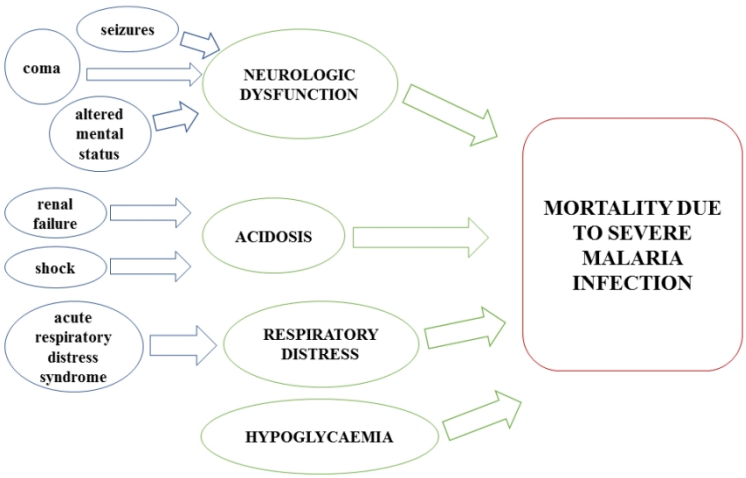
Figures Legends:

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

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



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



Predictive factors of disease severity and mortality in malaria infection

Appendix 1: PRISMA checklist for systematic reviews and meta-analysis.

Table 1

Section/topic	#	Checklist item	Reported on page #
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			
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., Web address), 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 characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact 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

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 (including 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 means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (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 review, 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) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest 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 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	14

Appendix 2: Information sources

Electronic sources

Table 1a: Search strategy for Medline database

Searches	**Search combinations**	**Search terms**	**Number of hits**
S1		"prognost* model" OR "predict* model" OR "Predictive Value of Tests"	208,974
S2		"predict* score" OR "prognos* score"	3,884
S3	S1 OR S2		211,947
S4		(MH "Malaria+") OR (MH "Malaria, Vivax") OR (MH "Malaria, Cerebral") OR (MH "Malaria, Falciparum+") OR (MH "Malaria, Avian")	63,536
S5		"Malaria" OR "vivax malaria" OR "falciparum malaria" OR "cerebral malaria" OR "severe malaria" OR "clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*	111,461
S6	S4 OR S5		111,510
S7	S3 AND S6		520

Table 1b: Search strategy for CINAHL database

Searches	Search combinations	Search terms	Number of hits
S1		"prognost* model" OR "predict* model" OR “Predictive Value of Tests”	49,434
S2		"predict* score" OR "prognos* score"	1,041
S3	S1 OR S2		50,217
S4		(MH "Malaria+")	7,468
S5		"Malaria" OR "vivax malaria" OR "falciparum malaria" OR "cerebral malaria" OR "severe malaria" OR "clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*	10,945
S6	S4 OR S5		10,945
S7	S3 AND S6		52

Table 1c: Search strategy for Global Health database

Searches	Search combinations	Search terms	Number of hits
S1		"prognost* model" OR "predict* model" OR “Predictive Value of Tests”	2,906
S2		"predict* score" OR "prognos* score"	368
S3	S1 OR S2		2,906
S4		"Malaria" OR "vivax malaria" OR "falciparum malaria" OR "cerebral malaria" OR "severe malaria" OR "clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*	89,436
S7	S3 AND S4		72

Appendix 3: The PROBAST tool used to assess the risk of bias and applicability of the studies used in the review

Study	Risk of bias				Applicability			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability
Conroy 2012	+	+	+	-	+	-		-	-
Conroy 2015*	+	+	+	-	+	+		-	+
Dondorp	+	+	+	-	+	+		-	+
Gerardin*	+	+	+	-	+	+		-	+
Grigg	+	+	+	-	+	+		-	+
Hanson 2010	+	+	+	-	+	+		-	+
Hanson 2014	+	+	+	-	+	+		-	+
Helbok 2003*	+	-	+	-	+	-		-	-
Helbok 2005*	+	-	+	-	+	-		-	-
Helbok 2006*	+	-	+	-	+	-		-	-
Helbok 2009	+	+	+	-	+	+		-	+
Jaffar	+	+	+	-	+	+		-	+
Krishna	+	+	+	-	+	-		-	-
Marsh	+	+	+	-	+	+		-	+
Mishra	+	+	+	-	+	+		-	+
Mohapatra 2009	+	+	+	-	+	+		-	+
Mohapatra 2014	+	+	+	-	+	+		-	+
Molyneux	+	+	+	-	+	+		-	+
Newton 2005	+	+	+	-	+	+		-	+
Newton 2013	+	+	+	-	+	+		-	+
Njim	+	+	+	-	+	+		-	+
von Seidlein	+	+	+	-	+	+		-	+
Webber	+	-	-	-	-	-		-	-
Wilairatana*	+	+	+	-	+	+		-	+

*Study was designed to externally validate existing models

PRISMA checklist for systematic reviews and meta-analysis.

Section/topic	#	Checklist item	Reported on page #
TITLE			1
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
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Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact 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
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Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
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BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030793.R2
Article Type:	Original research
Date Submitted by the Author:	04-Nov-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

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 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

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 [3 4].

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;

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 – 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

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

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 ≤ 2.2 mmol/L; parasitaemia > 106 ring forms/μL; white blood cell count > 15 x 10/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* [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 ≥ 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 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 asscoicated 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 – 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 ≥ 48 hours for children with sMODS ≥ 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

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].

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.

Acknowledgements: None.

Table 1: Summary of articles with models predicting complications in severe malaria

N	Authors	Year	Period of participant recruitment	Country	Type of study	Sample size	Statistics used	Name of model	Method internal of validation	Age profiles	Sex profiles	Outcome predicted	Variables used	Diagnostic properties	External validation	Use in clinical settings
Complications of malaria																
Severe anaemia																
1	Weber [15]	1997	July – December 1994	Gambia	Cohort	368	Logistic regression	None	None	Median age: 28 months (IQR: 14 – 48 months)	Females – 49%	Paediatric development of severe anaemia in malaria (packed cell volume < 15%)	Pallor of conjunctiva and pallor of palms	Sensitivity of 80% and a specificity of 85%.	None	NE
Development of sepsis																
2	Njim [8]	2018	June 2003 – May 2005	Bangladesh, India, Indonesia and Myanmar	Randomised Control Trial	1187	Logistic regression	None	Bootsrapping	17 – 87 years	Female – 24.3%	Development of clinical sepsis in adults with severe falciparum malaria	Sex, blood urea nitrogen levels, plasma anion gap, respiratory distress, shock on admission, parasitaemia, coma and jaundice	AUC: 0.789. Sensitivity – 70.0%; specificity – 69.4%	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: blood urea nitrogen; TNF: tissue necrotic factor

Table 2: Summary of articles with models predicting mortality in paediatric severe malaria

N	Authors	Year	Period of participant recruitment	Country	Type of study	Sample size	Statistics used	Name of model	Method internal of validation	Age profiles	Sex profiles	Outcome predicted	Variables used	Diagnostic properties	External validation	Use in clinical settings

Mortality															
1	Jaffar [21]	1997	1992 – 1994	Gambia	Retrospective analysis of data from a randomised control trial	624	Logistic regression	None	None	1 – 9.5 years	Females – 49%	Mortality in paediatric cerebral malaria	Cold periphery, deep coma and hypoglycaemia	Not done	None	NE
2	Molyneux [27]	1989	January 1987 – June 1988	Malawi	Cohort	131	Univariable analysis	Bedside prognostic index	None	7 months – 10 years	Females – 55.7%	Mortality in paediatric cerebral malaria	Blood glucose, parasitaemia, WBC count, age, coma score, absent corneal reflexes, decerebration, convulsions	Positive predictive value – 83%, sensitivity – 66%	None	NE
3	Conroy [16]	2012	1997 – 2009	Malawi	Cohort	155	Logistic regression	None	Hosmer-Lemeshow goodness-of-fit test	8 months – 14 years	Females – 54.4%	Mortality in patients with cerebral malaria	Age, Blantyre coma score, respiratory distress, severe anaemia, angiopoietin-1, angiopoietin-2 and sTie-2 levels	C-index of 0.79 (95% CI 0.72 – 0.84)	None	NE
4	Krishna [22]	1994	1988 – 1989	Gambia	Cohort study	115	:Logistic regression	None	Wald statistic and ROC analysis	18 months – 12 years	NC	Mortality in paediatric severe malaria	Coma score, whole blood lactate/glucose ratio, TNF level	Wald statistic: coma score (4.5), lactate/glucose ratio (8.36), TNF level (6.5)	None	NE
5	Marsh [23]	1995	May 1989 – November 1991	Kenya	Cohort	1844	Logistic regression	None	None	Mean: 26 months	NC	Mortality in children with severe malaria	Impaired consciousness, respiratory distress, hypoglycemia and jaundice	Predicted 92.2% of deaths	None	NE
6	Newton [28]	2005	January 2001 – December 2003	Malawi, Kenya and Ghana	Cohort	14605	Linear regression	None	AUROC	Mean age: 32 – 36 months	Females – 53 – 55%	Mortality in paediatric severe falciparu	Deep breathing, Blantyre Coma Score, inability to sit, weight-	C-statistic 0.83 – 0.88 in the three sites: Blantyre (0.88), Kilifi	None	NE

												m malaria	for-age Z score, hypoglycaemia, base excess and lactate concentration	(0.87) and Kumasi (0.83)		
7	Gérardin [32]	2006	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	Median: 8 years (IQR: 5 – 11 years)	Females – 40.5%	Mortality in children with falciparum malaria	Systolic blood pressure, temperature, mental status, heart rate, dilatation of pupils, pH, arterial CO_2, arterial PO_2, serum glucose, potassium, urea, creatinine, white blood cells, prothrombin time, platelet count	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	NE
8	Helbok [20]	2009	December 2000 – May 2005	Gambia, Malawi, Kenya, Ghana, and Gabon	Cohort	23890	Logistic regression	LODS (Lambaréné Organ Dysfunction Score)	Internal validation using Bonferroni correction	Mean: 30 – 38 months	Females – 41% – 47%	Mortality in children with severe falciparum malaria	Coma, prostration and deep breathing	AUROC: 80 0.80 (0.79 – 0.82)	Yes	NE
9	von Seidlein [30]	2012	2005 - 2010	Gambia, Mozambique, Nigeria, Rwanda, Kenya, DRC, Tanzania, Ghana, Uganda	Retrospective analysis	5426	Logistic regression	None	ROC analysis	Median: 2.8 years (1.7, 4.3)	NC	Mortality in paediatric severe falciparum malaria	Base deficit, Coma, convulsions, BUN and chronic illness	AUROC: 0.85 (95% CI: 0.83 - 0.87)	None	NE
10	Conroy [31]	2015	NC	Uganda	Cohort	1589	Logistic regression	SICK (Signs of Inflammation in Children	Hosmer-Lemeshow goodness of-fit	NC	Females – 54.3%	Mortality in malaria	Altered consciousness temperature, heart rate, respiratory	AUROC – 0.846	Yes	NE

bmjopen-2019-030799 on 20 November 2019

								that Kill) [38] – AUC[a]: 0.887 (sensitivity 84.1% specificity 82.2%)					rate, systolic blood pressure, capillary refill time and age			
								LODS [57]	Hosmer-Lemeshow goodness of-fit	NC	Females – 54.3%	Mortality in malaria	Prostration, coma (BCS) and deep breathing	AUROC – 0.898	Yes	NE
								PEDIA [39] – AUC[a]: 0.93 (95% CI 0.92 to 0.94)	Hosmer-Lemeshow goodness of-fit	NC	Females – 54.3%	Mortality in malaria	Kwashiokor*, jaundice, subcostal indrawing, prostration (seizures) and wasting	AUROC – 0.896	Yes	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: blood urea nitrogen; TNF: tissue necrotic factor

Table 3: Summary of articles with models predicting mortality in adult severe malaria

N	Authors	Year	Period of participant recruitment	Country	Type of study	Sample size	Statistics used	Name of model	Method internal of validation	Age profiles	Sex profiles	Outcome predicted	Variables used	Diagnostic properties	External validation	Use in clinical settings
Mortality																
1	Wilairatana [41]	1995	July 1991 – May 1993	Thailand	Cohort	72	Validation of APACHE II model (Original APACHE	APACHE II score [58]	ROC analysis	Mean age: 29.9	Females – 33.3%	Mortality in adult patients with cerebral	MAP, temperature, heart rate, respiratory rate, arterial pH, PaO_2,	Predicted mortality with 95.8% accuracy	None	NE

							II score use clinical judgement and physiologic relationships to assign weightings)					falciparum malaria	haematocrit, WBC count, creatinine, sodium, potassium and Glasgow coma score			
2	Dondorp [17]	2004	NC	Vietnam	Cohort	268	Logistic regression	None	Hosmer-Lemeshow goodness-of-fit test	15 – 79 years	Females – 19%	Mortality in adults with severe falciparum malaria	Plasma lactate, plasma strong anion gap and plasma creatinine	AUROC: 0.81	None	NE
3	Mishra [24]	2007	NC	India	Cohort	212	Linear regression	MSA (Malaria score for adults)	Not done	NC	NC	Mortality in adults with severe malaria	Severe anaemia, acute renal failure, respiratory distress, cerebral malaria	Sensitivity: 89.9%, specificity: 70.6%, positive predictive value: 94.1% with cut-off of 5/10	Yes [43]	NE
								MPS (Malaria prediction score)	Not done	NC	NC	Mortality in severe malaria	Age, serum creatinine level, haemoglobin level, cerebral malaria, presence of a pregnancy, use of a ventilator	NE	Yes [43]	NE
4	Hanson [18]	2010	June 2003 – May 2005	Bangladesh, India, Indonesia and Myanmar	Retrospective analysis of a randomised control trial	789	Logistic regression	CAM (coma acidosis malaria) score	Hosmer-Lemeshow goodness-of-fit	NC	NC	Mortality in adults with severe malaria	Coma and acidosis (base deficit	AUROC: 0.81 (95% CI: 0.77 – 0.84)	Yes [59]	NE
5	Mohapatra [26]	2009	January 200 – December 2004	India	Cohort study	2089	Logistic regression	MSS (Malaria severity score)	Hosmer-Lemeshow goodness-of-fit (internal validation by splitting	18 – 71 years	Female – 34.6%	Mortality in adult patients with severe falciparum malaria	neurologic, renal, haematologic, hepatic, respiratory, cardiovascular, and metabolic organ systems	AUROC: 0.9	None	NE

									data – 2089 vs 509)							
6	Newton [29]	2013	1986 – 2002	Thailand	Retrospective analysis	988	Logistic regression	MPI (Malaria prognostic index)	ROC curve analysis and internal validation by data splitting	15 – 74 years	Females – 43%	Mortality in adult severe falciparum malaria	Glasgow coma scale, parasitaemia, plasma lactate, serum bilirubin, pigmented parasites and treatment with ACT	AUROC: 0.97	None	NE
7	Mohapatra [25]	2014	NC	India	Cohort	112	NC	GCBRS (GCS, creatinine, respiratory rate, bilirubin and systolic BP) score	NC	Mean: 35.8 ± 15.1 years	Females – 16.1	Mortality in severe falciparum malaria	Cerebral malaria, renal failure, respiratory distress, jaundice and shock	Sensitivity: 85.3%. Specificity: 95.6%	None	NE
8	Hanson [19]	2014	1996 – 2013	Bangladesh, India, Indonesia, Vietnam and Myanmar	Randomised control trials and cohort studies	1801	Logistic regression	None	Hosmer-Lemeshow goodness-of-fit	21 – 45	Females – 24.4	48-hour survival and survival to discharge in patients with severe malaria	Shock, oligo-anuria, hypoglycaemia, respiratory rate, Glasgow Coma Score and absence of fever	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: blood urea nitrogen; TNF: tissue necrotic factor

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

N	Authors	Year	Period of participant recruitment	Country	Type of study	Sample size	Statistics used	Name of model	Method internal of validation	Age profiles	Sex profiles	Outcome predicted	Variables used	Diagnostic properties	External validation	Use in clinical settings
Severity of disease																
1	Helbok [35]	2003	October 1, 2001 – January 30, 2002	Thailand	Cohort	22	NC	MODS (Multi-organ dysfunction score) [44]	None	16 – 41 years	Female – 41.8%	Severity of disease in adult patients with uncomplicated falciparum malaria	Seven organ systems: (heart, blood vessel, blood, respiratory system, metabolism, gastrointestinal system, liver, kidney and urinary tract, immune system, and central nervous system)	None	None	NE
2	Helbok [34]	2005	October 1, 2001 – July 30, 2002	Thailand	Cohort	29	Survival analysis	MODS [44]	None	Mean age: 27.1 (± 10.6)	Female – 27.6%	Severity of disease in adult patients with severe falciparum malaria	Seven organ systems: (heart, blood vessel, blood, respiratory system, metabolism, gastrointestinal system, liver, kidney and urinary tract, immune system, and central nervous system)	None	None	NE
3	Helbok [36]	2006	August 2003 – May 2005	Gabon	Cohort	485	Survival analysis	Simplified MODS [35]	ROC analysis	4 months – 169 months	Females – 49%	Severity of disease and disability in children with severe falciparum malaria infection	Seven organ systems: (heart, blood vessel, blood, respiratory system, metabolism, gastrointestinal system, liver,	AUC to predict prolonged disease (>48 hours unable to walk): 0.92 (95%	None	NE

												kidney and urinary tract, immune system, and central nervous system)	CI, 0.89–0.95).		
4	Grigg [37]	2018	October 2012 – April 2016	Malaysia	Cohort	481 patients with *Plasmodium knowlesi*	Logistic regression	None	None	33 years (IQR: 21 – 49)	Female – 43.2%	Severity of *Plasmodium knowlesi* infection using WHO 2014 research criteria [45]	Age >45, abdominal pain, shortness of breath, increased parasite count, schizont proportion >10%, bicarbonate <18 mmol	None	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: blood urea nitrogen; TNF: tissue necrotic factor; WHO: World Health Organisation; IQR: Interquatile range

Table 5: Findings of review, research gaps and potential for future research

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

Most models have high risk of bias due to lack of use of up to date methods of internal validation	Models without risk of bias that use adequate statistical methods of internal validation	Internal validation and wide external validation to help integrate models into daily clinical practice	

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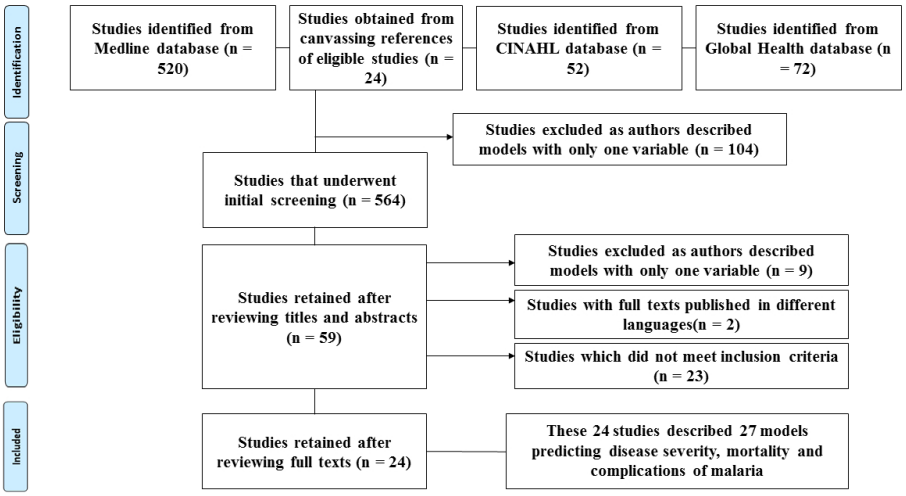
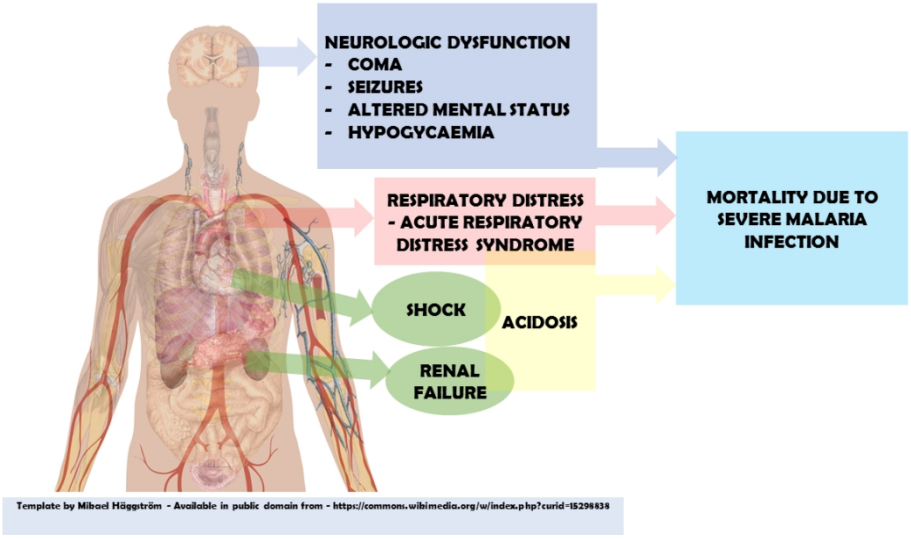
Figures Legends:

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

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



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



Predictive factors of disease severity and mortality in malaria infection

Appendix 1: PRISMA checklist for systematic reviews and meta-analysis.

Table 1

Section/topic	#	Checklist item	Reported on page #
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			
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., Web address), 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 characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact 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

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 (including 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 means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (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 review, 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) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest 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 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	14

Appendix 2: Information sources

Electronic sources

Table 1a: Search strategy for Medline database

Searches	**Search combinations**	**Search terms**	**Number of hits**
S1		"prognost* model" OR "predict* model" OR “Predictive Value of Tests”	208,974
S2		"predict* score" OR "prognos* score"	3,884
S3	S1 OR S2		211,947
S4		(MH "Malaria+") OR (MH "Malaria, Vivax") OR (MH "Malaria, Cerebral") OR (MH "Malaria, Falciparum+") OR (MH "Malaria, Avian")	63,536
S5		"Malaria" OR "vivax malaria" OR "falciparum malaria" OR "cerebral malaria" OR "severe malaria" OR "clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*	111,461
S6	S4 OR S5		111,510
S7	S3 AND S6		520

Table 1b: Search strategy for CINAHL database

Searches	Search combinations	Search terms	Number of hits
S1		"prognost* model" OR "predict* model" OR “Predictive Value of Tests”	49,434
S2		"predict* score" OR "prognos* score"	1,041
S3	S1 OR S2		50,217
S4		(MH "Malaria+")	7,468
S5		"Malaria" OR "vivax malaria" OR "falciparum malaria" OR "cerebral malaria" OR "severe malaria" OR "clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*	10,945
S6	S4 OR S5		10,945
S7	S3 AND S6		52

Table 1c: Search strategy for Global Health database

Searches	Search combinations	Search terms	Number of hits
S1		"prognost* model" OR "predict* model" OR “Predictive Value of Tests”	2,906
S2		"predict* score" OR "prognos* score"	368
S3	S1 OR S2		2,906
S4		"Malaria" OR "vivax malaria" OR "falciparum malaria" OR "cerebral malaria" OR "severe malaria" OR "clinical malaria" OR plasmodium OR antimalaria* OR anti-malaria*	89,436
S7	S3 AND S4		72

Appendix 3: The PROBAST tool used to assess the risk of bias and applicability of the studies used in the review

Study	Risk of bias				Applicability			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability
Conroy 2012	+	+	+	-	+	-		-	-
Conroy 2015*	+	+	+	-	+	+		-	+
Dondorp	+	+	+	-	+	+		-	+
Gerardin*	+	+	+	-	+	+		-	+
Grigg	+	+	+	-	+	+		-	+
Hanson 2010	+	+	+	-	+	+		-	+
Hanson 2014	+	+	+	-	+	+		-	+
Helbok 2003*	+	-	+	-	+	-		-	-
Helbok 2005*	+	-	+	-	+	-		-	-
Helbok 2006*	+	-	+	-	+	-		-	-
Helbok 2009	+	+	+	-	+	+		-	+
Jaffar	+	+	+	-	+	+		-	+
Krishna	+	+	+	-	+	-		-	-
Marsh	+	+	+	-	+	+		-	+
Mishra	+	+	+	-	+	+		-	+
Mohapatra 2009	+	+	+	-	+	+		-	+
Mohapatra 2014	+	+	+	-	+	+		-	+
Molyneux	+	+	+	-	+	+		-	+
Newton 2005	+	+	+	-	+	+		-	+
Newton 2013	+	+	+	-	+	+		-	+
Njim	+	+	+	-	+	+		-	+
von Seidlein	+	+	+	-	+	+		-	+
Webber	+	-	-	-	-	-		-	-
Wilairatana*	+	+	+	-	+	+		-	+

*Study was designed to externally validate existing models; + indicates low risk of bias/low concern regarding applicability; - indicates high risk of bias/high concern regarding applicability

PRISMA checklist for systematic reviews and meta-analysis.

Section/topic	#	Checklist item	Reported on page #
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			
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., Web address), 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 characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact 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

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 (including 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 means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (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 review, 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) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest 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 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14