Prospective cohort study of referred Malawian children and their survival by hypoxaemia and hypoglycaemia status

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Objective To investigate survival in children referred from primary care in Malawi, with a focus on hypoglycaemia and hypoxaemia progression. Methods The study involved a prospective cohort of children aged 12 years or under referred from primary health-care facilities in Mchinji district, Malawi in 2019 and 2020. Peripheral blood oxygen saturation (SpO2) and blood glucose were measured at recruitment and on arrival at a subsequent health-care facility (i.e. four hospitals and 14 primary health-care facilities). Children were followed up 2 weeks after discharge or their last clinical visit. The primary study outcome was the case fatality ratio at 2 weeks. Associations between SpO2 and blood glucose levels and death were evaluated using Cox proportional hazards models and the treatment effect of hospitalization was assessed using propensity score matching. Findings Of 826 children recruited, 784 (94.9%) completed follow-up. At presentation, hypoxaemia was moderate (SpO2: 90–93%) in 13.1% (108/826) and severe (SpO2: < 90%) in 8.6% (71/826) and hypoglycaemia was moderate (blood glucose: 2.5–4.0 mmol/L) in 9.0% (74/826) and severe (blood glucose: < 2.5 mmol/L) in 2.3% (19/826). The case fatality ratio was 3.7% (29/784) overall but 26.3% (5/19) in severely hypoglycaemic children and 12.7% (9/71) in severely hypoxaemic children. Neither moderate hypoglycaemia nor moderate hypoxaemia was associated with mortality. Conclusion Presumptive pre-referral glucose treatment and better management of hypoglycaemia could reduce the high case fatality ratio observed in children with severe hypoglycaemia. The morbidity and mortality burden of severe hypoxaemia was high; ways of improving hypoxaemia identification and management are needed.

Introduction

Global initiatives to reduce child mortality have generally focused on improving early access to basic treatment for common illnesses using tools such as the World Health Organization’s (WHO) Integrated Management of Childhood Illness strategy and integrated community case management. In the absence of gold-standard diagnostic techniques for conditions such as pneumonia, these approaches rely primarily on subjective clinical assessment for syndromic case management. Children with signs of severe illness are referred to hospital for supportive care. However, emergency care is weak in under-resourced health systems, referrals can be difficult for caregivers, there may be delays due to a lack of transportation, and financial barriers are common. Children may, therefore, arrive at referral hospitals when their illness is at a late stage and treatment may be less effective. In Malawi, 33% (39/118) of deaths reported among children at a tertiary referral hospital in 2017 occurred in the first 24 hours after admission. Hypoxaemia and hypoglycaemia are objective measures associated with paediatric mortality. Indeed, Integrated Management of Childhood Illness protocols include hypoxaemia, defined as peripheral blood oxygen saturation (SpO2) below 90%, as a referral criterion and the threshold for initiating oxygen treatment. General danger signs (Box 1) are inadequate for identifying hypoxaemia and children may not receive the oxygen they need. An SpO2 level below 93% has been associated with deaths in children with clinical pneumonia in sub-Saharan Africa but evidence is lacking on the optimal referral threshold.

Similarly, Integrated Management of Childhood Illness protocols recognize the risk posed by hypoglycaemia to children and recommend presumptive pre-referral treatment for those with danger signs. Currently, WHO defines hypoglycaemia in a well-nourished child as a blood glucose concentration below 2.5 mmol/L though increased mortality has been reported in children admitted with higher concentrations. A recent trial in Malawi found that hypoglycaemia treatment in hospitalized children with a blood glucose concentration between 2.5 and 5.0 mmol/L was not associated with survival. More evidence is needed on how best to detect, monitor and treat hypoglycaemia in children.

Early detection of moderate hypoxaemia (SpO2 between 90 and 93%) and moderate hypoglycaemia (blood glucose concentration between 2.5 and 4.0 mmol/L) in primary care may help reduce child mortality. The aim of our study was to investigate the survival of children referred from primary health-care facilities in Malawi, with a focus on clinical progression in those who presented with moderate hypoglycaemia or moderate hypoxaemia.
Methods

In this preplanned secondary analysis of a prospective cohort study, we assessed the survival of children referred from primary health-care facilities to hospitals in Mchinji district, Malawi. Mchinji had a population of approximately 600,000 in 2015 to 2016 and a mortality rate in children younger than 5 years of 123 per 1000 live births. In particular, we followed children with severe or moderate hypoxaemia or hypoglycaemia (Box 1) from recruitment to presentation at another facility (Fig. 1). Children were recruited at all 14 functional, government, primary health-care facilities in Mchinji district that provided outpatient paediatric care: two dispensaries, 11 health centres and one rural hospital with no inpatient care. Three rural hospitals and a district hospital acted as referral facilities. The nearest tertiary referral hospital was in the neighbouring district of Lilongwe (no data were collected from this facility). To be eligible for inclusion in the study, referred children had to be aged between 0 months and 12 years and be resident in Mchinji district. Recruitment started on 1 July 2019 and was intended to last 12 months. However, enrolment was terminated early, on 6 April 2020, because of the coronavirus disease 2019 (COVID-19) pandemic. Follow-ups were completed on 13 June 2020.

Data collection

We employed 20 non-clinical data collectors resident in Mchinji district. They underwent one week’s residential training in study procedures and blood glucose and SpO2 measurement. At the end of the training, data collectors were individually assessed on their interpretation of different clinical scenarios to verify their understanding of good-quality SpO2 and blood glucose measurements. Clinical staff at all study facilities attended a 2-day refresher training course provided by the district health management team that covered Integrated Management of Childhood Illness protocols. Attendees’ knowledge before and after training was not formally assessed.

Study participants were recruited during standard operating hours (i.e. 08:00 to 15:00, Monday to Friday) from the primary health-care facilities; emergency cases seen outside these times may have been missed. Children were assessed routinely by facility staff who alerted data collectors when a child was referred to another facility (Fig. 1). After obtaining informed consent from caregivers, data collectors measured SpO2 with a Lifebox pulse oximeter (Lifebox Foundation, London, England) using the big toe (or finger in children older than 2 years). Then the blood glucose concentration was measured in a capillary sample using Accu-Chek Aviva (Roche, Basel, Switzerland). If severe hypoglycaemia or hypoxaemia was detected, the health-care provider was alerted. Other clinical data were extracted from the child’s health passport or the caregiver’s report and contact details, sociodemographic information and details of care-seeking and treatment were obtained using a brief questionnaire. Enrolment was kept brief and study staff were instructed not to interfere with caregiver decision-making. A unique study barcode sticker was placed inside each recruited child’s health passport.

Outpatients and inpatients at the four referral hospitals and the 14 primary health-care facilities were screened daily by data collectors to document the onward care of recruited children. Both SpO2 and blood glucose were measured again by study staff at these locations when a recruited child was identified (Fig. 1). Children were followed up by phone or household visit 2 weeks after hospital discharge or their last confirmed outpatient visit to confirm survival and obtain details of any additional formal or informal care-seeking.

Box 1. Terminology used in the prospective cohort study of survival in children with hypoxaemia and/or hypoglycaemia on referral, Malawi, 2019–2020

Study outcome

Death: Death of a child from any cause between study recruitment and 14 days after hospital discharge or their last documented clinical visit, as recorded during hospital admission or in a follow-up interview

Exposure

Hypoxaemia
• Normoxaemia: SpO2: 94–100%
• Moderate hypoxaemia: SpO2: 90–93%
• Severe hypoxaemia: SpO2: < 90% (values < 50% were considered invalid)

Hypoglycaemia
• Normoglycaemia: Blood glucose concentration > 4.0 mmol/L
• Moderate hypoglycaemia: Blood glucose concentration 2.5–4.0 mmol/L in well-nourished and moderately malnourished children and 3.0–4.0 mmol/L in severely malnourished children
• Severe hypoglycaemia: Blood glucose concentration < 2.5 mmol/L in well-nourished and moderately malnourished children and < 3.0 mmol/L in severely malnourished children

Other

Danger signs
• Child aged < 2 months: Any documentation in the child’s health passport or the caregiver’s report of the following signs: (i) inability to drink or feed; (ii) convulsions; (iii) movement only when stimulated or no movement at all; (iv) fast breathing (i.e. ≥ 60 breaths per minute); (v) severe chest indrawing, and (vi) axillary temperature < 35.5 °C or ≥ 37.5 °C
• Child aged 2 months to 12 years: Any documentation in the child’s health passport or the caregiver’s report of the following signs: (i) vomiting everything; (ii) inability to drink or feed; (iii) convulsions; (iv) sleepy or lethargic; and (v) unconscious

Severely underweight: Weight-for-age z-score ≤ 3.0 or a recorded clinician diagnosis of severe malnutrition

Hospital admission: Admission to the district hospital or one of the three rural hospitals in Mchinji district within 2 weeks of study recruitment, as documented by a study data collector at the hospital

| SpO2: peripheral blood oxygen saturation. |
| Definitions of moderate hypoxaemia and hypoglycaemia were chosen for this study and are not standard definitions. |
| We did not extract information on movement as a danger sign and severe chest indrawing was not disaggregated from chest indrawing. |
| As 5–12 year olds are not included in Integrated Management of Childhood Illness protocols, we used the same danger signs as 2–59-month-olds. |
A new illness episode was registered if a child presented after the 2-week follow-up period had been completed and, therefore, it was possible for an individual child to be recruited more than once. Verbal autopsies were conducted for children who died using WHO’s 2016 verbal autopsy instrument. However, because of COVID-19, verbal autopsies were completed for only eight of the 29 children who died.

Data were entered and uploaded daily onto tablet computers using CommCare software (Dimagi Inc., Cambridge, United States of America) and the full list of currently recruited children was visible to all data collectors. Data collectors were supervised by the project manager (a clinical officer), the data manager, and study monitoring and evaluation staff. Problems with implementation were dealt with during frequent supervision visits and monthly group meetings. Ethical approval was obtained from the Research and Ethics Committee at the University of Malawi’s College of Medicine (P.11/18/2538). Caregivers provided informed verbal consent at recruitment and each subsequent interaction.

**Statistical analysis**

We recorded hypoxaemia and hypoglycaemia severity at recruitment and compared changes between recruitment and subsequent clinical visits using paired t-tests for means and Wilcoxon signed-rank tests for medians. The primary study outcome was the case fatality ratio and the primary exposures of interest were the SpO₂ level and the blood glucose concentration at recruitment (Box 1). The case fatality ratio was calculated as the number of deaths occurring between recruitment (day 0) and 14 days after hospital discharge or the last confirmed clinical visit divided by the number of children who completed follow-up. Associations with the case fatality ratio were estimated using multivariable Cox proportional hazards models, adjusted for recruitment facility clusters. The survival time was censored at death or 2 weeks after hospital discharge or the last confirmed clinical visit. For children who died on the day of recruitment, the survival time was taken to be 0.5 days. Missing SpO₂ values at recruitment were included as a distinct category because of previous evidence of an association with mortality. We adopted the same approach for missing glucose values. Models were adjusted for the presence of general danger signs (Box 1), severe underweight, age, sex and hospital admission.

We were unable to adjust for oxygen or dextrose treatment using multivariable adjustment, interaction terms, stratification or propensity score matching because of confounding by indication (i.e. the most severely ill children were more likely to receive oxygen but were less likely to survive). However, we conducted exploratory analyses using hospital admission as a proxy for treatment: we performed a stratified analysis by hospital admission and estimated the treatment effect of admission using propensity score matching. All analyses were performed using Stata v. 14 (StataCorp LLC, College Station, USA).

**Results**

In total, 834 episodes of child illness were screened and 826 children were recruited, of whom 784 (94.9%) completed follow-up (Fig. 2 and Table 1; available from: https://www.who.int/publications/publications/journals/bulletin/). Most...
follow-ups involved household visits (71.9%; 564/784) and caregivers were contacted on average 1.7 times (range: 1–12). The median follow-up time was 14 days (range: 0–77). The children’s median age was 36 months (interquartile range, IQR: 16–73) and more boys were recruited than girls: 52.9% (437/826) versus 47.1% (389/826), respectively.

We recorded 29 deaths within 2 weeks of hospital discharge or the last confirmed clinical visit, which gave a case fatality ratio of 3.7% (29/784). We recruited 13 children more than once, of whom two died (15.4%). The case fatality ratio was highest in infants younger than 2 months (15.8%; 6/38) and lowest in children aged 5 to 12 years (2.3%; 6/258; P-value: < 0.001). No significant difference in case fatality ratio was observed by sex (P-value: 0.850). The median time from recruitment to death was 1 day (IQR: 0–4) and 44.8% (13/29) of deaths occurred within 24 hours. Seven of the 13 children who died on the day of recruitment were not admitted (available in data repository). Following recruitment, 37.1% (306/826) of children were admitted to hospital and 41.7% (344/826) attended another facility.

### Hypoxaemia

Overall, 8.6% (71/826) of children were severely hypoxaemic at recruitment and 13.1% (108/826) were moderately hypoxaemic (Table 1). Severe hypoxaemia was significantly more frequent in children younger than 2 months (28.9%; 11/38) than in those aged 5 to 12 years (4.1%; 11/270; P-value: < 0.001). The case fatality ratio among children who completed follow-up was 13.9% (9/65) in those with severe hypoxaemia, 3.9% (4/104) in those with moderate hypoxaemia and 2.3% (14/605) in those with normoxaemia. Among all severely hypoxaemic children (Table 2), the most frequent diagnoses were acute respiratory infection (45.1%; 32/71) and malaria (39.4%; 28/71). Only 24.0% (17/71) of hypoxaemic children had a documented respiratory rate but chest indrawing was common: 42.3% (30/71) of severely hypoxaemic children and 33.3% (36/108) of moderately hypoxaemic children had this clinical sign.

After recruitment, 63.4% (45/71) of severely hypoxaemic children, 50.9% (55/108) of moderately hypoxaemic children and 37.5% (239/637) of normoxaemic children attended another facility (Table 3; available from: https://www.who.int/publications/journals/bulletin/). The median SpO2 increased after recruitment in both those with severe hypoxaemia (from 84% to 92%; P-value: < 0.001) and moderate hypoxaemia (from 92% to 95%; P-value: 0.006).

Of the 292 children who were admitted to hospital and completed follow-up, 34 (11.6%) were severely hypoxaemic on arrival (Fig. 3); 28 of the 34 (82.4%) received oxygen. Of the 49 children with moderate hypoxaemia who were admitted, 12 (24.5%) had progressed to severe hypoxaemia and one of the 12 died (case fatality ratio: 8.3%) – this child did not receive oxygen. Of the 42 children with severe hypoxaemia at recruitment who were admitted, 15 (35.7%) remained severely hypoxaemic on arrival at hospital and five of the 15 died (case fatality ratio: 33.3%). The case fatality ratio for children with an SpO2 below 90% at hospital admission was 20.6% (7/34), which was similar to the ratio for severely hypoxaemic children who were not admitted (17.4%; 4/23).

### Hypoglycaemia

Overall, 2.3% (19/826) of children were severely hypoglycaemic at recruitment and 9.0% (74/826) were moderately hypoglycaemic (Table 1). The case fatality ratio among children who completed follow-up was 27.8% (5/18) in those with severe hypoglycaemia, 5.6% (4/71) in those with moderate hypoglycaemia and 2.9% (20/687) in those with normoglycaemia. Of the 19 severely hypoglycaemic children overall (Table 4), 15 (79.0%) presented with a danger sign and the most frequent diagnoses were malaria (52.6%; 10/19), malnutrition (31.6%; 6/19) and sepsis or meningitis (21.1%; 4/19). Severe hypoglycaemia was more frequent in girls than boys: 3.1% (12/389) versus 1.6% (7/437), respectively (P-value: 0.160). Presentation at another facility after recruitment (Table 5; available from: https://www.who.int/publications/journals/bulletin/) was more frequent for children with severe hypoglycaemia (37.9%; 11/19) than for those with moderate hypoglycaemia (40.5%; 30/74) or normoglycaemia (41.2%; 299/725). Although there was no difference in the mean blood glucose concentration between recruitment and arrival at another facility overall, the mean was significantly higher on subsequent measurement for both severely and moderately hypoglycaemic children (Table 5). No severely or moderately hypoglycaemic child was given pre-referral glucose treatment at recruitment.

Of the 292 children admitted to hospital, six (2.1%) had severe hypoglycaemia at admission; four of the six (66.7%) received dextrose treatment (Fig. 4). Of the 26 children with moderate hypoglycaemia at admission who were subsequently admitted, two (7.7%) had severe hypoglycaemia at admission and 13 (50.0%) had a normal glucose level. The case fatality ratio was similar among children who had moderate or severe hypoglycaemia at admission: 17.7% (3/17) versus 16.7% (1/6), respectively. However, the ratio was 42.9% (3/7) among severely hypoglycaemic children who were not admitted.

### Survival and treatment effects

The results of the adjusted Cox proportional hazards model for survival are presented in Table 6. Both severe hypoxaemia (adjusted hazard ratio, aHR, compared with normoxaemia: 4.05; 95% confidence interval, CI: 1.65 to 9.49) and severe hypoglycaemia (aHR compared with normoglycaemia: 7.60; 95% CI: 2.07 to 27.92) at recruitment were independently associated with death. There was no significant association with either moderate hypoxaemia or moderate hypoglycaemia.

In the analysis in which children were stratified by hospital admission, admission appeared to decrease the hazard of death for both those with severe hypoxaemia and those with severe hypoglycaemia. Among children with severe hypoxaemia, the aHR for death compared with normoxaemia was 9.14 in those who were not admitted versus 2.34 in those who were. Among children with severe hypoglycaemia, the aHR for death compared with normoglycaemia was 15.74 in those who were not admitted versus 4.12 in those who were. However, the CIs for these hazard ratios were wide (available in the data repository). Overall, the treatment effect of hospital admission was estimated to be a 1.39% (95% CI: −6.81 to 4.02) reduction in the case fatality ratio among those admitted (data repository). The estimated effect was larger for children with moderate or severe hypoxaemia but was not significant.
Table 2. Children’s characteristics at recruitment, by blood oxygen level, prospective cohort study of survival in children with hypoxaemia and/or hypoglycaemia on referral, Malawi, 2019–2020

| Variable | No. (%) of children | Normoxaemic<sup>a</sup> (n = 637) | Moderately hypoxaemic<sup>b</sup> (n = 108) | Severely hypoxaemic<sup>c</sup> (n = 71) | Missing data (n = 10) |
|----------|---------------------|------------------------------------|---------------------------------------------|--------------------------------------|----------------------|
| **Demographic characteristic** | | | | | |
| Age | | | | | |
| <2 months | 18 (2.8) | 7 (6.5) | 11 (15.5) | 2 (20.0) |
| 2–11 months | 60 (9.4) | 22 (20.4) | 20 (28.2) | 3 (30.0) |
| 12–59 months | 310 (48.7) | 69 (63.9) | 29 (40.9) | 5 (50.0) |
| 5–12 years | 249 (39.1) | 10 (9.3) | 11 (15.5) | 0 (0.0) |
| Sex | | | | | |
| Male | 339 (53.2) | 57 (52.8) | 37 (52.1) | 4 (40.0) |
| Female | 298 (46.8) | 51 (47.2) | 34 (47.9) | 6 (60.0) |
| **Clinical characteristic** | | | | | |
| Fast breathing<sup>b</sup> | | | | | |
| Not present | 76 (11.9) | 18 (16.7) | 6 (8.5) | 2 (20.0) |
| Present | 51 (8.0) | 8 (7.4) | 11 (15.5) | 0 (0.0) |
| Missing data | 510 (80.1) | 82 (75.9) | 54 (76.1) | 8 (80.0) |
| Temperature, °C | | | | | |
| < 35.5 | 27 (4.2) | 1 (0.9) | 2 (2.8) | 1 (10.0) |
| 35.5–37.4 | 317 (49.8) | 45 (41.7) | 27 (38.0) | 5 (50.0) |
| ≥ 37.5 | 202 (31.7) | 55 (50.9) | 35 (49.3) | 4 (40.0) |
| Missing data | 91 (14.3) | 7 (6.5) | 7 (9.9) | 0 (0.0) |
| Malaria status | | | | | |
| mRDT-positive | 205 (32.2) | 37 (34.3) | 28 (39.4) | 2 (20.0) |
| mRDT-negative | 60 (9.4) | 17 (15.7) | 14 (19.7) | 2 (20.0) |
| No mRDT result | 372 (58.4) | 54 (50.0) | 29 (40.9) | 6 (60.0) |
| Chest indrawing<sup>c</sup> | | | | | |
| Not present | 576 (90.4) | 72 (66.7) | 40 (56.3) | 8 (80.0) |
| Present | 60 (9.4) | 36 (33.3) | 30 (42.3) | 2 (20.0) |
| Missing data | 1 (0.2) | 0 (0.0) | 1 (1.4) | 0 (0.0) |
| Danger signs<sup>d</sup> | | | | | |
| Not present | 325 (51.0) | 22 (20.4) | 11 (15.5) | 4 (40.0) |
| Present | 312 (49.0) | 86 (79.6) | 60 (84.5) | 6 (60.0) |
| Severely underweight | | | | | |
| No | 546 (85.7) | 88 (81.5) | 60 (84.5) | 8 (80.0) |
| Yes | 91 (14.3) | 20 (18.5) | 11 (15.5) | 2 (20.0) |
| **Routine diagnosis<sup>e,f</sup>** | | | | | |
| Acute respiratory infection or pneumonia | 45 (7.1) | 31 (28.7) | 32 (45.1) | 3 (30.0) |
| Malaria | 229 (36.0) | 53 (49.1) | 28 (39.4) | 3 (30.0) |
| Sepsis or meningitis | 63 (9.9) | 17 (15.7) | 12 (16.9) | 0 (0.0) |
| Diarrhoea | 14 (2.2) | 3 (2.8) | 1 (1.4) | 0 (0.0) |
| Fever (unclassified) | 22 (3.5) | 11 (10.2) | 6 (8.5) | 0 (0.0) |
| Skin condition | 33 (5.2) | 5 (4.6) | 0 (0.0) | 1 (10.0) |
| Malnutrition | 28 (4.4) | 6 (5.6) | 2 (2.8) | 0 (0.0) |
| Anaemia | 40 (6.3) | 8 (7.4) | 7 (9.9) | 0 (0.0) |
| Trauma | 190 (29.8) | 6 (5.6) | 4 (5.6) | 1 (10.0) |
| Other infectious condition | 12 (1.9) | 1 (0.9) | 0 (0.0) | 0 (0.0) |
| Other non-infectious condition | 89 (14.0) | 6 (5.6) | 12 (16.9) | 2 (20.0) |

<sup>a</sup> Definitions of normoxaemia and hypoxaemia are given in Box 1.

<sup>b</sup> Fast breathing was a rate ≥ 60 breaths/min in children aged < 2 months, ≥ 50 breaths/min in those aged 2–11 months, ≥ 40 breaths/min in those aged 12–59 months (World Health Organization Integrated Management of Childhood Illness 2014 guidelines) and ≥ 30 breaths/min in those aged 5–12 years (World Health Organization Integrated Management of Adolescent and Adult Illness 2012 guidelines).

<sup>c</sup> Severe chest indrawing in children aged < 2 months.

<sup>d</sup> Danger signs are described in Box 1.

<sup>e</sup> Diagnosis made by the health-care provider at recruitment.

<sup>f</sup> Children could receive more than one diagnosis.
Fig. 3. Case fatality ratio and oxygen treatment, by blood oxygen level at recruitment and hospital admission, prospective cohort study of survival in children with hypoxaemia and/or hypoglycaemia on referral, Malawi, 2019–2020

Classification at recruitment at primary health-care facility

292 children admitted to hospital

34 (11.6%) children with severe hypoxaemia at admission
Case fatality ratio: 20.8% (7 deaths)

15 children with severe hypoxaemia
12 (80.0%) children received oxygen
Case fatality ratio: 33.3% (5 deaths)

12 children with moderate hypoxaemia
11 (91.7%) children received oxygen
Case fatality ratio: 8.3% (1 death)

6 children with normoxaemia
4 (66.7%) children received oxygen
Case fatality ratio: 0.0% (0 deaths)

1 child with missing data
1 (100.0%) child received oxygen
Case fatality ratio: 100.0% (1 death)

28 (9.6%) children with moderate hypoxaemia at admission
Case fatality ratio: 7.1% (2 deaths)

10 children with severe hypoxaemia
1 (10.0%) child received oxygen
Case fatality ratio: 100.0% (1 death)

7 children with moderate hypoxaemia
2 (28.6%) children received oxygen
Case fatality ratio: 0.0% (0 deaths)

11 children with normoxaemia
1 (9.1%) child received oxygen
Case fatality ratio: 9.1% (1 death)

0 children with missing data

220 (75.3%) children with normoxaemia at admission
Case fatality ratio: 2.7% (6 deaths)

16 children with severe hypoxaemia
3 (18.8%) children received oxygen
Case fatality ratio: 0.0% (0 deaths)

7 children with moderate hypoxaemia
2 (28.6%) children received oxygen
Case fatality ratio: 14.3% (1 death)

11 children with normoxaemia
1 (9.1%) child received oxygen
Case fatality ratio: 9.1% (1 death)

3 children with missing data

10 (3.4%) children with missing data at admission
Case fatality ratio: 20.0% (2 deaths)

1 child with severe hypoxaemia

1 child with moderate hypoxaemia

1 child with normoxaemia

0 children with missing data

492 children not admitted to hospital

23 (4.7%) children with severe hypoxaemia
Case fatality ratio: 17.4% (4 deaths)

55 (11.2%) children with moderate hypoxaemia
Case fatality ratio: 3.6% (2 deaths)

408 (82.9%) children with normoxaemia
Case fatality ratio: 1.2% (5 deaths)

6 (1.2%) children with missing data
Case fatality ratio: 16.7% (1 death)

Note: Definitions of hypoxaemia and normoxaemia are given in Box 1.
Table 4. Children’s characteristics at recruitment, by blood glucose concentration, prospective cohort study of survival in children with hypoxaemia and/or hypoglycaemia on referral, Malawi, 2019–2020

| Variable | No. (%) of children |
|----------|---------------------|
|         | Normoglycaemic*     | Moderately hypoglycaemic* | Severely hypoglycaemic* | Missing data |
|         | (n = 725)           | (n = 74)                   | (n = 19)                  | (n = 8)      |
| Demographic characteristic | | | | |
| Age | | | | |
| <2 months | 32 (4.4) | 4 (5.4) | 1 (5.3) | 1 (12.5) |
| 2–11 months | 96 (13.2) | 4 (5.4) | 3 (15.8) | 2 (25.0) |
| 12–59 months | 358 (49.4) | 38 (51.4) | 13 (68.4) | 4 (50.0) |
| 5–12 years | 239 (33.0) | 28 (37.8) | 2 (10.5) | 1 (12.5) |
| Sex | | | | |
| Male | 387 (53.4) | 36 (48.7) | 7 (36.8) | 7 (87.5) |
| Female | 338 (46.6) | 38 (51.4) | 12 (63.2) | 1 (12.5) |
| Clinical characteristic | | | | |
| Fast breathingb | | | | |
| Not present | 93 (12.8) | 5 (6.8) | 4 (21.1) | 0 (0.0) |
| Present | 57 (7.9) | 11 (14.9) | 2 (10.5) | 0 (0.0) |
| Missing data | 575 (79.3) | 58 (78.4) | 13 (68.4) | 8 (100.0) |
| Temperature, °C | | | | |
| < 35.5 | 26 (3.6) | 2 (2.7) | 2 (10.5) | 1 (12.5) |
| 35.5–37.4 | 340 (46.9) | 40 (54.1) | 11 (57.9) | 3 (37.5) |
| ≥ 37.5 | 266 (36.7) | 23 (31.1) | 5 (26.3) | 2 (25.0) |
| Missing data | 93 (12.8) | 9 (12.2) | 1 (5.3) | 2 (25.0) |
| Malaria status | | | | |
| mRDT-positive | 244 (33.7) | 21 (28.4) | 5 (26.3) | 2 (25.0) |
| mRDT-negative | 79 (10.9) | 9 (12.2) | 4 (21.1) | 1 (12.5) |
| No mRDT result | 402 (55.5) | 44 (59.5) | 10 (52.6) | 5 (62.5) |
| Chest indrawingc | | | | |
| Not present | 613 (84.6) | 61 (82.4) | 15 (79.0) | 7 (87.5) |
| Present | 112 (15.5) | 12 (16.2) | 3 (15.8) | 1 (12.5) |
| Missing data | 0 (0.0) | 1 (1.4) | 1 (5.3) | 0 (0.0) |
| Danger signsd | | | | |
| Not present | 323 (44.5) | 32 (43.2) | 4 (21.0) | 3 (37.5) |
| Present | 402 (55.5) | 42 (56.8) | 15 (79.0) | 5 (62.5) |
| Severely underweight | | | | |
| No | 636 (87.7) | 51 (68.9) | 9 (47.4) | 6 (75.0) |
| Yes | 89 (12.3) | 23 (31.1) | 10 (52.6) | 2 (25.0) |
| Routine diagnosise,f | | | | |
| Acute respiratory infection or pneumonia | 100 (13.8) | 6 (8.1) | 3 (15.8) | 2 (25.0) |
| Malaria | 274 (37.8) | 27 (36.5) | 10 (52.6) | 2 (25.0) |
| Sepsis or meningitis | 74 (10.2) | 13 (17.6) | 4 (21.1) | 1 (12.5) |
| Diarrhoea | 15 (2.1) | 1 (1.4) | 1 (5.3) | 1 (12.5) |
| Fever (unclassified) | 32 (4.4) | 6 (8.1) | 0 (0.0) | 1 (12.5) |
| Skin condition | 38 (5.2) | 1 (1.4) | 0 (0.0) | 0 (0.0) |
| Malnutrition | 21 (2.9) | 9 (12.2) | 6 (31.6) | 0 (0.0) |
| Anaemia | 44 (6.1) | 8 (10.8) | 2 (10.5) | 1 (12.5) |
| Trauma | 189 (26.1) | 11 (14.9) | 0 (0.0) | 1 (12.5) |
| Other infectious condition | 11 (1.5) | 2 (2.7) | 0 (0.0) | 0 (0.0) |
| Other non-infectious condition | 91 (12.6) | 13 (17.6) | 3 (15.8) | 2 (25.0) |

mRDT: malaria rapid diagnostic test.

* Definitions of normoglycaemia and hypoglycaemia are given in Box 1.

b Fast breathing was a rate ≥ 60 breaths/min in children aged < 2 months, ≥ 50 breaths/min in those aged 2–11 months, ≥ 40 breaths/min in those aged 12–59 months (World Health Organization Integrated Management of Childhood Illness 2014 guidelines)1 and ≥ 30 breaths/min in those aged 5–12 years (World Health Organization Integrated Management of Adolescent and Adult Illness 2012 guidelines).25

c Severe chest indrawing in children aged < 2 months.

d Danger signs are described in Box 1.

e Diagnosis made by the health-care provider at recruitment.

f Children could receive more than one diagnosis.
Discussion

We found that severe hypoxaemia and severe hypoglycaemia were significantly associated with death among children referred from primary health-care facilities to hospitals in Malawi. Although neither moderate hypoxaemia nor moderate hypoglycaemia was significantly associated with increased mortality, our exploratory analyses suggested that hospital admission may decrease the risk. Only 37% (292/784) of children in the study were admitted to hospital and, overall, more than 95% of those with moderate hypoxaemia or hypoglycaemia who were not admitted survived, irrespective of the presence of danger signs. However, over a quarter of referred children with severe hypoglycaemia died and these deaths predominantly occurred within 24 hours, which suggests that the severity of the disease may have been recognized late and care-seeking may have been delayed, as has been observed in previous studies in Malawi.28

The Integrated Management of Childhood Illness protocol recommends presumptive hypoglycaemia treatment before referral.1 In 2019, the majority of facilities in Mchinji had a glucometer and a stock of dextrose.27 Although it would be unreasonable to expect that blood glucose measurements would be carried out routinely at our study facilities as they are not included in the protocol, the fact that no hypoglycaemic child reportedly received presumptive glucose treatment points to a gap in the protocol’s implementation. Nevertheless, we observed an increase in the mean glucose concentration after recruitment in both moderately and severely hypoglycaemic children, which suggests that health-care providers may have given caregivers advice on feeding. Alternatively, many of the most acutely hypoglycaemic children may have died before hospital admission. Our findings support the use of presumptive glucose treatment. However, greater efforts must be made to ensure this happens, along with subsequent glucose monitoring and management.39

In the Integrated Management of Childhood Illness algorithm for respiratory infections, an SpO\textsubscript{2} below 90% is an indication for referral.1 In agreement with previous reports,28 we found that hypoxaemia was relatively common, even in the absence of pneumonia. Although functional oximeters were reportedly available in 29.8% (14/47) of sampled facilities in Malawi,36 health-care workers often made referral decisions without using pulse oximetry. We found that 28.9% of infants younger than 2 months were severely hypoxaemic, similar to the 22.6% (53/235) reported in a previous study from Malawi.3 The quality of oximetry measurements in these infants can be poor due to badly fitting probes, non-cooperation or perfusion issues. However, reported diagnoses were consistent with conditions where hypoxaemia was expected (e.g. congenital heart disease, asphyxia, apnoea, pneumonia and sepsis). Given the role of pulse oximetry in detecting congenital heart disease in neonates,32 which is often asymptomatic, neonatal SpO\textsubscript{2} measurements must be feasible and reliable. More broadly, we observed that respiratory rates were rarely documented, which corresponds with previous findings that respiratory examinations are often poorly conducted in Malawi.33–35 There is, therefore, a need to improve pneumonia diagnosis and management.

We found that both moderate hypoxaemia and moderate hypoglycaemia at recruitment were associated with a non-significant increase in the hazard of death among children, which contradicts previous hospital-based studies.7,8,14,15 Moreover, our exploratory analysis, though it lacked statistical power, suggested that hospitalization may have reduced mortality in these patient groups. Strikingly, 11 of the 12 children with moderate hypoxaemia who progressed to severe hypoxaemia by hospital admission survived – the child who died did not receive oxygen. In contrast, a third of children admitted with persistently severe hypoxaemia died, even though most received oxygen. These findings suggest that earlier identification and prompt care-seeking could reduce mortality.57 However, given confounding by indication (i.e. the most severely ill children are more likely to receive oxygen but also to die) and potential survivorship bias (i.e. children have to survive long enough to reach hospital), well-designed trials are needed to provide evidence for guideline reviews.

The influence of dextrose treatment on survival was less clear. Although moderate hypoglycaemia at recruitment was not a significant risk factor for death, the case fatality ratio in children with moderate hypoglycaemia at hospital admission was 17.7%, higher than for any other admission hypoglycaemia category. The recent SugarFACT trial in Malawi failed to show that treatment improved survival in children with hypoglycaemia,18 which reinforces the need for better understanding of the management of these patients. Our observation that blood glucose and SpO\textsubscript{2} categories changed between recruitment and hospitalization in most children raises the important question of whether serial measurements are preferable to one-off spot checks for case management and for identifying the need for urgent care and outpatient monitoring.28

Although few infants younger than 2 months were recruited, they had the highest case fatality ratio of all age groups. We were surprised to find that 32.7% (270/826) of children recruited were aged 5 to 12 years and that their case fatality ratio was comparable to that of children aged 12 to 59 months: 2.3% (6/258) versus 3.1% (12/390), respectively. This older age group is overlooked, being neither explicitly included in an Integrated Management of Childhood Illness chart booklet nor targeted by sustainable development goals.17 Moreover, measurement of SpO\textsubscript{2} and blood glucose levels do not appear to be informative for this age group and more research is warranted.

Our study had three key limitations. First, because of the COVID-19 pandemic, we stopped recruitment before the planned closure date and verbal autopsies were not completed for all deaths. During follow-ups and verbal autopsies, we asked about care-seeking to validate data collection at facilities. Given that the response rate varied by survival status, we chose not to use these data and it is possible, therefore, that we were not able to confirm all instances of onward care. To minimize the possibility that children admitted out of hours were missed, hospital-based data collectors reviewed patient charts each morning. Nevertheless, children who presented to primary-care facilities out of hours would have been missed, resulting in lower recruitment and the under-ascertainment of onward care. Second, we used non-clinical data collectors and it is plausible that some of the variation in hypoxaemia category between recruitment and subsequent care resulted from
**Fig. 4.** Case fatality ratio and dextrose treatment, by blood glucose concentration at recruitment and hospital admission, prospective cohort study of survival in children with hypoxaemia and/or hypoglycaemia on referral, Malawi, 2019–2020

| Classification at recruitment at primary health-care facility | Number of children | Case fatality ratio | Dextrose treatment |
|-------------------------------------------------------------|--------------------|---------------------|--------------------|
| Severe hypoglycaemia                                       | 6 (2.1%)           | 16.7% (1 death)     | 2 (100.0%) children received dextrose |
| Moderate hypoglycaemia                                     | 17 (5.8%)          | 17.7% (3 deaths)    | 0 children with severe hypoglycaemia |
| Normoglycaemia                                              | 292 children admitted to hospital |
| Missing data                                                | 2 children with severe hypoglycaemia |
|                                                           | 2 children with moderate hypoglycaemia |
|                                                           | 0 children with normoglycaemia |
|                                                           | 0 children with missing data |
|                                                           | 1 (12.5%) children received dextrose |
|                                                           | 9 children with moderate hypoglycaemia |
|                                                           | 0 children with normoglycaemia |
|                                                           | 0 children with missing data |
|                                                           | Case fatality ratio: 11.1% (1 death) |
|                                                           | Case fatality ratio: 25.0% (2 deaths) |
|                                                           | Case fatality ratio: 0.0% (0 deaths) |
|                                                           | Case fatality ratio: 11.1% (1 death) |
|                                                           | Case fatality ratio: 25.0% (2 deaths) |
|                                                           | Case fatality ratio: 0.0% (0 deaths) |
|                                                           | Case fatality ratio: 11.1% (1 death) |
|                                                           | Case fatality ratio: 25.0% (2 deaths) |
|                                                           | Case fatality ratio: 0.0% (0 deaths) |
|                                                           | Case fatality ratio: 11.1% (1 death) |
|                                                           | Case fatality ratio: 25.0% (2 deaths) |
|                                                           | Case fatality ratio: 0.0% (0 deaths) |
|                                                           | Case fatality ratio: 11.1% (1 death) |
|                                                           | Case fatality ratio: 25.0% (2 deaths) |
|                                                           | Case fatality ratio: 0.0% (0 deaths) |
|                                                           | Case fatality ratio: 11.1% (1 death) |
|                                                           | Case fatality ratio: 25.0% (2 deaths) |
|                                                           | Case fatality ratio: 0.0% (0 deaths) |
|                                                           | Case fatality ratio: 11.1% (1 death) |
|                                                           | Case fatality ratio: 25.0% (2 deaths) |
|                                                           | Case fatality ratio: 0.0% (0 deaths) |
|                                                           | Case fatality ratio: 11.1% (1 death) |
|                                                           | Case fatality ratio: 25.0% (2 deaths) |
|                                                           | Case fatality ratio: 0.0% (0 deaths) |
|                                                           | Case fatality ratio: 11.1% (1 death) |
|                                                           | Case fatality ratio: 25.0% (2 deaths) |
|                                                           | Case fatality ratio: 0.0% (0 deaths) |
|                                                           | Case fatality ratio: 11.1% (1 death) |
|                                                           | Case fatality ratio: 25.0% (2 deaths) |
|                                                           | Case fatality ratio: 0.0% (0 deaths) |
|                                                           | Case fatality ratio: 11.1% (1 death) |
|                                                           | Case fatality ratio: 25.0% (2 deaths) |
|                                                           | Case fatality ratio: 0.0% (0 deaths) |
|                                                           | Case fatality ratio: 11.1% (1 death) |
|                                                           | Case fatality ratio: 25.0% (2 deaths) |
|                                                           | Case fatality ratio: 0.0% (0 deaths) |
|                                                           | Case fatality ratio: 11.1% (1 death) |
|                                                           | Case fatality ratio: 25.0% (2 deaths) |
|                                                           | Case fatality ratio: 0.0% (0 deaths) |
|                                                           | Case fatality ratio: 11.1% (1 death) |
|                                                           | Case fatality ratio: 25.0% (2 deaths) |
|                                                           | Case fatality ratio: 0.0% (0 deaths) |
|                                                           | Case fatality ratio: 11.1% (1 death) |
|                                                           | Case fatality ratio: 25.0% (2 deaths) |
|                                                           | Case fatality ratio: 0.0% (0 deaths) |

| Children not admitted to hospital                          | Number of children | Case fatality ratio | Dextrose treatment |
|-------------------------------------------------------------|--------------------|---------------------|--------------------|
| Severe hypoglycaemia                                       | 7 (1.4%)           | 16.7% (3 deaths)    | 0 children with severe hypoglycaemia |
| Moderate hypoglycaemia                                     | 45 (9.1%)          | 4.4% (2 deaths)     | 45 (88.4%) children with normoglycaemia |
| Normoglycaemia                                              | 435 (88.4%)        | 1.6% (7 deaths)     | 5 (1.0%) children with missing data |
| Missing data                                                | 5 (1.0%)           | 0.0% (0 deaths)     | Case fatality ratio: 0.0% (0 deaths) |

Note: Definitions of hypoglycaemia and normoglycaemia are given in Box 1.
measurement quality issues as oximetry in young infants requires skill. Finally, we relied on routine clinical assessment and decision-making by health-care workers for deciding on study eligibility and it is possible that some hypoxaemic children who should have been referred were missed. We were unable to validate key clinical variables and problems with routine data quality were apparent (e.g. the absence of respiratory rate data) despite Integrated Management of Childhood Illness refresher training.

Mortality among children with severe hypoxaemia or hypoglycaemia who were referred from primary care in Malawi was high. For hypoglycaemia, our findings support current recommendations for presumptive glucose treatment but further research is needed to determine the optimal threshold for treatment and the best management for this group. For hypoxaemia, timely care-seeking, routine pulse oximetry, and earlier identification and referral of severely hypoxaemic children could reduce the risk of death. However, given that most referred children in our study were not subsequently admitted to hospital but survived, greater understanding of how best to manage moderately hypoxaemic children is needed. Optimal management must take into account the burden placed by referral on the health system and on patients as well as the clinical benefits of treatment.

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Table 6. Factors associated with death, adjusted Cox proportional hazards model, prospective cohort study of survival in children with hypoxaemia and/or hypoglycaemia on referral, Malawi, 2019–2020

| Factor                        | Hazard of death\(^a\) | P     |
|-------------------------------|-----------------------|-------|
| Blood oxygen level            |                       |       |
| Normoxaemia\(^d\)             | Reference             | NA    |
| Moderate hypoxaemia\(^d\)     | 1.27 (0.40 to 3.97)   | 0.648 |
| Severe hypoxaemia\(^d\)       | 4.05 (1.65 to 9.94)   | 0.002 |
| Missing data                  | 1.84 (0.24 to 14.08)  | 0.559 |
| Blood glucose concentration   |                       |       |
| Normoglycaemia\(^d\)          | Reference             | NA    |
| Moderate hypoglycaemia\(^d\)  | 2.04 (0.54 to 7.64)   | 0.291 |
| Severe hypoglycaemia\(^d\)    | 7.60 (2.07 to 27.92)  | 0.002 |
| Missing data                  | ND                    | ND    |
| Danger signs\(^f\)            |                       |       |
| No                            | Reference             | NA    |
| Yes                           | 2.51 (0.84 to 7.50)   | 0.098 |
| Severely underweight          |                       |       |
| No                            | Reference             | NA    |
| Yes                           | 1.45 (0.67 to 3.18)   | 0.347 |
| Hospital admission            |                       |       |
| No                            | Reference             | NA    |
| Yes                           | 1.20 (0.53 to 2.73)   | 0.659 |
| Sex                           |                       |       |
| Male                          | Reference             | NA    |
| Female                        | 1.19 (0.50 to 2.84)   | 0.700 |
| Age                           |                       |       |
| 5–12 years                    | Reference             | NA    |
| 12–59 months                  | 0.72 (0.22 to 2.32)   | 0.579 |
| 2–11 months                   | 1.07 (0.28 to 4.05)   | 0.924 |
| < 2 months                    | 2.98 (0.68 to 13.12)  | 0.149 |

\(^a\) Hazard ratio; CI: confidence interval; NA: not applicable; ND: not determined.

\(^b\) The analysis included data on 776 children.

\(^c\) The proportional hazards assumption was tested using Schoenfeld residuals and was found not to be violated (P-value: 0.201).

\(^d\) The hazard of death between study recruitment and 14 days after hospital discharge or the last clinical visit.

\(^e\) Definitions of normoxaemia, hypoxaemia, normoglycaemia and hypoglycaemia are given in Box 1.

\(^f\) As all eight children with missing data survived, they were dropped from the model because of perfect prediction.

\(^g\) Danger signs are described in Box 1.
Étude de cohorte prospective sur les enfants malawites ayant fait l'objet d'un transfert et leur survie en cas d'hypoglycémie et d'hypoxémie

Objectifs
Méthodes. Cette étude a été menée sur une cohorte prospective de 826 enfants transférés depuis les centres de santé primaires au Malawi en 2019 et 2020 dans le district de Mchinji, au Malawi, en 2019 et 2020. La saturation en oxygène du sang périphérique (SpO2) et la glycémie ont été mesurées lors de la sélection et à l'admission dans le centre de soins primaires. La survie des enfants transférés a été suivie sur une période de deux semaines après leur sortie ou leur dernière visite médicale. Les enfants étaient suivis deux semaines après leur sortie ou leur dernière visite médicale. Les résultats de l'étude primaire correspondent au taux de survie à deux semaines. Nous avons utilisé des modèles à risques proportionnels de Cox pour identifier les liens entre la SpO2, le taux de glycémie et la survie.

Résultats. Sur 826 enfants sélectionnés, 784 (94,9%) sont arrivés au centre de soins primaire. Les enfants étaient suivis deux semaines après leur sortie ou leur dernière visite médicale. Les enfants souffrant d'hypoglycémie sévère (glycémie : < 2,5 mmol/L) chez 2,3% d'entre eux (19/826). Le taux de survie à deux semaines était de 3,7% (29/784) pour l'ensemble des enfants, mais pour les enfants souffrant d'hypoglycémie, il était de 26,3% (5/19) chez les enfants souffrant d'hypoglycémie sévère. La survie à deux semaines chez les enfants souffrant d'hypoglycémie sévère était de 93,9% (24/25) pour les enfants souffrant d'hypoglycémie modérée (SpO2 : 90–93%) chez 13,1% (108/826) et sévère (SpO2 : < 90%) à 12,7% (7/55) chez les enfants souffrant d'hypoglycémie sévère.

Conclusion. L'intervention préventive pourrait réduire le taux de mortalité en cas d'hypoglycémie et d'hypoxémie.
соответствующее медицинское учреждение (четыре больницы измерялись во время набора в исследование и по прибытии в выписки или последнего визита ребенка в клинику. Первичным
Последующее наблюдение проводили через 2 недели после
и 14 учреждений первичной медико-санитарной помощи).

Резюме
Проспективное когортное исследование малавийских детей, направленных на лечение, и их
выживаемость при гипогликемии и гипоксемии
Цель
Изучить выживаемость детей, направленных из учреждений
первичной медико-санитарной помощи в Малави, с упором на
гипогликемию и прогрессирование гипоксемии.
Методы
В исследование была включена проспективная когорта
детей в возрасте до 12 лет включительно, направленных из
учреждений первой медико-санитарной помощи в районе
Мчинджи, Малави, в 2019 и 2020 годах. Насыщение кислородом
периферической крови (SpO₂) и уровень глюкозы в крови
измерялись во время набора в исследование и по прибытии
в соответствующее медицинское учреждение (четыре больницы
и 14 учреждений первой медико-санитарной помощи).
Последующее наблюдение проводили через 2 недели после
выписки или последнего визита ребенка в клинику. Первичным
результатом исследования был показатель летальности
через 2 недели. Взаимосвязь между SpO₂ уровнями глюкозы
в крови и смертностью оценивалась с использованием
модели пропорциональных рисков Кокса. Терапевтический
эффект госпитализации оценивался с использованием
псевдорандомизации.

Результаты
Из 826 детей, включенных в исследование, 784 (94,9 %)
прошли последующее наблюдение. На момент первого
осмотра гипоксемия была умеренной степени (SpO₂: 90–93 %)
у 13,1 % детей (108/826) и тяжелой степени (SpO₂ < 90 %)
у 8,6 % детей (71/826). Гипогликемия была умеренной степени
(глюкоза в крови: 2,5–4,0 ммоль/л) у 9,0 % детей (74/826) и тяжелой
степени (глюкоза в крови: < 2,5 ммоль/л) у 2,3 % детей (19/826).
Показатель летальности составил 3,7 % (29/784) в целом,
но 26,3 % (5/19) у детей с тяжелой гипогликемией и 12,7 % (9/71) у
детей с тяжелой гипоксемией. Ни умеренная гипогликемия,
ни умеренная гипоксемия не были связаны со смертностью.

Вывод
Пробное догоспитальное лечение глюкозой и более
эффективное лечение гипогликемии могут снизить высокий
показатель летальности, наблюдаемый у детей с тяжелой
гипоксемией. Бремя заболеваемости и смертности от
тяжелой гипоксемии было высоким, поэтому необходимы
способы совершенствования механизмов выявления и лечения
гипоксемии.

References
1. Integrated Management of Childhood Illness [internet]. Geneva: World Health
Organization; 2022. Available from: https://www.who.int/teams/maternal-
newborn-child-adolescent-health-and-aging/child-health/integrated-
management-of-childhood-illness [cited 2022 Feb 4].
2. WHO/UNICEF joint statement. Integrated community case management
(iCCM). Geneva & New York: World Health Organization & United Nations
Children’s Fund; 2012. Available from: https://www.who.int/maternal_child-
adolescent/documents/statement_child_services_access_whounicfs.pdf
[cited 2022 Feb 4].
3. Integrated Management of Childhood Illness: management of the sick
young infant aged up to 2 months: IMCI chart booklet. Geneva: World Health
Organization, 2019. Available from: https://apps.who.intiris/handle/10665/
326448 [cited 2022 Feb 4].
4. Nolan T, Angos P, Cunha AJ, Muhe L, Qazi S, Simoes EA, et al. Quality of hospital
care for seriously ill children in less-developed countries. Lancet. 2001 Jan
13;357(9250):106–10. doi: http://dx.doi.org/10.1016/S0140-6736(00)03542-X
PMID: 11197397
5. King C, Banda M, Bar-Zeev N, Beard J, French N, Makwenda C, et al. Care-seeking
patterns amongst suspected paediatric pneumonia deaths in rural Malawi.
Gates Open Res. 2021 May 6;4(18):178. doi: http://dx.doi.org/10.12688/
gatesopenres.13208.2 PMID: 33537357
6. Pettenon S, Nsungwa-Sabiiti J, Were W, Nsabagasani X, Magumba G, Nambooze
J, et al. Coping with paediatric referral – Ugandan parents’ experience.
Lancet. 2004 Jun 12;363(9425):1955–6. doi: http://dx.doi.org/10.1016/S0140-
6736(04)16411-8 PMID: 15194257
7. Ngwalangwa F, Phiri CAH, Dube Q, Langton J, Hildenwall H, Baker T. Risk factors for mortality in severely ill children admitted to a tertiary referral hospital in Malawi. Am J Trop Med Hyg. 2019 Sep;101(3):670–5. doi: http://dx.doi.org/10.4269/ajtmh.19-0127 PMID: 31287044

8. Nadim B, Mtwete G, Amos B, Hildenwall H, Nakusa A, Mtei F, et al. Blood glucose as a predictor of mortality in children admitted to the hospital with febrile illness in Tanzania. Am J Trop Med Hyg. 2013 Aug;89(2):232–7. doi: http://dx.doi.org/10.4269/ajtmh.13-0161 PMID: 23817332

9. Acheke R, Osipiyi N, English M. Mini-review: management of hypoglycaemia in children aged 0–59 months. J Trop Pediatr. 2010 Aug;56(4):227–34. doi: http://dx.doi.org/10.1093/heapm/fmp109 PMID: 19333785

10. Lazzenni M, Songe M, Pellegrin MC. Hypoglycaemia as a mortality risk factor in acute lower respiratory infections in children in low and middle-income countries: systematic review and meta-analysis. PLoS One. 2015 Sep 15;10(9):e0136166. doi: http://dx.doi.org/10.1371/journal.pone.0136166 PMID: 26372640

11. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Geneva: World Health Organization; 2006. Available from: https://www.who.int/publications/i/item/9241569662 [cited 2022 Feb 4]

12. Colbourn T, King C, Beard J, Phiri T, Mdala M, Zadutsa B, et al. Predictive value of pulse oximetry for mortality in infants and children presenting to primary care with clinical pneumonia in rural Malawi: a data linkage study. PLoS Med. 2020 Oct 23;17(10):e1003300. doi: http://dx.doi.org/10.1371/journal.pmed.1003300 PMID: 33095763

13. McColllum ED, King C, Deula R, Zadutsa B, Nambiar B, et al. Pulse oximetry for children with pneumonia treated as outpatients in rural Malawi. Bull World Health Organ. 2016 Dec;1–4:192–93. doi: http://dx.doi.org/10.2471/BLT.16.173401 PMID: 27994282

14. Hooi S, Colbourn T, Lufesi N, Costello A, Nambiar B, Thammasaitoon S, et al. Predicting hospitalised paediatric pneumonia mortality risk: an external validation of RISC and mRISC, and local tool development (RISC-Malawi) from Malawi. PLoS One. 2016 Dec;21(12):e0168126. doi: http://dx.doi.org/10.1371/journal.pone.0168126 PMID: 28251843

15. Chev R, Zhang M, Chanda A, Lufesi Y. The impact of pulse oximetry on diagnosis, management and outcomes of acute febrile illness in low-income and middle-income countries: a systematic review. BMC Med. 2021 Nov 8;19(1):e002782. doi: http://dx.doi.org/10.1186/s12916-021-02782-3 PMID: 34566231

16. Oser PH, Berkley JA, Ross A, Sanderson F, Mohammed S, Newton CR. Abnormal glucose concentration on admission to a rural Kenyan district hospital: prevalence and outcome. Arch Dis Child. 2003 Jul;88(7):621–5. doi: http://dx.doi.org/10.1136/adc.88.7.621 PMID: 12818911

17. Usenya NED, Anwadi EC, Nwokeye IC, NduKU, Eke CB. Relationship between glycemic levels and treatment outcome among critically ill children admitted into emergency room in Enugu. BMC Pediatr. 2017 May 16;17(1):126. doi: http://dx.doi.org/10.2471/BLT.21.287265

18. Baker T, Ngwalangwa F, Masanjala H, Dube Q, Langton J, Marrone G, et al. Pediatric Emergency Triage, Assessment and Treatment (ETAT) – preparedness for implementation at primary care facilities in Malawi. Glob Health Action. 2021 Jan 11;14(1):1989807. doi: http://dx.doi.org/10.1080/16549761.2021.1989807 PMID: 34779363

19. Gerner A, Vellanki M, Myers A, Bangara F, Bangura S, Koroema AM, et al. Reducing mortality from severe malaria in Sierra Leonean children by applying the WHO Management of Child illness guidelines: a protocol for the Malawi Management of Childhood Illness guidelines: a nationally representative study. Paediatr Int Child Health. 2014 Feb;34(1):29–36. doi: http://dx.doi.org/10.1179/0261403413Y.0000000070 PMID: 24091151

20. Neves R, Pinho R, Ribeiro J, Almeida P, Falcão T, Bento A, et al. Diagnosis and determinants of pneumonia diagnosis using integrated Management of Childhood Illness guidelines: a nationally representative study in Malawi. BMJ Glob Health. 2018 Apr;3(4):e005506. doi: http://dx.doi.org/10.1136/bmjgh-2017-000506 PMID: 29662688

21. Bjornstad PE, Predis GA, Lufesi N, Dixon OS, Kamthunzi P, Hosseinipour MC, et al. Determining the quality of MCI pneumonia care in Malawian children. Paediatr Child Health. 2014 Feb;44(1):29–36. doi: http://dx.doi.org/10.11179/204665513710000000107 PMID: 24091151

22. Uwemmedio OT, Lewis TE, Essen LA, Chan GJ, Noona H, Krusk ME, et al. Distribution and determinants of pneumonia diagnosis using Integrated Management of Childhood Illness guidelines: a systematically representative study in Malawi. BMJ Glob Health. 2018 Apr;3(4):e005506. doi: http://dx.doi.org/10.1136/bmjgh-2017-000506 PMID: 29662688

23. Boashashim M, Mvamanda D, Noona H, Namuyonga RJ, Shah MP, Bauleni E, et al. Quality of case management and discharge from health centers seen at health facilities in southern Malawi. Am J Trop Med Hyg. 2017 May;96(5):1107–16. doi: http://dx.doi.org/10.4269/ajtmh.16-0945 PMID: 28500813

24. Johansson EW, Noona H, Carvajal-Aguile AM, Amouzou A, Hildenwall H. Determinants of Integrated Management of Childhood Illness (IMCI) non-severe pneumonia classification and care in Malawian health facilities: analysis of a national facility census. J Glob Health. 2017 Dec;7(2):020408–020408. doi: http://dx.doi.org/10.1179/204665517X.000000000107 PMID: 29613934

25. Desmond NA, Nyirenda D, Dube Q, Mallewa M, Molyneux E, Laloo DG, et al. Recognising and treating those seeking for acute bacterial meningitis in adults and children in resource-poor settings: a qualitative study. PLoS One. 2013 Jul 4;8(7):e68163. doi: http://dx.doi.org/10.1371/journal.pone.0068163 PMID: 23861864

26. Chandra A, Osborn J, Bastard G, Bell D, Burza S, D'Acremont V, et al. Anticipating the future: prognostic tools as a complementary strategy to improve care for patients with febrile illnesses in resource-limited settings. BMJ Glob Health. 2021 Jul;6(7):e006057. doi: http://dx.doi.org/10.1136/bmjgh-2021-006057 PMID: 34330761

27. Resolution A/RES/70/1. Transforming our world: the 2030 agenda for sustainable development. In: Seventeenth United Nations General Assembly, New York, 25 September 2015. New York: United Nations; 2015. Available from: http://www.un.org/ga/search/view_doc.asp?symbol=A/RES/70/1&Lang=E [cited 2022 Feb 24].
### Table 1. Children's characteristics at recruitment, prospective cohort study of survival in children with hypoxaemia and/or hypoglycaemia on referral, Malawi, 2019–2020

| Variable | Recruited \( n = 826 \) | Completed follow-up \( n = 784 \) | Lost to follow-up \( n = 42 \) |
|----------|-------------------|-----------------|-----------------|
| **Demographic** | | | |
| Age | | | |
| < 2 months | 38 (4.6) | 38 (4.9) | 0 (0.0) |
| 2–11 months | 105 (12.7) | 98 (12.5) | 7 (16.7) |
| 12–59 months | 413 (50.0) | 390 (49.7) | 23 (54.8) |
| 5–12 years | 270 (32.7) | 258 (32.9) | 12 (28.6) |
| Sex | | | |
| Male | 437 (52.9) | 419 (53.4) | 18 (42.9) |
| Female | 389 (47.1) | 365 (46.6) | 24 (57.1) |
| **Socioeconomic** | | | |
| Mother's age in years, mean (SD) | 28.9 (7.8) | 28.9 (7.7) | 28.9 (8.9) |
| Maternal education | | | |
| None | 79 (9.6) | 73 (9.3) | 6 (14.3) |
| Primary | 659 (79.8) | 624 (79.6) | 35 (83.3) |
| Secondary or further | 85 (10.3) | 85 (10.8) | 0 (0.0) |
| Missing data | 3 (0.4) | 2 (0.3) | 1 (2.4) |
| Maternal marital status | | | |
| Married | 703 (85.1) | 664 (84.7) | 39 (92.9) |
| Not married | 122 (14.8) | 119 (15.2) | 3 (7.1) |
| Missing data | 1 (0.1) | 1 (0.1) | 0 (0.0) |
| **Clinical** | | | |
| SpO₂ Mean value (SD), % | 94.9 (5.9) | 94.9 (5.9) | 94.4 (6.5) |
| Normoxaemia | 637 (77.1) | 605 (77.2) | 32 (76.2) |
| Moderate hypoxaemia | 108 (13.1) | 104 (13.3) | 4 (9.5) |
| Severe hypoxaemia | 71 (8.6) | 65 (8.3) | 6 (14.3) |
| Missing data | 10 (1.2) | 10 (1.3) | 0 (0.0) |
| Blood glucose Mean concentration (SD), mmol/L | 5.8 (2.0) | 5.8 (2.0) | 5.8 (2.4) |
| Normoglycaemia | 725 (87.8) | 687 (87.6) | 38 (90.5) |
| Moderate hypoglycaemia | 74 (9.0) | 71 (9.1) | 3 (7.1) |
| Severe hypoglycaemia | 19 (2.3) | 18 (2.3) | 1 (2.4) |
| Missing data | 8 (1.0) | 8 (1.0) | 0 (0.0) |
| Routine diagnosis<sup>e</sup><sup,f</sup> | | | |
| Acute respiratory infection or pneumonia | 111 (13.6) | 105 (13.5) | 6 (14.6) |
| Malaria | 313 (38.3) | 301 (38.7) | 12 (29.3) |
| Sepsis or meningitis | 92 (11.3) | 86 (11.1) | 6 (14.6) |
| Diarrhoea | 18 (2.2) | 18 (2.3) | 0 (0.0) |
| Fever (unclassified) | 39 (4.8) | 38 (4.9) | 1 (2.4) |
| Skin condition | 39 (4.8) | 37 (4.8) | 2 (4.9) |
| Malnutrition | 36 (4.4) | 34 (4.4) | 2 (4.9) |
| Anaemia | 55 (6.7) | 53 (6.8) | 2 (4.9) |
| Trauma | 201 (24.6) | 193 (24.8) | 8 (19.5) |
| Other infectious condition | 13 (1.6) | 12 (1.5) | 1 (2.4) |
| Other non-infectious condition | 109 (13.3) | 101 (13.0) | 8 (19.5) |

<sup>a</sup> All values in the table represent absolute numbers and percentages unless otherwise stated.
<sup>b</sup> Definitions of normoxaemia, hypoxaemia, normoglycaemia and hypoglycaemia are given in Box 1.
<sup>c</sup> Reasons for missing data were: (i) six children too agitated (6); (ii) three children unconscious and receiving care; and (iii) a biologically plausible value could not be obtained for one child.
<sup>d</sup> Reasons for missing data were: (i) no test strips available (one child); (ii) no lancet available (two children); (iii) glucometer not working (four children); and (iv) transport for referral was found before the test could be completed (one child).
<sup>e</sup> Diagnosis made by the health-care provider at recruitment.
<sup>f</sup> Children could receive more than one diagnosis.
### Table 3. Care-seeking and clinical progression after recruitment, by blood oxygen level, prospective cohort study of survival in children with hypoxaemia and/or hypoglycaemia on referral, Malawi, 2019–2020

| Group                        | No. in group | Children who received further care, a no. (%) | Hours to receipt of further care, b median (IQR) | SpO₂, % Median (IQR) | P c  |
|------------------------------|--------------|-----------------------------------------------|-------------------------------------------------|----------------------|------|
|                              |              |                                               |                                                 | At study recruitment | At subsequent facility |
| All children                 | 826          | 344 (41.7)                                    | 5.0 (2.9–8.0)                                   | 97 (94–98)           | 97 (95–98) | 0.060 |
| Normoxaemic children         | 637          | 239 (37.5)                                    | 5.2 (3.3–11.3)                                  | 98 (96–98)           | 97 (95–98) | 0.121 |
| Moderately hypoxaemic children | 108             | 55 (50.9)                                    | 4.2 (3.2–7.0)                                   | 92 (91–93)           | 95 (90–97) | 0.006 |
| Severely hypoxaemic children | 71           | 45 (63.4)                                     | 3.3 (2.0–5.4)                                   | 84 (75–87)           | 92 (87–96) | < 0.001 |
| Children with missing data   | 10           | 5 (50.0)                                      | 17.6 (7.1–28.3)                                 | ND                   | 96 (95–96) | NA    |

IQR: interquartile range; NA: not applicable; ND: not determined; SpO₂: peripheral blood oxygen saturation.

a Further care included both hospital admission (306 children) and outpatient care at a hospital or health-care facility (38 children).

b The time from recruitment to presentation at the first subsequent facility.

c Medians were compared using the Wilcoxon signed-rank test.

d Definitions of normoxaemia and hypoxaemia are given in Box 1.

### Table 5. Care-seeking and clinical progression after recruitment, by blood glucose concentration, prospective cohort study of survival in children with hypoxaemia and/or hypoglycaemia on referral, Malawi, 2019–2020

| Group                        | No. in group | Children who received further care, a no. (%) | Hours to receipt of further care, b median (IQR) | Blood glucose concentration, mmol/L Mean (95% CI) | P c  |
|------------------------------|--------------|-----------------------------------------------|-------------------------------------------------|-------------------------------------------------|------|
|                              |              |                                               |                                                 | At study recruitment At subsequent facility     |
| All children                 | 826          | 344 (41.7)                                    | 5.0 (2.9–8.0)                                   | 5.92 (5.70 to 6.14) 6.31 (6.10 to 6.52) | 0.603 |
| Normoglycaemic children      | 725          | 299 (41.2)                                    | 5.0 (3.1–7.9)                                   | 5.86 (5.66 to 6.06) 6.03 (5.82 to 6.24) | 0.018 |
| Moderately hypoglycaemic children | 74             | 30 (40.5)                                     | 4.3 (3.2–25.7)                                  | 3.48 (3.33 to 3.61) 4.75 (4.18 to 5.32) | < 0.001 |
| Severely hypoglycaemic children | 19            | 11 (57.9)                                     | 3.9 (2.3–7.1)                                   | 2.39 (2.15 to 2.63) 4.48 (3.35 to 5.62) | 0.001 |
| Children with missing data   | 8            | 4 (50.0)                                      | 3.8 (2.9–6.6)                                   | ND                   | 7.17 (4.06 to 10.27) | NA    |

CI: confidence interval; IQR: interquartile range; NA: not applicable; ND: not determined.

a Further care included both hospital admission (306 children) and outpatient care at a hospital or health-care facility (38 children).

b The time from recruitment to presentation at the first subsequent facility.

c Means were compared using a t-test.

d Definitions of normoglycaemia and hypoglycaemia are given in Box 1.