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Advancing approaches to identify young children at risk for post-discharge mortality: Protocol for a prospective observational cohort study in Western Kenya

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ABSTRACT

Introduction Childhood mortality rates following hospital discharge may outpace inpatient mortality rates in some sub-Saharan African settings. Broadly validated risk assessment tools and biomarkers to identify children at risk for post-discharge mortality (PDM) are lacking. Moreover, clinical diagnoses (eg, pneumonia, sepsis, etc.) that confer high risk of PDM share a common pathobiology that culminates in endothelial dysfunction. The objectives of this study are to (1) externally validate existing risk assessment tools for PDM at 60 days and (2) test the association between a marker of endothelial dysfunction (ie, the global arginine bioavailability ratio [GABR]) and 60-day PDM among young children.

Methods and analysis This is a prospective, observational cohort study of neonates (aged 0–28 days, n=1000) and infants and children (aged 1–59 months, n=1000) consecutively discharged from two hospitals in Western Kenya (ie, Jaramogi Oginga Odinga Teaching and Referral Hospital [JOOTRH] and Siaya County Referral Hospital). Candidate variables for previously developed risk assessment tools identified through a systematic review and plasma samples will be collected on the day of hospital discharge. Caregivers of participants will receive telephone calls 30 days and 60 days following discharge to ascertain participants' vital status. Test characteristics and area under the receiver operating characteristic curves will be calculated for each risk tool to determine their discriminatory value. Risk predictiveness and calibration of each tool will also be determined. Mean and median levels of GABR will be compared between cases and matched controls, and conditional logistic regression will be used to test the association between GABR and PDM.

Ethics and dissemination This protocol has received clearance from the Kenya Medical Research Institute Scientific Ethics Review Unit, the JOOTRH Ethics Research Committee, and the Emory University institutional review board. Our results will be disseminated through scientific presentations at national and international conferences and peer-reviewed publications.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ Mortality following hospital discharge contributes to the persistently high rates of mortality among young children in sub-Saharan Africa.

⇒ Several risk assessment tools have been developed to accurately identify young children at risk for post-discharge mortality (PDM), yet none have been broadly validated or incorporated prognostic biomarkers.

WHAT THIS STUDY HOPES TO ADD

⇒ This study will broadly validate risk assessment tools for PDM prediction and will test the association of the global arginine bioavailability ratio and PDM through a prospective cohort study at two hospitals in Western Kenya.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Risk assessment tools to identify young children at risk for PDM may be incorporated into clinical practice and policy to reduce childhood mortality rates in sub-Saharan Africa.

INTRODUCTION

More than half of the nearly 5 million annual deaths among children aged <5 years occur in sub-Saharan Africa,[1 2] a region with a childhood mortality rate of 74/1,000 live births.[3] This mortality rate is the highest in the world.[3] Childhood mortality rates following hospitalisation for an illness (ie, the post-discharge period) may outpace rates of inpatient mortality in some settings in sub-Saharan Africa.[4 5] Rates of post-discharge mortality (PDM) among young children in sub-Saharan Africa are as high as 3–13% within a few months of hospital discharge,[4] far outpacing

the mere 0.1% of US children who die following hospital discharge.[6] Clinical practice recommendations targeting the post-discharge period may help mitigate this inequitable vulnerability for PDM among young children in sub-Saharan Africa.[7]

Accurately identifying young children at risk for PDM in sub-Saharan Africa is critically important to inform interventions in settings where resources are limited and follow-up care can be challenging to families. Rigorously derived and validated risk assessment tools can be used at the bedside to reduce uncertainty and improve accuracy in medical decision making across a wide range of settings, including those with limited resources.[8–10] To be translated into clinical practice, tools must be rigorously derived, validated and implemented, and their impact must be assessed.

Several risk assessment tools have been developed to identify young children at risk for PDM in sub-Saharan Africa.[11–18] However, only two of these have been externally validated and none have been broadly validated (ie, in patient populations that differ from the derivation population) or implemented.[12 19 20] Additionally, some of the previously developed risk assessment tools were derived in specific populations such as those with sepsis or those with diarrhoeal illness,[12 14] making their applicability to broader patient populations unclear. Moreover, owing to the lack of broadly validated risk assessment tools, the decision to safely discharge a young child from a hospital in sub-Saharan Africa is driven by a clinician's judgement, which often does not accurately identify children at risk for PDM in some settings.[21]

Biomarkers have shown promise in improving the performance of clinical risk assessment tools to identify young children at risk of severe disease.[22 23] Clinical diagnoses with especially high risk of PDM, such as community-acquired pneumonia, malaria, sepsis, and sickle cell disease, share a common pathobiology that leads to endothelial dysfunction.[4 15 24–28] The global arginine bioavailability ratio (GABR) is a novel biomarker of endothelial dysfunction predictive of long-term mortality in many populations in outpatient studies in sub-Saharan Africa and the US.[24 29–31] Reduced GABR is the result of impaired de novo arginine synthesis, coupled with greater arginine consumption, and is a promising clinical biomarker for mortality risk stratification[31–33] in diseases with endothelial dysfunction, which are common among young children in sub-Saharan Africa.[4 15 24–28] However, to date, the predictive value of GABR for PDM has not been assessed, and no risk assessment tools for PDM have incorporated objective biomarkers.

Thus, our objectives are to (1) externally validate existing risk assessment tools for PDM 60 days following discharge among young children in Western Kenya, (2) test the association between GABR and 60-day PDM among young children, and (3) assess the potential additive role of GABR when incorporated into existing risk assessment tools for PDM among young children in Western Kenya.

METHODS AND ANALYSIS

Study Design

This is a prospective, observational cohort study of neonates (aged 0–28 days at discharge) and infants and children (aged 1–59 months at the time of hospital discharge) who will be consecutively discharged from two hospitals in Western Kenya (figure 1). Enrolment began in June 2025 and is expected to continue up to December 2026. Reporting of this protocol is in accordance with Strengthening the Reporting of Observational Studies in

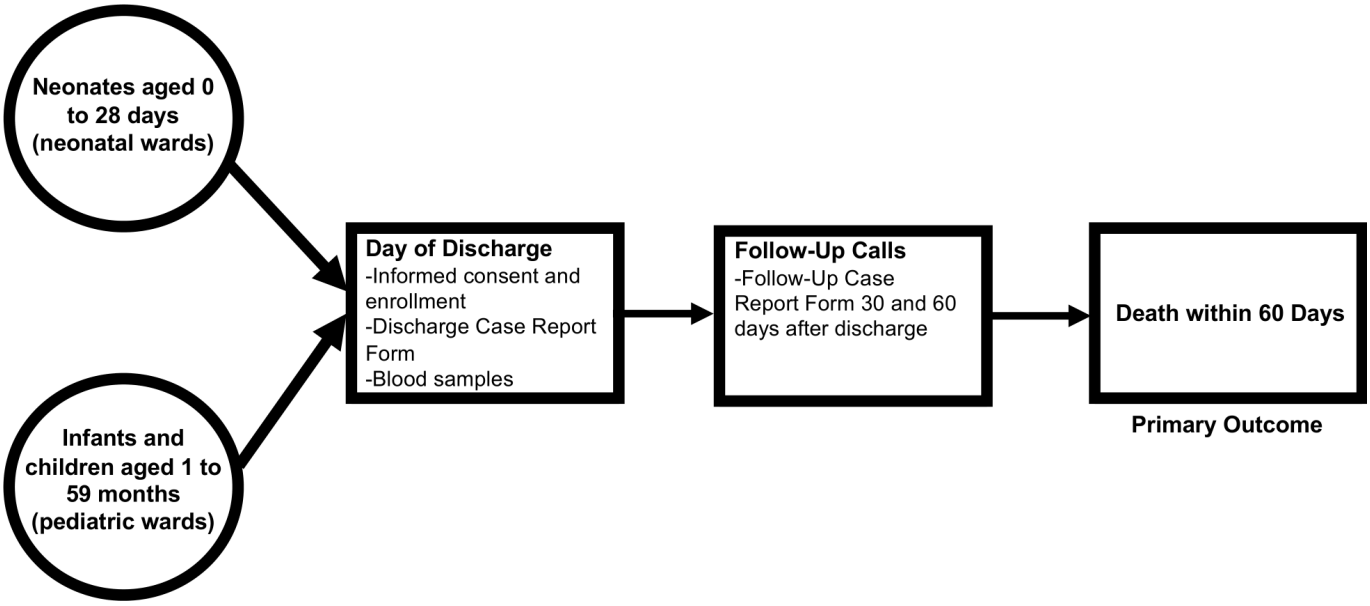

Figure 1 Study design for the external validation of risk assessment tools to identify young children at risk for post-discharge mortality at two hospitals in Western Kenya.

Epidemiology (STROBE) guidelines for cohort studies (online supplemental file 1).

This protocol was developed collaboratively with investigators at the Emory University School of Medicine (United States of America), the Kenya Medical Research Institute ([KEMRI] Kisumu and Siaya, Kenya), Muhimbili University of Health and Allied Sciences (Dar es Salaam, Tanzania), University of Pittsburgh (United States of America), and Boston Children's Hospital (United States of America).

Patient and Public Involvement

Patients, caregivers and the public were not involved in the development of the study protocol. The protocol was developed to inform approaches to prevent childhood mortality in a region with disproportionately high rates of mortality among children aged <5 years (ie, 72 deaths/1,000 live births in Western Kenya).[34]

Primary and Secondary Objectives

The primary objective of this study is to externally validate previously developed risk assessment tools for PDM among (1) neonates and (2) infants and children in a cohort discharged from hospitals in Western Kenya.[11–18] Secondary objectives of this study are to (1) test the association between GABR and 60-day PDM among young children, (2) assess the potential additive role of GABR when incorporated into existing risk assessment tools for PDM, (3) externally validate a risk assessment tool to identify neonates at risk for unplanned hospital readmissions[35] and (4) explore the link between hospital diagnoses and postmortem-determined causes of death in cases that enrol in both the present study and an ongoing childhood mortality surveillance study (ie, Child Health and Mortality Prevention Surveillance [CHAMPS]).[36 37]

Study Setting

This study is being conducted in Western Kenya in Kisumu (Jaramogi Oginga Odinga Teaching and Referral Hospital [JOOTRH]) and Siaya (Siaya County Referral Hospital [SCRH]). Additional hospitals may be added in the same region if needed for the purposes of reaching requisite sample size. This region was selected because they are sites for an ongoing child mortality surveillance study (ie, CHAMPS)[36 37] and are sites with long-standing collaboration with the KEMRI. JOOTRH is a large referral hospital with a catchment area of approximately 1.2 million individuals. SCRH is located in the rural town of Siaya and has a geographic catchment area with 800 000 individuals. Both hospitals are operated by the Ministry of Health of the Republic of Kenya and have separate paediatric wards and newborn units.

Eligibility

As most childhood deaths in sub-Saharan Africa occur in young children aged <5 years,[2] the enrolled population will be restricted to neonates, infants and children aged 1–59 months. Participants will be included if their caregivers (ie, parents or other family members who are the primary caregivers) are willing/able to provide written consent, their caregivers allow for contact after hospital discharge through telephone calls 30 and 60 days after discharge (either through their own or a shared telephone) and are discharged alive from JOOTRH or SCRH with any discharge diagnosis (eg, not limited to infectious causes such as pneumonia or sepsis but also including cases of trauma or surgery). Participants aged <5 years will be excluded if they die during hospitalisation, they have non-consenting caregivers, are healthy newborns with no diagnoses during hospital admission following delivery, or they are unwilling/unable to provide a blood sample.

Sample Size

Based on review of hospital registries, there are approximately 80 neonates at JOOTRH and 50 neonates at SCRH discharged each month. Also based on a review of hospital registries, there are approximately 60 infants and children aged 1–59 months discharged from JOOTRH each month and approximately 40 infants and children aged 1–59 months discharged from SCRH per month. Although our prior work on post-discharge outcomes yielded consent rates of >90%,[16 17] here, we conservatively estimate 80% of participants who are approached will enrol because of the planned collection of blood samples (ie, we anticipate that ~20% of caregivers who are approached may refuse because of the blood draw). Based on prior work, an estimated lost-to-follow-up rate of <5% is anticipated.[16 17] Thus, this study aims to enrol and retain at least 56 infants and children and 56 neonates per month over 18 months. Based on prior studies assessing PDM in SSA over 60 days, an estimated 3–4% of enrolled cases will experience PDM. One thousand participants in each cohort (ie, 1000 neonates and 1000 infants and children) are necessary to be able to identify at least 30 in each cohort who experience PDM in order to externally validate existing risk assessment tools.

Standard of Care

All clinical care for hospitalised neonates and young children will be provided by hospital staff and not by study staff. Clinical care at these facilities is provided based on Kenyan national guidelines from the Ministry of Health and in accordance with hospital protocols. Study staff will not participate in the clinical care of participants or influence the decision to discharge a child in any way.

Recruitment, Screening and Enrolment Procedures

All families with an eligible child who is being discharged will be approached consecutively. To identify participants, research assistants will ask nurses in charge about planned discharges, will attend inpatient medical rounds at JOOTRH and SCRH, and will ask clinical care providers about potential discharges from the paediatric ward or newborn unit each day (i.e., during the day). As most discharges occur during the day, enrolment will occur during that time, noting that some children stay

in the hospital after discharge while awaiting transport home or settling of hospital bills. Caregivers of young children to be discharged will be approached by research assistants prior to discharge to discuss potential enrolment. Research assistants will review inclusion and exclusion criteria with clinicians and potential participants to determine eligibility.

Consenting caregivers will provide written consent after discussion with research assistants. Participation in this study is completely voluntary. Caregivers can deny permission to collect data without subsequent consequences. On the day of discharge, demographic, socioeconomic, clinical and anthropometric data will be collected by research assistants after review of medical records, discussion with healthcare providers and brief interviews with caregivers to obtain demographic information. All data will be captured by research staff using secured tablets or laptops using the data collection software REDCap (online supplemental file 2).[38] All demographic, clinical, and anthropometric data to be captured have been found to be associated with post-discharge mortality in prior studies conducted among children in sub-Saharan Africa and documented in a recent systematic review of risk assessment tools for PDM.[19]

Based on rates used in other studies at JOOTRH and SCRH, caregivers of enrolled participants in this study will receive Ksh 300–500 at the time of enrollment to compensate them for their time, which is their only compensation for initial enrollment in the study. Based on experience among the team in conducting similar studies in Western Kenya, this amount is large enough to encourage participation but not large enough to be coercive or to infringe on autonomy.

Research assistants will also notify phlebotomists of enrolled participants on the day of discharge. Phlebotomists at each site will collect whole blood (at least 2 mL for neonates and 4 mL for infants and children), which will be promptly aliquoted into serum and plasma separator tubes then frozen at −80°C in the KEMRI laboratory space at JOOTRH and SCRH. Samples will be labelled with the corresponding participant identification number. Once a week, samples will be taken from JOOTRH and SCRH in KEMRI vehicles and maintained on dry ice to maintain their temperature in transport to the Kisian laboratory, which is a CDC/KEMRI facility with ample freezer space for storage of all samples at −80°C. Regular checks will be performed to ensure the cold chain is retained throughout the study.

Follow-Up

Research staff will make telephone calls to caregivers of enrolled participants 30 (±7) and 60 (±7) days after hospital discharge, making the total duration for individual participants 60 days. During follow-up telephone calls, research assistants will inquire about the participants' vital status as well as about any intercurrent illnesses and healthcare seeking done since hospital discharge and fill out a secured case report form (online supplemental file 3). During these telephone calls, research staff will use mobile money to transfer airtime worth Ksh 150–200 for each call (total Ksh 300–400 for telephone call follow-ups). For participants who are not reachable through follow-up telephone calls, community health volunteers in these regions will visit homes of enrolled participants (in as much as the participant lives in a region with existing surveillance systems through the Kenyan Health and Demographic Surveillance System [HDSS]). Participants not located through repeated telephone calls and possible home visits will be classified as lost to follow-up.

Quality Assurance

Study staff underwent a rigorous, week-long protocol training prior to the initiation of enrolment and refresher trainings are planned for every 6 months of the study. The case report forms in REDCap have built-in quality checks that will help minimise the entry of data beyond expected ranges for quantitative data. Moreover, quality checks and quality assurance of all uploaded data will take place weekly and will be conducted by KEMRI investigators on all data uploaded to REDCap. Emory investigators, site investigators, and research assistants will hold weekly virtual or in-person meetings to review data and address any intercurrent issues that arise. Feedback on data quality and retraining on data quality will be conducted as needed.

Outcome Measures

The primary outcome of PDM is defined as all-cause mortality within 60 days of hospital discharge as reported by caregivers during follow-up telephone calls. Questions regarding cause of death and retrospective inquiry of events prior to death will also be asked. For cases of PDM that occur within the Kenya HDSS, we will attempt to link verbal autopsy data to ascertain cause of death and we will rely on caregiver report for deaths that occur among participants who live outside the HDSS region. The Kenya HDSS conducts the verbal autopsy in accordance with the WHO 2016 Verbal Autopsy.[19 39 40] Moreover, it is anticipated that some cases of PDM among participants will also enrol in the full CHAMPS procedures, which includes collection of clinical data, verbal autopsy, and extensive post-mortem testing followed by cause of death determination through expert panel review.[36 37] Thus, for such cases definitive causes of death, as determined by expert panel review of clinical, verbal autopsy, microbiologic and histopathologic data will be used.

Hospital readmissions and healthcare seeking following discharge (eg, antibiotic use and outpatient healthcare encounters) will also be captured as reported by caregivers during follow-up telephone calls.

Candidate Variables

All candidate variables that will be collected have been identified as significantly associated with, or protective against, PDM among children in sub-Saharan Africa.[11–18] Candidate variables were identified through a systematic review of risk assessment tools for PDM (table 1).[19] These variables include demographic characteristics, clinical parameters, and anthropometric measures. Although

Table 1 Variables to be collected in study to externally validate risk assessment tools to identify young children at risk for post-discharge mortality in Western Kenya

Demographic variables	Anthropometric variables	Clinical variables
► Age at discharge ► Sex ► Number of people living in the home ► Number of children aged<60 months in the home ► Number of rooms in the home used for sleeping ► Time to reach hospital from home ► Water source in the home ► Number of prior pregnancies	► Birth weight (for neonates enrolled) ► Mid-upper arm circumference ► Weight (for weight-for-age Z score determination)	► Duration of illness leading to hospital admission ► Oral intake prior to hospital admission ► Ability to tolerate oral intake before admission *Symptoms* ► Diarrhoea ► Cough *Vital Signs Before Discharge* ► Respiratory rate ► Temperature ► Pulse oximetry/receipt of supplemental oxygen ► Cyanosis ► Pallor *Clinical Signs* ► Lower chest indrawing during hospital admission ► Nasal flaring ► Auscultory crackles ► Abnormal hair (eg, sparse) ► Pedal oedema ► Lympadenopathy ► Ear discharge ► Altered consciousness ► Prostration ► Jaundice *Diagnoses* ► All hospital diagnoses ► HIV positive ► Oral candidiasis ► Cancer ► Sepsis ► Seizures ► Chronic medical conditions ► Meconium aspiration ► Congenital birth defects ► Haematological diseases *Laboratory Results* ► Haemoglobin (last measured) ► Bacteremia during hospital admission ► Malaria positive ► Discharge against medical advice ► Transferred to another facility ► Month of admission ► Prior hospital admission

some prior studies used clinical data collected at the time of hospital admission, data for this study will be collected near the time of hospital discharge as clinical parameters (e.g., oxygen saturation, etc.) change during hospital admission, and the current aim is to identify which risk assessment tool can best identify young children at risk of PDM using data available at the time of hospital discharge.

Statistical Analysis Plan

Standard test characteristics including sensitivity, specificity, and positive and negative likelihood ratios with accompanying 95% confidence intervals for each risk assessment tool for PDM will be calculated. Area under the receiver operating characteristic curves (AUROC) will be constructed to determine their discriminatory value. The AUROCs will be compared using the DeLong test, which evaluates differences in level of discriminatory value across models. Risk predictiveness curves will be used to show cumulative risk by predicted risk. Calibration graphs to illustrate the predicted probabilities against the observed prevalence of PDM will be used.[41]

A nested case-control study will be conducted within the prospective observational cohort of 2000 neonates, infants and young children to determine the discriminatory value of plasma GABR at discharge for PDM. Since the outcome of 60-day PDM will not be known at the

time participants enrol (ie, at hospital discharge), blood samples will be collected from all enrolled participants and will be processed immediately and then frozen. Once enrolment and follow-up are completed and cases (ie, neonates, infants and children who experienced PDM) are identified, the previously established ratio to match three controls for every case will be used,[42] and those samples will be processed to determine levels of GABR in those who died and those who did not. Controls and cases will be matched based on potential confounders to be identified on the review of cases of PDM at the completion of enrolment and follow-up. As up to a 4% rate of PDM (n=80) is anticipated, 240 matched controls will have amino acids processed to assess GABR. Mean and median GABR levels among cases that experience PDM and matched controls will be compared and conditional logistic regression will be used to test the association between GABR and PDM. GABR will also be included as an additional candidate variable in the existing risk assessment tools for PDM in this cohort of children who are enrolled in Western Kenya.

Prior studies assessing PDM have used verbal autopsies as the standard of determining cause of death,[13 15 43] which have low sensitivity compared with postmortem tissue examination, leading to imprecision in the determined causes of death.[44 45] Thus, this study will allow us to link hospital diagnoses to post-mortem determined causes of death among cases of PDM that concurrently enrol in the full CHAMPS procedures.

Ethics and Dissemination

This protocol has been granted clearance by the KEMRI Scientific Ethics Review Unit (KEMRI SERU), the JOOTRH Ethics Research Committee, and the Emory University institutional review board. Ethical approval for research activities at SCRH falls under KEMRI SERU approvals. The National Commission for Science, Technology, and Innovation in Kenya has provided a research permit but did not conduct an ethical and scientific review. Our results will be disseminated in the form of scientific presentations at national and international conferences and through peer-reviewed publications.

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Contributors All authors contributed to study conceptualisation, study design, sample size calculations and writing of the protocol for this study. KAI and CAR prepared the first draft of the manuscript. All authors contributed to critical revisions of the manuscript and have read and approved the final manuscript. CAR is the guarantor of the work.

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Competing interests No, there are no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained from parent(s)/guardian(s)

Ethics approval This study involves human participants and was approved by This protocol has been granted clearance by the KEMRI Scientific Ethics Review Unit (KEMRI SERU), the JOOTRH Ethics Research Committee, and the Emory University institutional review board. Ethical approval for research activities at SCRH falls under KEMRI SERU approvals. The National Commission for Science, Technology, and Innovation in Kenya has provided a research permit but did not conduct an ethical and scientific review. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement No data are available.

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