International Journal of Infectious Diseases 134 (2023) 240–247

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Prostration and the prognosis of death in African children with severe malaria

Selidji T. Agnandji[1,2,3], Mario Recker[1,4,*], Benjamin Mordmüller[1,2,3,5], Stephan Glöckner[6,7], Akim A. Adegnika[1,2,3], Bertrand Lell[2,8], Lucas Otieno[9], Walter Otieno[9], Seth Owusu-Agyei[10], Kwaku P. Asante[10], Tsiri Agbenyega[11], Daniel Ansong[11], Eusebio Macete[12], Pedro Aide[12], Hermann Sorgho[13], Halidou Tinto[13], Neema Mturi[14], John P.A. Lusingu[15], Samwel Gesase[15], Irving Hoffman[16,17], Nahya Salim Masoud[18], Charles R. Newton[19,20], Kalifa Bojang[21], Gérard Krause[6,7], Peter Gottfried Kremsner[1,2,3]

[1] *Institute for Tropical Medicine, University Hospital Tübingen, Tübingen, Germany*
[2] *Centre de Recherches Médicales de Lambaréné (CERMEL), Lambaréné, Gabon*
[3] *Translational Thematic Unit Malaria, German Center for Infection Research (DZIF), Tübingen, Germany*
[4] *Department of Ecology and Conservation, University of Exeter, Exeter, UK*
[5] *Radboud University Medical Centre, Department of Medical Microbiology, Nijmegen, The Netherlands*
[6] *Department of Epidemiology, Helmholtz Centre for Infection Research, Braunschweig, Germany*
[7] *Translational Infrastructure Epidemiology, German Center for Infection Research (DZIF), Braunschweig, Germany*
[8] *Department of Medicine I, Division of Infectious Diseases and Tropical Medicine, Medical University of Vienna, Vienna, Austria*
[9] *Kenya Medical Research Institute, KEMRI-Walter Reed Project, Kombewa, Kenya*
[10] *Kintampo Health Research Center, Kintampo, Ghana*
[11] *Kwame Nkrumah University of Science and Technology, Agogo, Ghana*
[12] *Centro de Investigação em Saúde de Manhiça, Manhiça, Mozambique*
[13] *Institut de Recherche en Science de la Santé, Nanoro, Burkina Faso*
[14] *Kenya Medical Research Institute, KEMRI-Wellcome Trust Research Programme, Centre Medicine Research, Kilifi, Kenya*
[15] *NjugNational Institute for Medical Research, Korogwe, Tanzania*
[16] *University of North Carolina (UNC), Division of Infectious Diseases, North Carolina, USA*
[17] *University of North Carolina (UNC) Project, Lilongwe, Malawi*
[18] *Muhimbili University of Health and Allied Sciences (MUHAS), Dar es Salaam and Ifakara Health Institute, Bagamoyo, Tanzania*
[19] *Kenya Medical Research Institute, KEMRI-Wellcome Trust Programme, Kilifi, Kenya*
[20] *Department of Psychiatry, University of Oxford, Oxford, UK*
[21] *Medical Research Council (MRC) Unit at London School of Hygiene and Tropical Medicine, Banjul, The Gambia*

ARTICLE INFO

Article history:
Received 6 March 2023
Revised 19 June 2023
Accepted 29 June 2023

Keywords:
Severe malaria
Mortality
Prostration
Deep breathing
Coma

ABSTRACT

Objectives: Malaria is still one of the main reasons for hospitalization in children living in sub-Saharan Africa. Rapid risk stratification at admission is essential for optimal medical care and improved prognosis. Whereas coma, deep breathing, and, to a lesser degree, severe anemia are established predictors of malaria-related death, the value of assessing prostration for risk stratification is less certain.

Methods: Here we used a retrospective multi-center analysis comprising over 33,000 hospitalized children from four large studies, including two observational studies from the Severe Malaria in African Children network, a randomized controlled treatment study, and the phase-3-clinical RTS,S-malaria vaccine trial, to evaluate known risk factors of mortality and with a specific emphasis on the role of prostration.

Results: Despite comparable age profiles of the participants, we found significant inter- and intra-study variation in the incidence of fatal malaria as well as in the derived risk ratios associated with the four risk factors: coma, deep breathing, anemia, and prostration. Despite pronounced variations, prostration was significantly associated with an increased risk of mortality (P <0.001) and its consideration resulted in improved predictive performance, both in a multivariate model and a univariate model based on the Lambaréné Organ Dysfunction Score.

* Corresponding author.
E-mail address: mario.recker@uni-tuebingen.de (M. Recker).

https://doi.org/10.1016/j.ijid.2023.06.022

Conclusion: Prostration is an important clinical criterion to determine severe pediatric malaria with possible fatal outcomes.

Background

In order to reduce the number of children dying from severe malaria, health workers require valid, rapid, and simple scoring systems to stratify patients into different levels of clinical care, i.e., treatment as outpatient, hospitalization, or if available intensive care. This is particularly important in settings with a large patient-to-care provider ratio and weak health systems. Between 2010 and 2018, the total number of malaria patients decreased from 75 to 57 cases per 1000 population at risk, but the decrease has clearly slowed down in recent years [1]. Almost all malaria-related deaths are due to infections with the parasite *Plasmodium falciparum*, which is the parasite responsible for the highest burden of disease, especially in low-income countries in sub-Saharan Africa [1].

Once infection is confirmed, a severely ill patient should receive parenteral artesunate [2] together with rapid and good supportive treatment (i.e., blood transfusion for severe malaria anemia, glucose for hypoglycemia, and good care). Severely ill children at a high risk of a complicated, potentially fatal course need to be identified immediately upon arrival at a health facility. This identification is conducted with a list of clinical signs and symptoms that predict risk of death due to malaria [3–6]. For healthcare workers, it is crucial to perform this identification as fast as possible, ideally within minutes. Simplified scores used in routine care are already established, but their predictive values require further evaluation. In general, risk of death for patients with severe malaria is difficult to study and requires a large sample size due to the low proportion of fatalities when clinical care is good.

A systematic review of predictors for mortality in African children with severe malaria suggested only a weak association between death and prostration, while coma and deep breathing were predictive [7]. The meta-analysis relied on published aggregated data and could only perform univariate analysis for each prognostic factor [7]. Prostration is among the predictors (together with deep breathing and coma) used in the Lambaréné Organ Dysfunction Score (LODS) [6,7], an evidence-based simple, and widely used tool for rapid risk stratification and predicting death due to malaria in African children [8].

In this study, we analyzed multi-center data of severe malaria cases in children from observational and interventional studies across sub-Saharan Africa and demonstrate the benefit of considering prostration as an additional risk factor for fatal malaria.

Methods

Study designs and selection criteria

The study populations comprised hospitalized African children with severe malaria aged 15 years or younger, obtained from four independent and previously analyzed studies. Patients included in this analysis needed a valid assessment of death or survival, prostration, coma, and deep breathing or an approximation of those predictors using other variables as described below. The exact descriptions of the populations are available in the original publications. Note, some studies included repeated episodes in the same individuals, such that the number of data points may exceed the number of individuals in the respective studies; to avoid confusion we therefore simply refer to the total number of episodes instead of the number of individuals.

The first study was an observational study on severe malaria in African children (SMAC) conducted between December 2000 and May 2005 on children hospitalized with *P. falciparum* and treated with quinine [9–11]; this study is here referred to as 'ObservStudy'. The study was performed in the following study centers: Medical Research Unit, Albert Schweitzer Hospital, Lambaréné, Gabon; Medical Research Unit, study site Libreville, Gabon; Medical Research Council Laboratories, Banjul, The Gambia, study site Edward Francis Small Teaching Hospital (formerly Royal Victoria Teaching Hospital); University of Science and Technology, Kumasi, Ghana; Kenya Medical Reserach Institute (KEMRI) Centre for Geographic Medicine Research (Coast), Kilifi, Kenya; and Malaria Project, Blantyre, Malawi. From this study, a total number of N = 25,831 patients were included.

The second study was a randomized controlled phase III trial conducted between March 2009 and January 2014 investigating the efficacy and safety of RTS,S/AS01 malaria vaccine [12]; this study is here referred to as 'VaccineRCT'. Only children who were diagnosed with severe malaria during the trial were considered for this analysis. If a child developed severe malaria more than once, all episodes during the trial were used as independent measurements. As data records in this study did not contain data about deep breathing, respiratory distress was used as a surrogate. From this study, a total number of N = 1590 episodes were included.

The third study, here referred to as 'TreatmentRCT', was a randomized controlled trial conducted between January 2011 and October 2012 investigating different artesunate regimens [13]. As the treatment groups showed no differences in mortality, we ignored the assigned group structure of the trial. From this study, 1043 episodes were included in our analysis.

The fourth study ('AQUAMAT') was a randomized trial undertaken between 2005 and 2010 across 11 centers in nine African countries, where children under the age of 15 years with severe malaria were randomly assigned to artesunate or quinine [2]. From this study, 5421 episodes were included in our analysis.

Risk factors

We considered five risk factors for a fatal outcome in total: age, anemia, coma, deep breathing, and prostration. However, as no association between age and mortality was found, this was later dropped from the analyses. We defined coma according to a Blantyre coma score (BCS) ≤ 2 and used the SMAC Network definition for severe malaria [10]. Prostration is an age-specific variable and was defined as the inability to suck or breastfeed for infants, the inability to sit for children older than 8 months, the inability to stand for children older than 14 months, and the inability to walk in children older than 18 months. By this definition, any patient with coma also is prostrate. We excluded patients from the analysis showing a combination of a BCS <5 in the absence of prostration for lack of plausibility (n = 135). If the assessment of coma was missing but there was a negative entry for prostration, then the patient was treated as having a negative entry for coma as well. Patients with a missing value for prostration, but a BCS <5 were treated as having a positive entry for prostration.

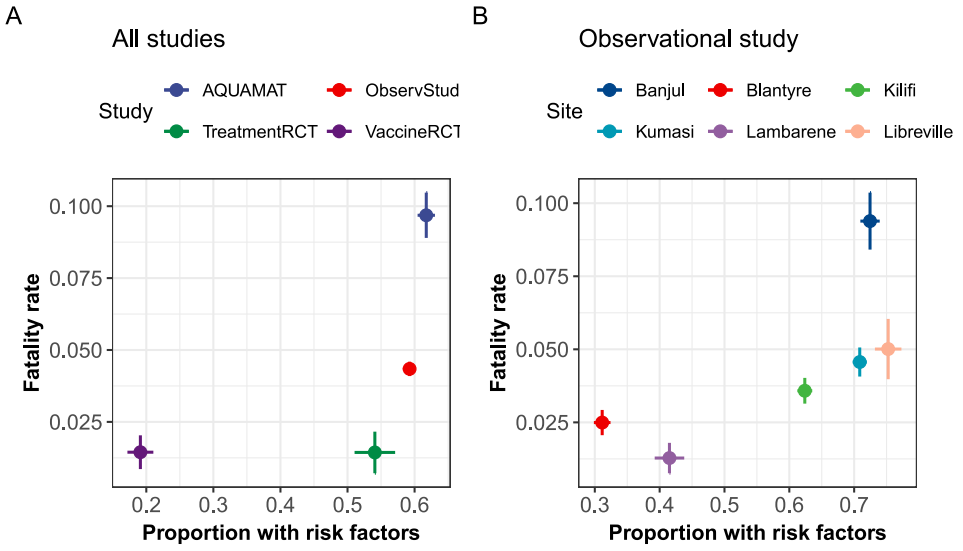

Fig. 1. Fatality rate vs presence of risk factors. Despite pronounced variation in fatality rates between the different studies (A) and between sites of the Observational Study (B), there is a general trend toward an increased risk of death with higher percentage of individuals recorded with one or more risk factors.

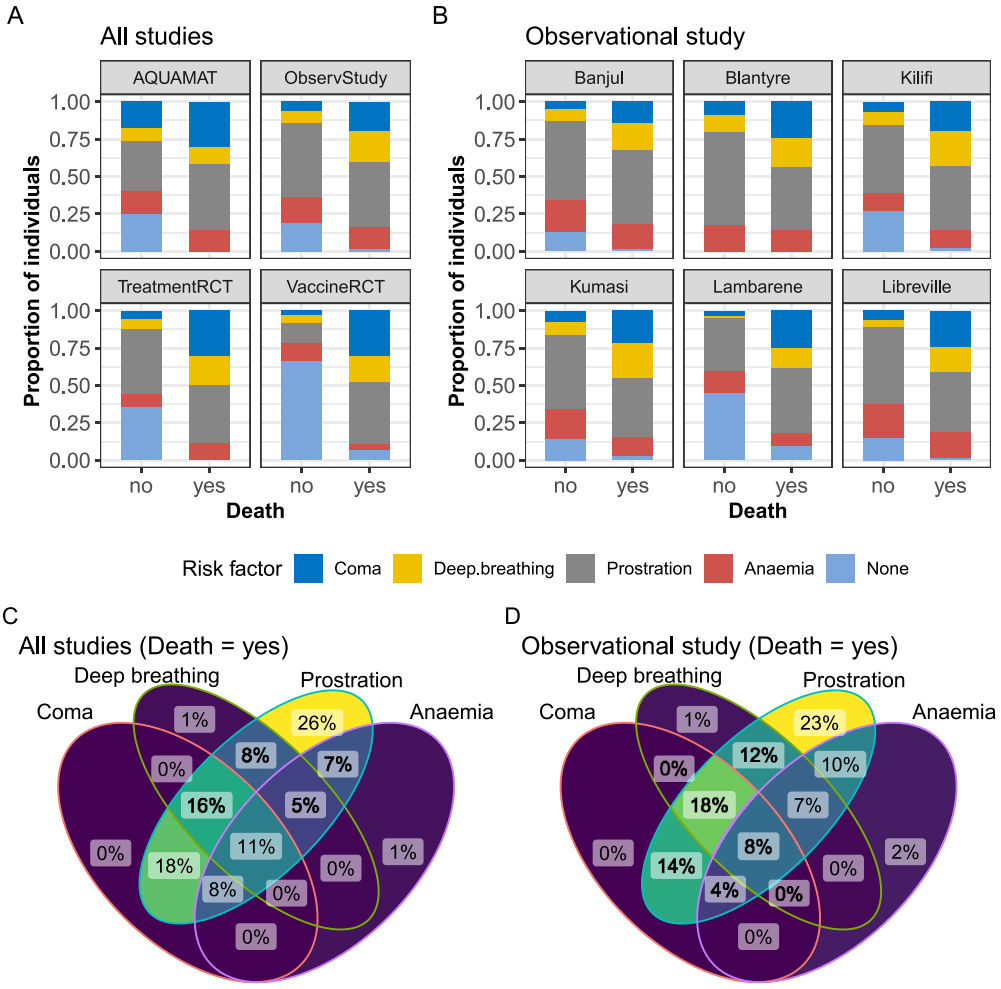

Fig. 2. Risk factor distribution associated with outcome. (A, B) Proportional representation of the number of individuals recorded with a particular risk factor, stratified by outcome (death yes/no) and study site (all studies, left; observational study, right). (C, D) Venn diagrams illustrating a general trend toward being positive for multiple risk factors in children who died of malaria.

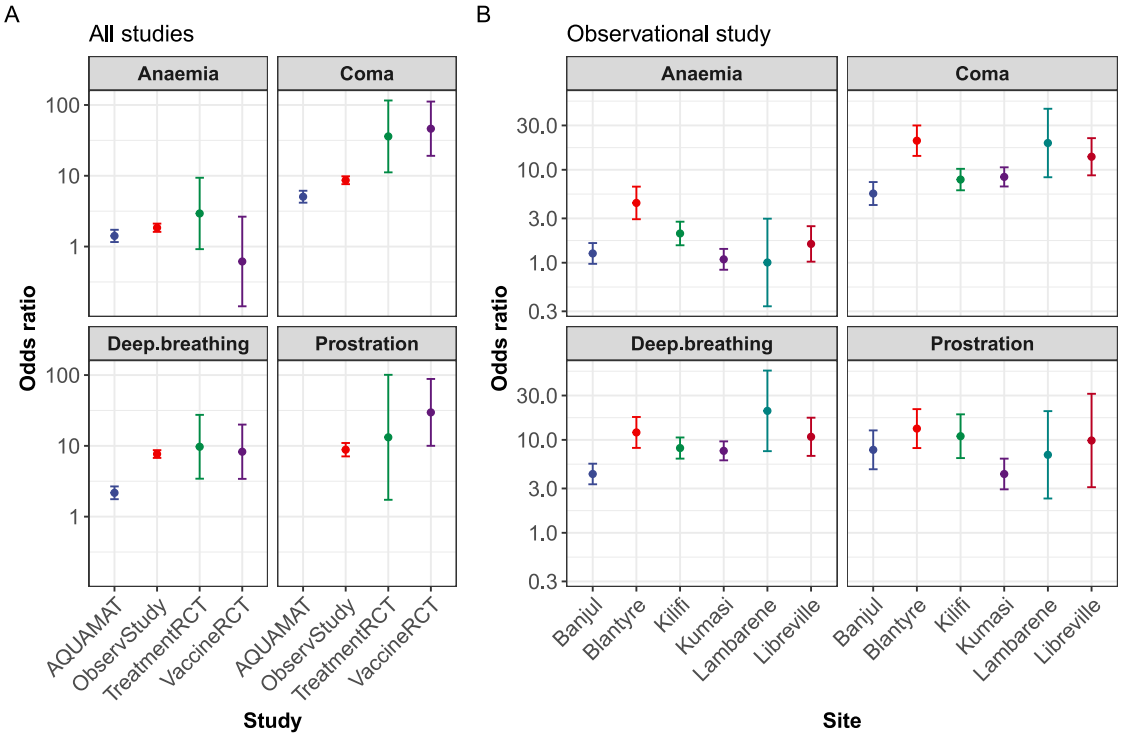

Fig. 3. Relative risk ratios of the four risk factors stratified by study site. There is significant variation in the risk of death associated with the presence/absence of the risk factors under consideration, spanning almost an order of magnitude (risk ratio displayed on a log scale). Note, all diseased individuals in the AQUAMAT study were positive for prostration, precluding the calculation of a meaningful risk ratio.

Statistical analysis

Odds ratios, and their 95% confidence intervals, for individual risk factors were derived by comparing fatal outcomes in individuals recorded positive for a specific risk factor irrespective of other diagnostics; this was done using the *epitools* R package [14].

The data was further modeled using generalized linear models (GLM), with fatal malaria (*Death* = yes/no) as the response variable and *age, coma, deep breathing, prostration,* and *anemia* as fixed predictors variables. We also included *study* or *study site* as fixed effects as the number of studies/sites was insufficient to obtain robust estimates of their variances when included as random effects. Interaction terms were initially considered; however, after model selection showed no significant increase in model performance these were removed in favor of the simpler model.

Due to significant differences in participant numbers between the individual studies, we first modeled each study separately. Because prostration was recorded as present for every individual who died in the AQUAMAT study, this study was excluded from the statistical analyses in order to prevent bias. In addition to reporting study-specific effect sizes, by means of log-transformed odds ratios, we also report the pooled effect sizes, calculated using the inverse-variance meta-analysis approach, with weights for each variable being proportional to their inferred variance from the study-specific analysis, as encoded in the *meta* R package (https://github.com/guido-s/meta/). To further investigate smaller-scale heterogeneities, we also performed a site-stratified analysis for the ObservStudy. Although site-specific data was available for some of the other studies, the number of samples and in particular the number of fatal outcomes for each site was insufficient to permit robust inferences. As before, pooled effect sizes were determined using the inverse-variance method.

As an additional analysis, we considered two different versions of the LODS [6]. The original score was based on the number of positive indicators for deep breathing, coma, and prostration. In addition, we considered another scored (LODS2) based on coma and deep breathing only, with coma adding twice the score of deep breathing. Instead of conducting study- or site-stratified analyses, all the data was pooled, and *Study* or *Site* included as fixed effects as the focus here was simply the direct comparison between models with and without prostration.

Models were assessed and compared using Akaike information criteria (AICs) and area under the receiver operator characteristic curve (AUC). Due to the low number of fatal outcomes, less than 5% on average, the dataset was highly imbalanced, which makes model performance metrics based on sensitivity or specificity unreliable, especially when using the standard 0.5 decision threshold in a logistic regression model. In order to obtain less biased estimates we fitted the data using a *random forest* machine learning algorithm, using the *randomForest* R package [15] with 1000 trees and balanced sample sizes, and compared model performances by means of leave-one-out cross-validation. Due to the aforementioned imbalance, where incidence of fatal outcomes is very low compared to survival, we also report positive and negative predictive values, which take the prevalence of particular outcomes into consideration.

All statistical analyses were performed with R Version 4.2.0 [16].

Results

Inter-study risk variation

We analyzed a total of N = 33,885 malaria episodes in children collected from four different studies (see Methods). Despite com-

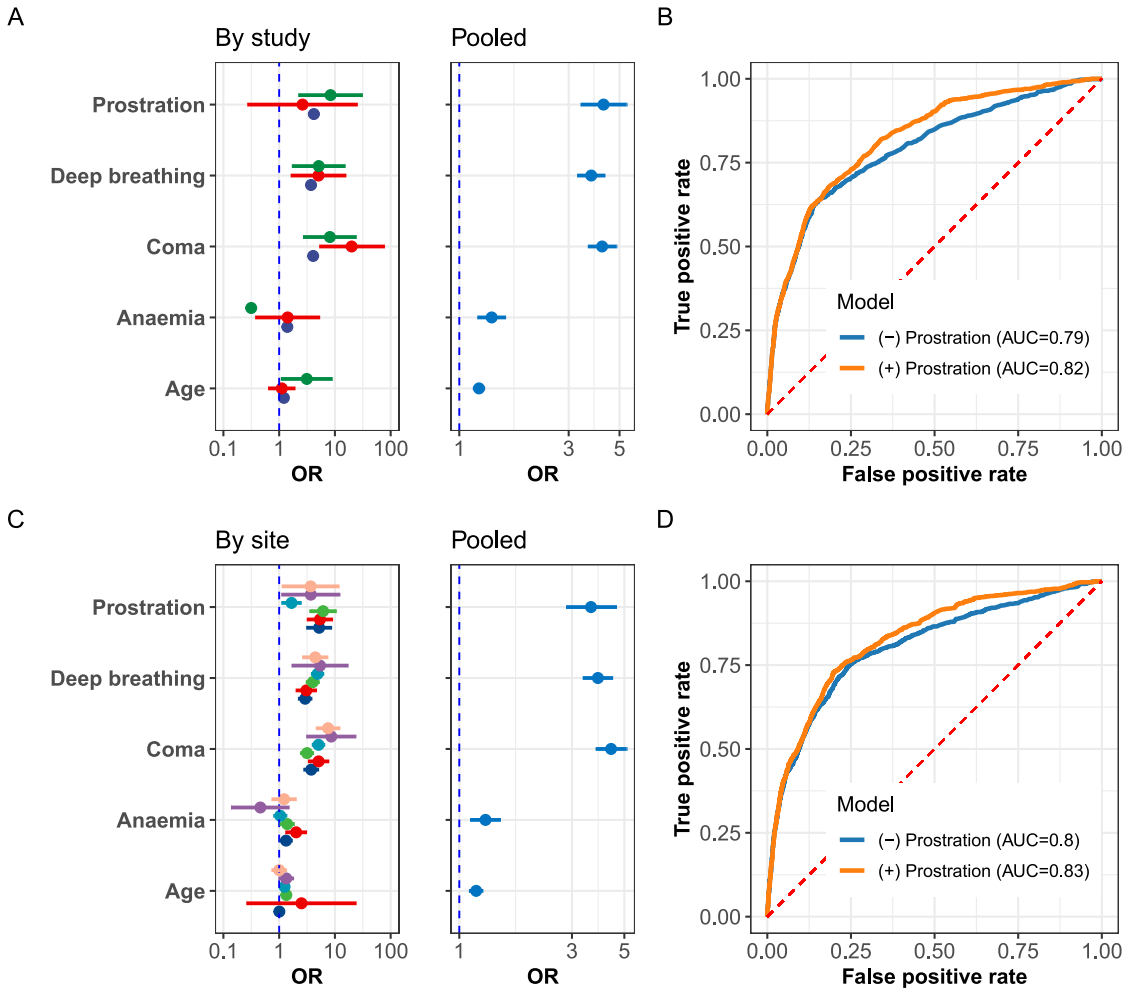

Fig. 4. Prostration is significantly associated with increased mortality risk. Comparison of estimated effect sizes (OR) and model performances based on all data (A, B) and ObservStudy, only (C, D). Different colors correspond to individual studies (blue: ObservStudy, red: TreatmentRCT, green: VaccineRCT) and individual sites, respectively (blue: Banjul, red: Blantyre, green: Kilifi, light blue: Kumasi, purple: Lambaréné, orange: Libreville). Pooled effect sizes are derived by inverse-variance meta-analysis. Receiver operator characteristic curves are based on generalized linear mixed models with (orange) and without prostration (blue). AUC, area under the receiver operator characteristic curve; OR, odds ratio.

parable age profiles of children, fatality differed considerably between the individual studies, ranging from 1-2% in the TreatmentRCT and VaccineRCT studies to nearly 10% in the AQUAMAT study (see Fig. 1A). Equally high variations in the proportion of children who died were also observed between study sites within the ObservStudy, which ranged from just over 1% in Lambaréné to nearly 10% in Banjul (Fig. 1B). Although there was a general trend for higher fatality in settings with a higher proportion of risk factor-positive children, this was not consistent across studies.

Inter and intra-study risk factor distribution

Next, we examined the distributions of recorded risk factors both between studies and within the ObservStudy and how these differed between individuals who survived or not. As shown in Fig. 2A, B, despite expected differences there were commonalities between the individual studies, such that children with fatal outcomes were significantly more likely to be recorded positive for respiratory problems, prostration, and/or coma. Anemia, however, did not show a general pattern across the different datasets.

The association with increased risk of death and multiple risk factors was further explored by means of Venn diagrams, which provide a more detailed differentiation of the combinations of risk factors stratified by outcome. As shown in Fig. 2C, D, the majority of individuals who died were recorded with coma together with deep breathing and/or anemia.

Risk factors and their association with fatal malaria

As shown in Fig. 3, not only do we find significant variation in the estimated odds ratios of the four risk factors but also pronounced differences between the different studies and among the various sites of the ObservStudy. The scale at which these estimates differ exceeds the abovementioned inter- and intra-study differences in the baseline risk of death and remains to be resolved. Note, the large confidence intervals are due to low number of fatal outcomes in these settings.

Prostration as a risk factor for fatal outcomes

We fitted GLMs to the data (see Methods) to assess the association between prostration and fatal outcomes when considered alongside other risk factors. In line with the aforementioned inter and intra-study variability, the derived odds ratios associated

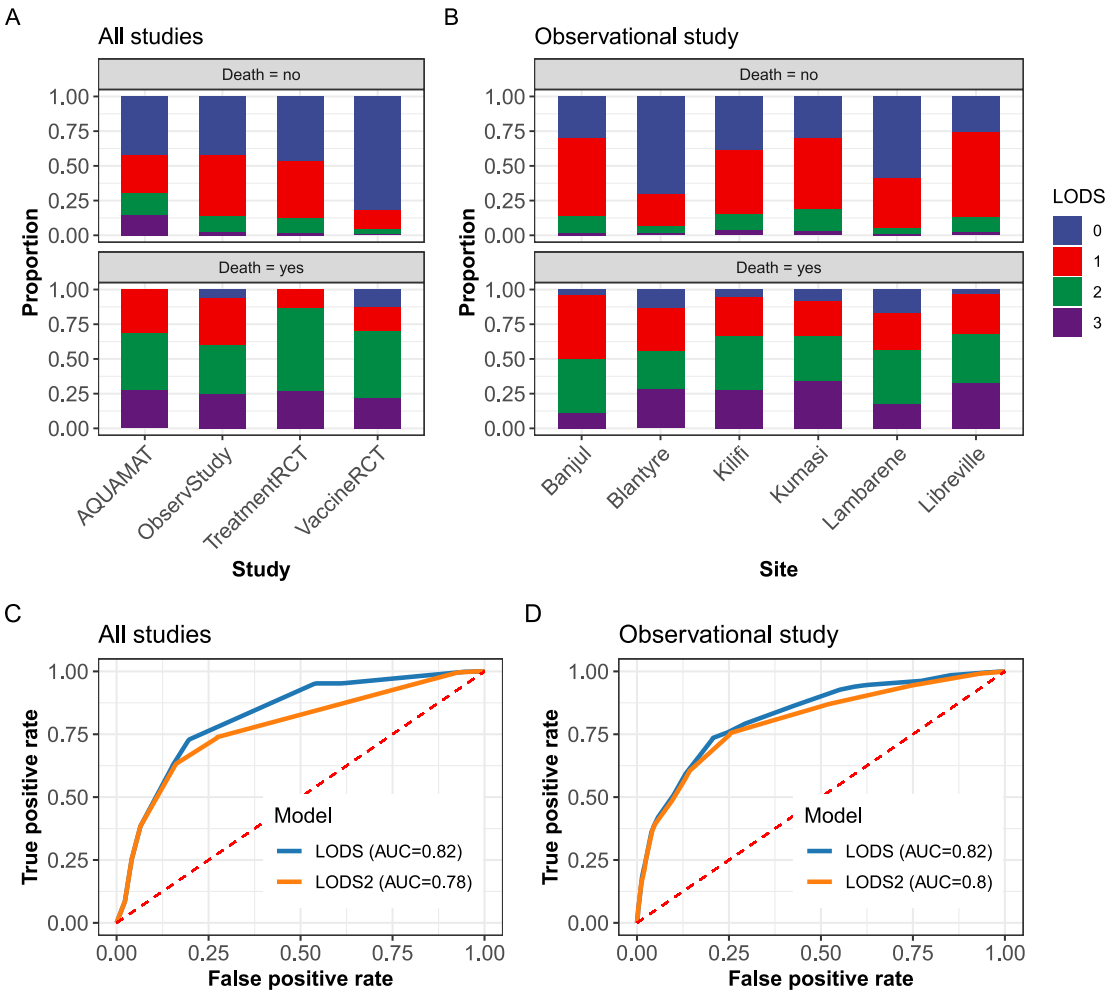

Fig. 5. Outcome-stratified LODS-distributions. (A, B) Whereas most of individuals who survived were recorded with no or only one risk factor (LODS 0 or 1), more than half of those who died had LOD scores of 2 or 3. (C, D) Prostration has a positive effect on model performance when included in LOD score; LODS2 does not include prostration. AUC, area under the receiver operator characteristic curve; LODS, Lambaréné Organ Dysfunction Score.

with prostration showed significant variation but with strong support for a significant effect on mortality (P <0.001, GLM), which was similar in magnitude to deep breathing and coma (Fig. 4A, C). The same general results were obtained when calculating pooled effect sizes using a meta-analytic approach (see Methods).

As shown in Fig. 4B and C, considering prostration as an additional risk factor increases model performance as measured by AUC (b, all studies: 0.82 vs 0.79; d, ObservStudy: 0.83 vs 0.8). The inclusion of prostration was further supported by means of AIC (7291 vs 7494 for the model without prostration based on all studies, and 6856 vs 7014 for the models based on the ObservStudy only).

We next assessed the influence of prostration on model performance in terms of sensitivity and specificity as well as positive and negative predictive values (PPV and NPV, respectively). As the data is highly imbalanced, due to the low number of recorded deaths, obtaining reliable accuracy measures is challenging (e.g., a model always predicting survival would in this case have an accuracy of over 95%). In an attempt to get a more unbiased estimate of how prostration affects predictive accuracy, we employed a random forest approach and compared the models' performances based on leave-one-out cross-validation. This showed that considering data from all studies, the inclusion of prostration increases model sensitivity from 0.62-0.64, which was offset by a decrease in specificity from 0.86-0.85. With regards to positive and negative predictive values, which take into account the low incidence of death, the inclusion of prostration leads to a marginal reduction in PPV (from 0.152-0.149) and marginal increase in NPV (from 0.982-0.983). Considering only the data from the observation study, the inclusion of prostration increases model sensitivity from 0.69-0.72; specificity remained the same at 0.8. Equally, PPV increases from 0.127-0.139 and NPV from 0.984-0.985.

The use of Lambaréné Organ Dysfunction Score for predicting death

In addition to examining particular combinations of risk factors in children who survived or died of malaria, we also considered the distribution of LOD scores and their use as a simple predictive tool for fatal malaria. In line with expectations based on Fig. 2, we found that the majority of individuals who died had more recorded risk factors, and hence higher LODS, than those who survived (Fig. 5A, B).

Similar to the multivariate approach above, conducting a model comparison based on study site and the LODS demonstrates that prostration increases model performance (AUC_{LODS} = 0.82 vs AUC_{LODS2} = 0.78 using all data, and AUC_{LODS} = 0.82 vs AUC_{LODS2} = 0.80 using data from the observational study only). Equally, model selection based on AIC favors the model based on LODS (AIC_{LODS} = 11,102 vs AIC_{LODS2} = 11,540).

Importantly, the performance of the model based on LODS was similar to the multivariate approach in terms of sensitivity, specificity, PPV, and NPV (e.g., 0.62, 0.85, 0.148, and 0.983, respectively, for the LODS-based (inter-study) model compared to 0.64, 0.85, 0.149, and 0.983 for the multivariate model).

Together, these results imply that the consideration of prostration helps to identify individuals at risk of death after a severe malaria episode and that LODS is a simple but robust risk marker of fatal malaria.

Discussion

Our analysis suggests that prostration is a relevant component of a prognostic score for mortality in serve malaria in children.

A previous study by Cominetti et al. [17], who reanalyzed the population previously described in Jallow et al. [18] that likely included patients that were also present in our study, described an increase in mortality for two clusters of patients with respiratory distress. The one with higher mortality was associated with unusual sleepiness – a feature of prostration – while unusual sleepiness on its own was not. This is in line with our findings, which showed that although mortality is associated with prostration, prostration by itself is only a weak predictor of fatal outcomes. It is therefore the combination of different risk factors that allow for more precise and balanced predictions.

Overall, we found that models including prostration can show greater sensitivity than those without, at the expense of a decrease in specificity. In a clinical setting, where a quick informed decision on the level of care must be taken, sensitivity usually prevails over specificity. However, it is important to note that in this case, mortality as an outcome is a relatively rare event that depends on the level of immunity and rapid and good bedside care [19]. This means that an increase in sensitivity, i.e., correctly identifying individuals at risk of a fatal outcome, disproportionally increases the number of false positives. For example, in our dataset, this equated to up to 10 individuals falsely predicted to be at risk of death for each additional individual correctly identified. This means that if the ultimate aim is to prevent death by treating most individuals as high risk, then an approach based on all risk factors, including deep breathing, coma, and prostration would be optimal. In a resource-limited environment, however, this balance might swing in favor of trying to prevent healthcare settings from becoming overwhelmed, where prostration could be considered too unreliable. Importantly, these results held irrespective of using a multivariate approach or one based on a single risk score (LODS).

Even though multifactorial analyses are desirable, we have demonstrated that an established score like the LODS can equally be used and would yield comparative results. This may not be too surprising, given that the three main risk factors (deep breathing, coma, and prostration) had similar estimated odds ratios based on the multivariate analysis, with anemia not contributing much in terms of identifying children with elevated risk. However, it is important to reiterate that it is the combination of the three risk factors that are indicative of risk because the model with LODS based on all three symptoms performed significantly better than the one without prostration. Based on the results presented here we believe that the evidence for prostration being associated with fatal outcomes, especially in combination with other known risk factors, is likely to be stronger than commonly assumed.

Taken together, our results strongly suggest that information about prostration should be used to identify children at risk of mortality when seen by health providers. Furthermore, we demonstrate that LODS has a similar predictive value for mortality compared to more complex multifactorial schemes while being easier to apply in settings where severe malaria is frequent.

Declarations of Competing Interest

The authors have no competing interests to declare.

Funding

STA is an EDCTP Senior Fellow, grant no. TMA-2017SF-1946.

Ethical approval

This study did not require ethical approval.

Acknowledgments

Thanks to Alison Gooda for reviewing the initial draft of this manuscript.

Author contributions

Study design, data analysis, data interpretation and manuscript writing: PGK, MR, BM, KA, SG, GK. Data collection: STA, AAA, BL, PGK, LO, WO, SOA, KPA, TA, DA, EM, PA, HS, HT, NM, JPAL, SG, IH, NSM, CRN, KB. Project administration: CO Writing – review & editing: STA, AAA, BL, PGK, LO, WO, SOA, KPA, TA, DA, EM, PA, HS, HT, NM, JPAL, SG, IH, NSM, CRN, KB.

References

[1] . World Health Organization*World Malaria Report 2021*. Geneva: World Health Organization; 2021.
[2] Dondorp AM, Fanello CI, Hendriksen ICE, Gomes E, Seni A, Chhaganlal KD, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet* 2010;**376**:1647–57. doi:10.1016/S0140-6736(10)61924-1.
[3] Bartoloni A, Zammarchi L. Clinical aspects of uncomplicated and severe malaria. *Mediterr J Hematol Infect Dis* 2012;**4**:e2012026. doi:10.4084/MJHID.2012.026.
[4] Severe falciparum malaria. World Health Organization, communicable diseases cluster. *Trans R Soc Trop Med Hyg* 2000;**94**:S1–90.
[5] von Seidlein L, Olaosebikan R, Hendriksen ICE, Lee SJ, Adedoyin OT, Agbenyega T, et al. Predicting the clinical outcome of severe falciparum malaria in african children: findings from a large randomized trial. *Clin Infect Dis* 2012;**54**:1080–90. doi:10.1093/cid/cis034.
[6] Helbok R, Kendjo E, Issifou S, Lackner P, Newton CR, Kombila M, et al. The Lambaréné Organ Dysfunction Score (LODS) is a simple clinical predictor of fatal malaria in African children. *J Infect Dis* 2009;**200**:1834–41. doi:10.1086/648409.
[7] Sypniewska P, Duda JF, Locatelli I, Althaus CR, Althaus F, Genton B. Clinical and laboratory predictors of death in African children with features of severe malaria: a systematic review and meta-analysis. *BMC Med* 2017;**15**:147. doi:10.1186/s12916-017-0906-5.
[8] Conroy AL, Hawkes M, Hayford K, Namasopo S, Opoka RO, John CC, et al. Prospective validation of pediatric disease severity scores to predict mortality in Ugandan children presenting with malaria and non-malaria febrile illness. *Crit Care* 2015;**19**:47. doi:10.1186/s13054-015-0773-4.
[9] Kremsner PG, Valim C, Missinou MA, Olola C, Krishna S, Issifou S, et al. Prognostic value of circulating pigmented cells in African children with malaria. *J Infect Dis* 2009;**199**:142–50. doi:10.1086/595295.
[10] Taylor T, Olola C, Valim C, Agbenyega T, Kremsner P, Krishna S, et al. Standardized data collection for multi-center clinical studies of severe malaria in African children: establishing the SMAC network. *Trans R Soc Trop Med Hyg* 2006;**100**:615–22. doi:10.1016/j.trstmh.2005.09.021.
[11] Kendjo E, Agbenyega T, Bojang K, Newton CRJC, Bouyou-Akotet M, Pedross F, et al. Mortality patterns and site heterogeneity of severe malaria in African children. *PLoS One* 2013;**8**:e58686. doi:10.1371/journal.pone.0058686.
[12] RTS S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. *Lancet* 2015;**386**:31–45. doi:10.1016/S0140-6736(15)60721-8.
[13] Kremsner PG, Adegnika AA, Hounkpatin AB, Zinsou JF, Taylor TE, Chimalizeni Y, et al. Intramuscular artesunate for severe malaria in African children: a multicenter randomized controlled trial. *PLoS Med* 2016;**13**:e1001938. doi:10.1371/journal.pmed.1001938.
[14] Aragon TJ, Fay MP, Wollschlaeger D, Omidpanah A. *epitools: epidemiology Tools*. R core developement team; 2020 *https://cran.r-project.org/web/packages/epitools/epitools.pdf*.
[15] Liaw & Wiener, The R Journal: Classification and regression by randomForest, R News, 2002.

[16] Fehske H, Schneider R, Weiße A. *Computational Many-Particle Physics*. Berlin, Heidelberg: Springer; 2015.
[17] Cominetti O, Smith D, Hoffman F, Jallow M, Thézénas ML, Huang H, et al. Identification of a novel clinical phenotype of severe malaria using a network-based clustering approach. *Sci Rep* 2018;**8**:12849. doi:10.1038/s41598-018-31320-w.
[18] Jallow M, Casals-Pascual C, Ackerman H, Walther B, Walther M, Pinder M, et al. Clinical features of severe malaria associated with death: a 13-year observational study in the Gambia. *PLoS One* 2012;**7** e45645. doi:10.1371/journal.pone.0045645.
[19] Biai S, Rodrigues A, Gomes M, Ribeiro I, Sodemann M, Alves F, et al. Reduced in-hospital mortality after improved management of children under 5 years admitted to hospital with malaria: randomised trial. *BMJ* 2007;**335**:862. doi:10.1136/bmj.39345.467813.80.