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Papers

Prognostic indicators of early and late death in children admitted to district hospital in Kenya: cohort study

J A Berkley, A Ross, I Mwangi, F H A Osier, M Mohammed, M Shebbe, B S Lowe, K Marsh, C R J C Newton

Abstract

Objectives To identify clinical indicators of immediate, early, and late mortality in children at admission to a sub-Saharan district hospital and to develop prognostic scores.

Design Prospective cohort study.

Setting One district hospital in Kenya.

Participants Children aged over 90 days admitted to hospital from 1 July 1998 to 30 June 2001.

Main outcome measures Prognostic indicators of mortality.

Results Of 8091 children admitted up to 1 June 2000, 436 (5%) died. Sixty (14%) died within four hours after admission (immediate), 193 (44%) after 4-48 hours (early), and 183 (42%) after 48 hours (late). There were marked differences in the clinical features associated with immediate, early, and late death. Seven indicators (neurological status, respiratory distress (subcostal indrawing or deep breathing), nutritional status (wasting or kwashiorkor), severe anaemia, jaundice, axillary temperature, and length of history) were included in simplified prognostic scores. Data from 4802 children admitted from 1 July 2000 to 30 June 2001 were used to validate the scores. For simplified prognostic scores the areas under the receiver operating characteristic curves were 0.93 (95% confidence interval 0.92 to 0.94), 0.82 (0.80 to 0.83), and 0.82 (0.81 to 0.84) for immediate, early, and late death, respectively.

Conclusion In children admitted to a sub-Saharan hospital, the prognostic indicators of early and late deaths differ but a small number of simple clinical signs predict outcome well.

Introduction

One in six African children dies before the age of 5 years.[1] District hospitals have an important role in reducing mortality[2] but resources are often limited and care may be of limited quality.[3] The implementation of simple guidelines[4 5] for common childhood illnesses may lead to improvements, but tools are needed to evaluate the quality of care between hospitals and over time.[3 6]

Scores designed to predict mortality enable adjustment for severity of illness.[7] For example, the PRISM score has recently been used to standardise and evalu-ate outcome in paediatric meningococcal disease in the United Kingdom.[8 9] An appropriately developed score might be useful in audit, research, and clinical practice in sub-Saharan Africa.

Although prognostic indicators have been described for specific diseases—including malaria,[10 11] lower respiratory tract infection,[12 13] gastroenteritis,[14 15] and malnutrition[16 17]—children commonly present with multiple problems. These typically include malnutri-tion, anaemia, malaria parasitaemia, or HIV infection. Malnutrition increases the risk of death in children admitted to hospital, and presents with almost every illness.[18] Additionally, without adequate laboratory facilities clinical features of malaria may be indistin-guishable from lower respiratory tract infection[19] or meningitis.[20]

We identified prognostic indicators in children admitted to a rural district hospital in Kenya, irrespec-tive of diagnosis, to produce practical prognostic scores.

Methods

Location

Kilifi district hospital is located on the Kenyan coast. It serves a mainly rural population of about 200 000 people. A Kenya Medical Research Institute (KEMRI) research centre is situated within the hospital. The out-patient department is staffed by government employed clinical officers who refer admissions to the paediatric ward (35 beds) or the high dependency ward (six beds). Research clinicians provide inpatient paediatric clini-cal cover.

The KEMRI Scientific Steering Committee and National Ethical Review Committee approved the study.

Participants and clinical methods

Data were prospectively collected on admission and at death or discharge for all 8477 admissions of children age over 90 days who were admitted from 1 July 1998 to 30 June 2001. We excluded children who were admitted for trauma or elective procedures. Trained clinical assistants collected demographic data, and research clinical officers and doctors from Kenya and Europe with 2-12 years' paediatric experience col-lected clinical data. Training was given in the recognition of clinical signs, including videos for respi-

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ratory signs.[21] Data were recorded on standardised proforma that also served as the clinical notes. Table 1 gives definitions of clinical signs.

Sampling and laboratory methods

After we obtained consent from the carers in their own languages a blood sample was taken from all children admitted. For diagnosis of malaria thick and thin blood smears were examined at ×1000. A full blood count was performed with a Coulter MDII-18 counter (Beckman-Coulter, USA). Results were available immediately to clinicians. We investigated the association between HIV infection and mortality in a nested case-control study using stored plasma samples from all children who died during a six month period. We used a random number table to select four times as many controls as cases, stratified by age (<18 months and ≥18 months). Anonymous HIV testing was performed using enzyme linked immunosorbent assay (ELISA, Vironostika, Organon Teknika, USA) and by an IgG antibody capture particle agglutination test (Central Public Health Laboratory, London). Samples from children age <18 months in which results were positive were confirmed by polymerase chain reaction (PCR) for proviral DNA.[22] All laboratory procedures were monitored through internal and external quality assessment protocols.

Immediate, early, and late deaths

We had observed differences in presentation between children who died soon after admission and those who died later. Furthermore, there seemed to be a bimodal distribution of deaths. For example, most deaths in children with a clinical syndrome similar to acute severe malaria occurred within 48 hours after admission, while other deaths generally occurred later. We therefore hypothesised that the predictors of early and late mortality differed and developed these as separate models. We also wanted to distinguish children close to death on admission, in whom a model might be the diagnosis of the process of dying rather than prediction. Thus we divided deaths into immediate (within four hours after admission), early (4-48 hours), and late (>48 hours).

Statistical methods

We double entered and verified data using FoxPro for Windows. We used EpiInfo 6.04b and Stata 6.0 for statistical analysis.

We used data from children admitted in the first two years to investigate the prognostic ability of clinical features and to derive prognostic models. The positive

and negative likelihood ratios were calculated for immediate, early, and late deaths. We selected variables that were univariately predictive, with a likelihood ratio ≥2 or ≤0.5, and adjusted them for potential confounding of related variables in a multivariate analysis according to the method of Spiegelhalter and Knill-Jones.[23] [24] The final indicators were chosen by further excluding any variables with an adjusted likelihood of ≤1.5 and ≥0.67, suggesting they were of little independent predictive value. Simplified prognostic scores were constructed by assigning points approximating to the natural logarithm of the adjusted likelihood ratio for each indicator. When potential for a negative score existed we added a constant.

We prospectively validated the prognostic scores using data collected from children in the third year of the study. We used receiver operating curve characteristic analysis and calculated the area under the curve.

Results

Patient characteristics

From 1 July 1998 to 30 June 2000, 8477 children (47% girls) aged 90 days to 13 years were admitted. Of these, we excluded 386 who were admitted electively or after trauma. Of the 8091 included children, 4314 (53%) were <2 years of age, 2687 (33%) were 2-5 years, and 1090 (14%) were >5 years old. The mean z scores for weight for age and height for age were –1.95 (SD 1.41) and –1.32 (SD 1.21), respectively. Carers of 2031 (25%) children reported that the child had had convulsions, 974 (12%) children were prostrate, 572 (7%) had impaired consciousness, and 1853 (23%) had respiratory distress (deep breathing or subcostal indrawing). In 4537 (56%) children test results for malaria were positive, and 1264 (16%) were severely anaemic.

Four hundred and thirty six children (5%) died while in hospital. Sixty (14%) deaths were classified as immediate, 193 (44%) as early, and 183 (42%) as late. HIV infection was detected in 17/79 (22%) children who died between 1 October 1999 and 31 March 2000 and in 13/311 (4%) children who were discharged alive (odds ratio 6.29, 2.71 to 14.7). The proportion was similar in children who died before and after 48 hours after admission.

Clinical prognostic indicators

Table 2 shows the crude likelihood ratios for clinical features in predicting immediate, early, and late deaths. Table 3 shows the adjusted likelihood ratios.

For immediate deaths, severe anaemia, jaundice, subcostal indrawing, deep breathing, neurological status, and axillary temperature were univariately predictive (table 2). When we included these features in a multivariate analysis they all remained predictive (table 3).

Jaundice, subcostal indrawing, deep breathing, neurological status, axillary temperature, wasting, and kwashiorkor were univariately predictive for early deaths (table 2). When we included these features in the multivariate model, the likelihood ratios for deep breathing and axillary temperature were poorly predictive and were excluded (table 3).

For late deaths, neurological status, axillary temperature, wasting, kwashiorkor, history >7 days, seizures, fever, and diarrhoea were univariately predic-

Table 1 Definitions of clinical signs

	Definition (age to which it applies)
Prostrate	Inability to sit unassisted (≥1 year); inability to drink or breast feed (<1 year)
Impaired consciousness	Inability to localise a painful stimulus (>8 months); non-directed eye movements (≤8 months)
Raised respiratory rate	>50/min (<12 months); >40/min (≥1 year)
Subcostal recession	Indrawing of lower chest wall*
Severe anaemia	Haemoglobin concentration <50 g/l
History of diarrhoea	≥3 episodes in 24 hours
Hyperthermia	Axillary temperature >39°C
Hypothermia	Axillary temperature <36°C
Wasting	WAZ <–3†

*Differentiated from deep breathing (Kussmaul's respiration).
† Weight for age (WAZ) and height for age (HAZ) z scores calculated with reference data from American National Center for Health Statistics (NCHS). Scores <–3 indicate severe wasting.

tive and were included in the multivariate analysis (table 2). The adjusted likelihood ratios for a history of fever, seizures, and diarrhoea had reduced prognostic ability so we excluded these variables from the late score (table 3). The resulting prognostic scores ranged from 0 to 10 for immediate deaths and from 0 to 7 for early and late deaths.

Validation of prognostic scores

Between 1 July 2000 and 30 June 2001, 4995 children age >90 days were admitted. We excluded 193 who were admitted for trauma or elective admissions. This left 4802 children, of whom 222 (4.6%) died: 26 (12%) immediate, 88 (40%) early, and 108 (48%) late. Table 4 shows the distributions of immediate, early, and late

prognostic scores. The areas under the receiver operating characteristic curves for the scores were 0.93 (95% confidence interval 0.92 to 0.94) for immediate, 0.82 (0.80 to 0.83) for early, and 0.82 (0.81 to 0.84) for late deaths (fig).

Discussion

Our prognostic scores showed good predictive ability despite being based on simple clinical signs. None of the indicators was specific for aetiology, which suggests that they could be applicable throughout the region. Our results need to be externally validated, ideally, in areas of differing HIV prevalence and malaria transmission. About half of the children admitted and

Table 2 Clinical predictors of immediate, early, and late death in children admitted to hospital in Kenya. Figures are numbers of children* and likelihood ratios

	Alive (n=7655)	Immediate (n=60)	Early (n=193)	Late (n=183)	Crude likelihood ratio (95% CI)		
					Immediate	Early	Late
Length of history (days):							
≤7	6729	54	152	92	0.96 (0.87 to 1.07)	0.89 (0.83 to 0.96)	0.57 (0.49 to 0.66)
>7	898	9	41	91	1.27 (0.70 to 2.33)	1.80 (1.37 to 2.38)	4.22 (3.61 to 4.95)
History of fever:							
No	1002	13	24	50	1.66 (1.02 to 2.69)	0.95 (0.65 to 1.39)	2.09 (1.64 to 2.66)
Yes	6653	47	168	133	0.90 (0.79 to 1.03)	1.01 (0.95 to 1.06)	0.84 (0.76 to 0.91)
History of diarrhoea:							
No	5928	47	139	96	1.01 (0.89 to 1.16)	0.93 (0.86 to 1.02)	0.68 (0.59 to 0.78)
Yes	1727	13	53	87	0.96 (0.59 to 1.56)	1.22 (0.97 to 1.54)	2.11 (1.80 to 2.47)
History of cough:							
No	4028	36	95	71	1.14 (0.92 to 1.40)	0.94 (0.81 to 1.09)	0.74 (0.61 to 0.89)
Yes	3626	24	97	112	0.84 (0.62 to 1.15)	1.07 (0.93 to 1.23)	1.29 (1.15 to 1.45)
History of seizures:							
No	5722	41	130	163	0.91 (0.77 to 1.09)	0.91 (0.82 to 1.00)	1.19 (1.13 to 1.26)
Yes	1930	19	62	20	1.26 (0.86 to 1.82)	1.27 (1.03 to 1.57)	0.43 (0.29 to 0.66)
Jaundice:							
No	7502	55	184	179	0.95 (0.89 to 1.02)	0.97 (0.94 to 0.99)	1.00 (0.98 to 1.02)
Yes	152	4	9	4	3.41 (1.31 to 8.91)	2.36 (1.22 to 4.55)	1.10 (0.41 to 2.94)
Severe anaemia (haemoglobin <50 g/l):							
No	3436	30	148	149	0.62 (0.49 to 0.79)	0.91 (0.85 to 0.99)	0.96 (0.90 to 1.03)
Yes	1160	27	43	34	3.10 (2.15 to 4.10)	1.47 (1.13 to 1.93)	1.22 (0.89 to 1.66)
Wasting:							
No	6241	39	162	65	0.85 (0.72 to 1.01)	0.75 (0.67 to 0.84)	0.44 (0.36 to 0.53)
Yes	1405	17	74	118	1.65 (1.11 to 2.46)	2.12 (1.76 to 2.55)	3.51 (3.12 to 3.95)
Kwashiorkor:							
No	6844	50	144	84	0.93 (0.83 to 1.04)	0.84 (0.78 to 0.91)	0.51 (0.44 to 0.60)
Yes	806	10	47	99	1.58 (0.89 to 2.80)	2.34 (1.81 to 3.02)	5.13 (4.43 to 5.96)
Temperature:							
<36°C	203	7	13	22	4.70 (2.32 to 9.52)	2.61 (1.52 to 4.49)	4.54 (3.00 to 6.88)
36-39°C	4934	41	128	143	1.13 (0.97 to 1.33)	1.06 (0.96 to 1.17)	1.21 (1.12 to 1.31)
>39°C	2490	8	46	17	0.44 (0.23 to 0.83)	0.75 (0.57 to 0.97)	0.29 (0.18 to 0.45)
Raised respiratory rate:							
No	5373	26	98	119	0.75 (0.57 to 0.97)	0.73 (0.64 to 0.85)	0.94 (0.85 to 1.05)
Yes	2176	23	90	58	1.63 (1.21 to 2.20)	1.66 (1.42 to 1.94)	1.14 (0.92 to 1.41)
Subcostal indrawing:							
No	6213	24	107	135	0.49 (0.36 to 0.47)	0.68 (0.60 to 0.77)	0.91 (0.83 to 0.99)
Yes	1432	36	86	48	3.20 (2.59 to 3.96)	2.38 (2.02 to 2.80)	1.40 (1.09 to 1.79)
Deep breathing:							
No	7182	26	132	166	0.46 (0.35 to 0.62)	0.73 (0.66 to 0.80)	0.97 (0.92 to 1.04)
Yes	468	34	61	17	9.26 (7.30 to 11.8)	5.17 (4.12 to 6.47)	1.52 (0.96 to 2.41)
Neurological status:							
Not prostrated	6851	13	91	162	0.24 (0.15 to 0.39)	0.53 (0.45 to 0.61)	0.99 (0.94 to 1.04)
Prostrated with seizures	206	1	11	1	0.62 (0.09 to 4.35)	2.12 (1.17 to 3.82)	0.20 (0.03 to 1.44)
Prostrated without seizures	364	17	43	9	5.94 (3.93 to 9.00)	4.67 (3.53 to 6.20)	1.03 (0.54 to 1.97)
Impaired consciousness with seizures	147	12	17	6	10.4 (6.13 to 17.7)	4.59 (2.83 to 7.42)	1.71 (0.76 to 3.81)
Impaired consciousness without seizures	67	17	30	5	32.4 (20.3 to 51.7)	17.8 (11.8 to 26.7)	3.12 (1.27 to 7.65)

*Data are missing where numbers are less than the totals given in each column.

Table 3 Adjusted likelihood ratios and simplified prognostic scores for death in children admitted to hospital in Kenya

	Adjusted likelihood ratios		Simplified scores	
Indicators	**Indicator present**	**Indicator absent**	**Indicator present**	**Indicator absent**
Immediate deaths				
Severe anaemia (haemoglobin <50 g/l)	1.76	0.79	+1	+0
Jaundice	1.89	0.97	+1	+0
Subcostal indrawing	2.51	0.57	+1	−1
Deep breathing	2.08	0.77	+1	+0
Prostrated with seizures	2.03	0.99	+1	+0
Prostrated without seizures	14.1	0.80	+3	+0
Impaired consciousness with seizures	9.27	0.70	+2	+0
Impaired consciousness without seizures	32.2	0.72	+3	+0
Axillary temperature <36 °C	1.75	0.96	+1	+0
Axillary temperature >39 °C	0.59	1.17	−1	+0
Constant			+2	
Early deaths				
Jaundice	1.99	0.98	+1	+0
Subcostal indrawing	2.18	0.71	+1	+0
Prostrated with seizures	4.70	0.94	+2	+0
Prostrated without seizures	5.11	0.93	+2	+0
Impaired consciousness with seizures	6.97	0.78	+2	+0
Impaired consciousness without seizures	21.2	0.84	+3	+0
Wasting	1.58	0.84	+1	+0
Kwashiorkor	2.55	0.83	+1	+0
Constant			+0	
Late deaths				
History >7 days	1.88	0.78	+1	+0
Prostrated with seizures	0.54	1.01	−1	+0
Prostrated without seizures	1.53	0.99	+0	+0
Impaired consciousness with seizures	2.24	1.03	+1	+0
Impaired consciousness without seizures	3.16	0.98	+1	+0
Axillary temperature <36 °C	2.30	0.94	+1	+0
Axillary temperature >39 °C	0.57	1.15	−1	+0
Wasting	2.05	0.63	+1	+0
Kwashiorkor	2.09	0.74	+1	+0
Constant			+2	

a third of those who died had a malaria parasitaemia, and the overall rate of HIV infection was about 6%. However, nearly a quarter of children who died and were tested were infected with HIV.

Clinical indicators

Our findings overlap with those of some studies of disease specific prognostic indicators. The principal indicators of immediate and early death are similar to those for malaria[10][11] and severe lower respiratory tract infection,[12] particularly with respect to the increased risk in afebrile, malnourished children. Importantly, diarrhoea or seizures (other than in prostrate children or those with impaired consciousness) were not signifi-

cant independent predictors of death. Among prostrate children or those with impaired consciousness, a history of seizures was associated with a better outcome, suggesting a postictal state in many of these children. We did not include biochemical or microbiological variables in our models as laboratory facilities are not widely available.

Our treatment practices did not differ significantly from those recommended by WHO[4] or in other well established guidelines for common illnesses. In common with other African hospitals, the paediatric ward was often overcrowded. Close monitoring was possible only in the high dependency unit. Basic drugs were available throughout the study period but affordable antibiotics—for example, such as penicillin, chloramphenicol, and gentamicin—were normally used. While laboratory services were good, radiography was not always available. The presence of the research unit may have reduced inpatient mortality, though the level of care was not beyond that possible at a district hospital.[2]

Prognostic scoring systems are usually developed from patients given treatment, which may influence their outcome. "False positives" are therefore expected as many children are admitted in extremis but receive prompt lifesaving treatments such as fluid resuscitation. In practice, although some patients inevitably die despite treatment, prognostic models derived from treated cohorts remain valuable in identifying areas for improvement and in identifying individuals at high risk.[7] "False negatives" may also occur when the condition of a child deteriorates after admission. This was seen in the early score, where 11 children in the validation year died early despite having had an early score of zero at admission. The use of negative likelihood ratios allowed the possibility of the inclusion of the prognostic value of the absence of a clinical sign.
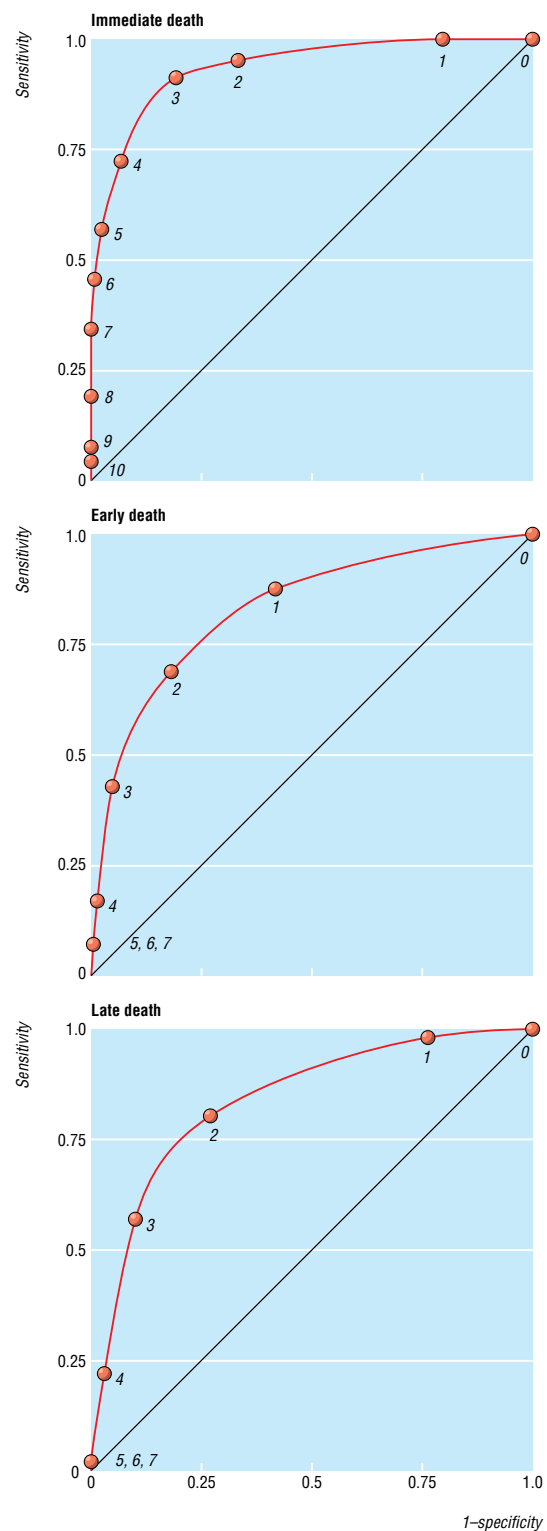
Current strategies

The WHO/Unicef integrated management of childhood illness (IMCI) strategy is aimed at improving community based care and referral. Current efforts to improve health care at the first referral level include an algorithm for emergency assessment and triage (ETAT). It is aimed at prioritising children who need admission or urgent resuscitation. Our prognostic scores differ in that the main outcome is inpatient mortality. Mortality varies considerably between hospitals, with patterns of use depending on location and availability of other healthcare options. By adjusting for

Table 4 Distribution of prognostic scores and outcome in 4802 children admitted to hospital in Kenya

	Immediate		Early		Late	
Score	**No admitted**	**No (%) who died**	**No admitted**	**No (%) who died**	**No admitted**	**No (%) who died**
0	698	0	2779	11 (0.4)	15	0
1	2196	1 (0.1)	1101	16 (1.5)	1081	2 (0.2)
2	657	1 (0.2)	668	23 (3.4)	2310	18 (0.8)
3	612	5 (0.8)	183	23 (13)	869	26 (3.0)
4	217	4 (1.8)	55	10 (18)	347	38 (11)
5	72	3 (4.2)	15	5 (33)	170	22 (13)
6	34	3 (8.8)	1	0	10	2 (20)
7	31	4 (13)	0	0	0	0
8	12	3 (25)	—	—	—	—
9	2	1 (50)	—	—	—	—
10	1	1 (100)	—	—	—	—

risk of death, outcomes could be compared either between centres or over time.

We have shown that a small number of important clinical indicators are prognostic for death in children admitted to a rural Kenyan district hospital, irrespective of clinical diagnosis. If these scores can be suitably

What is already known on this topic

Prognostic indicators have been described for individual diseases—including malaria, lower respiratory tract infection, diarrhoea, and malnutrition—in African children

Making a single diagnosis is often difficult or inappropriate as many children are admitted with several coexisting problems, the clinical features of common illnesses may be indistinguishable, and laboratory facilities are often inadequate

What this study adds

The signs that are prognostic of immediate, early, and late deaths in children admitted to hospital in Africa differ

A small number of simple clinical signs have good sensitivity and specificity for predicting outcome and could be used for risk assessment in individuals or groups

validated elsewhere in the region, we believe they could be valuable in assessing the clinical care at district hospitals, standardising clinical studies, and identifying children "at risk."

Receiver operating characteristic curves for immediate, early, and late death scores in 4802 children. Numbers on curves refer to scores

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