Contribution of Malaria to Inhospital Mortality in Papua New Guinean Children from a Malaria-Endemic Area: A Prospective Observational Study

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Abstract. We aimed to identify clinical and laboratory predictors of mortality in children from a malaria-endemic area of Papua New Guinea hospitalized for severe illness. Children aged 0.5–10 years presenting with any WHO-defined feature of severe malarial illness were eligible for recruitment. Each child was assessed with a detailed clinical examination, blood film microscopy, malaria rapid diagnostic testing (RDT), a full blood examination, and blood glucose and lactate concentrations. Clinical care was coordinated by local medical staff in accordance with national guidelines. Daily study assessments were conducted until death or discharge. Other biochemical tests and malaria polymerase chain reaction (PCR) tests were performed subsequently. Logistic regression identified independent predictors of death. Of 787 evaluable children with severe illness, 336 had confirmed severe malaria (microscopy and PCR positive) and 58 (6.6%) died during hospitalization. The independent predictors of mortality were hyperlactatemia (adjusted odds ratio [95% CI]: 2.85 [1.24–6.41], $P = 0.01$), malnutrition (2.92 [1.36–6.23], $P = 0.005$), renal impairment (3.85 [1.53–9.24], $P = 0.002$), plasma albumin (0.93 [0.88–0.98] for a 1 g/L increase, $P = 0.004$), and Blantyre coma score (BCS) ≤ 2 (10.3 [4.77–23.0] versus a normal BCS, $P < 0.0001$). Confirmed severe malaria (0.11 [0.03–0.30] versus non-malarial severe illness, $P < 0.0001$) was independently associated with lower mortality. Although established risk factors were evident, malaria was inversely associated with mortality. This highlights the importance of accurate diagnosis through blood film microscopy, RDTs, and, if available, PCR to both guide management and provide valid epidemiological data.

INTRODUCTION

There has been a slow and steady global decline in death rates in children younger than 5 years (under-5s).¹ Despite this trend, there are still countries in malaria-endemic regions with unacceptably high infant and childhood mortality. A case in point is Papua New Guinea (PNG). Based on the modeling of survey, census, vital registration, and verbal autopsy data, the mortality rate in PNG under-5s is estimated to be 53 per 1,000 live births, the highest in the Asia-Pacific region.^{2,3}

Although malaria has been listed among the most common causes of death in PNG children,⁴ available mortality data have been collected largely from highland regions⁵ where malaria transmission is low compared with that in coastal areas. From an epidemiological perspective, this might indicate that its contribution to pediatric mortality across the country as a whole may have been underestimated. By contrast, and despite clear recommendations that a parasitological diagnosis of malaria should always be made,⁶ childhood deaths in PNG are often attributed to malaria without objective evidence of this diagnosis. Indeed, because of limited diagnostic laboratory capacity even in the main provincial hospitals, the risk factors for, and etiology of, most inpatient childhood deaths in PNG remain unknown. Papua New Guinea is not unusual in this regard and there have been few detailed studies in other malaria-endemic countries that have assessed the value of readily available clinical features and bedside investigation findings to identify children at the highest risk of death.⁷

The aim of the present study was, therefore, to identify the predictors, especially malaria infection, for mortality in

children treated for severe illness in a provincial coastal PNG hospital.

PATIENTS AND METHODS

Study site and setting. The present study was carried out at Modilon Hospital, the main referral hospital in the Madang Province on the north coast of mainland PNG. The estimated age-specific number of children in Madang Province at the time of the study (between October 2006 and December 2009) was 12,000 for those aged < 1 year, 60,000 for those aged 1–4 years, and 45,000 for those aged 5–9 years.⁸

Malaria parasites are transmitted in Madang Province by a number of mosquito vectors, including *Anopheles punctulatus* complex, *Anopheles farauti*, and *Anopheles koliensis*.⁹ The local annual entomological inoculation rate is estimated at 37 for *Plasmodium falciparum* and 24 for *Plasmodium vivax*.⁹ In healthy, asymptomatic Madang children aged 1–10 years, the spleen rate is 13% and the prevalence of parasitemia by microscopy 8.2% for *P. falciparum* (median [interquartile range (IQR)] density 1,360 [453–2,881]/ μ L) and 14.1% (348 [226–727]/ μ L) for *P. vivax*.¹⁰ Approximately 90% of local children have the alpha-thalassemia trait.¹¹ The national HIV seroprevalence is 0.9%.¹²

Ethical approval, study design, and enrolment criteria. This study was approved by the PNG Medical Research Advisory Committee (MRAC 06.08) and the PNG Institute of Medical Research Institutional Review Board. All children aged 0.5–10 years admitted to Modilon Hospital during the study period were assessed for recruitment to a prospective observational study of severe pediatric illness. Inclusion criteria included any of the following: 1) impaired consciousness/coma (Blantyre coma score [BCS] < 5),¹³ 2) prostration (inability to sit/stand unaided), 3) multiple seizures, 4) hyperlactatemia (blood lactate > 5 mmol/L), 5) severe anemia (hemoglobin < 50 g/L), 6) dark urine, 7) hypoglycemia (blood glucose ≤ 2.2 mmol/L), 8) jaundice, 9) respiratory distress, 10)

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persistent vomiting, 11) abnormal bleeding, or 12) signs of shock. These criteria reflect the current WHO definition of severe malarial illness.¹⁴

Clinical procedures. After recruitment, a standardized case report form that recorded demographic and medical data was completed.¹⁵ This included details of immunizations, past medical history, and recent treatment with antimalarial drugs and antibiotics, as documented in each child's hand-held medical record book. Vaccination history was identified from the health record book where available, but it was assumed children without a documented vaccination history were unvaccinated.

The ethnicity of each child was defined according to the province of origin of his or her parents. Children with ethnicity defined as "Madang" or "Sepik" had both parents originating from these provinces, respectively. "Mixed" ethnicity was defined as neither "Madang" nor "Sepik," but with both parents from one or other of Madang, Sepik, or Morobe provinces. The remaining children with ethnicity recorded were classified as "Other."

Trained study nurses carried out clinical assessments on admission. One of two study clinicians (L. M. and M. L.) conducted regular nurse training to ensure the consistency of these assessments. In addition, one study clinician performed a detailed neurological examination on all children admitted with a BCS ≤ 4 , regardless of the time of admission. A BCS ≤ 2 was considered deep coma and a BCS ≤ 4 as impaired consciousness at 0.5, 1, or 6 hours after correction of hypoglycemia, a seizure, or parenteral anticonvulsant therapy, respectively. Respiratory distress was considered present if the child had 1) deep breathing, 2) intercostal in-drawing, 3) subcostal recession, 4) persistent alar flaring, 5) tracheal tug, and/or 6) respiratory rate > 60 /minute. Because of variable availability, chest radiography was performed in a minority of children with respiratory symptoms. In the present analysis, we applied a mid-upper arm circumference (MUAC) < 12.5 cm to be indicative of malnutrition.¹⁶ However, in post hoc analyses we also applied a cutoff of MUAC < 11.5 cm to indicate severe malnutrition.

Sample collection and laboratory procedures. Where possible, up to a maximum of 10 mL of venous blood was obtained from each child at presentation. A 5-mL aliquot was collected into lithium heparin tubes and promptly centrifuged. Separated plasma was stored in aliquots at -80°C , and red cell pellets containing parasite DNA at -20°C , before analysis. A further 1–3 mL was placed in BactecTM Peds PlusTM/F bottles (Becton Dickinson, Franklin Lakes, NJ). Approximately 0.5 mL was taken for full blood examination using a COULTER[®] Ac-T diffTM analyzer (Beckman Coulter, Brea, CA). A rapid diagnostic test (RDT; ICT Malaria Combo Cassette Test [MR2]; ICT Diagnostics, Brookvale, Australia) for malaria was performed and a confirmatory blood smear prepared. Hemoglobin and blood glucose were analyzed using Glucose 201+ and Hb 201+ analyzers, respectively (HemoCue, Ängelholm, Sweden). Blood lactate was measured using Lactate ProTM (Arkray, Kyoto, Japan). Hyperlactatemia and severe anemia were defined as whole-blood lactate ≥ 5 mmol/L and hemoglobin < 50 g/L, respectively.¹⁴

Giemsa-stained thick blood smears were examined independently by two skilled microscopists who were blind to RDT and nested PCR results, with discrepancies adjudicated by a third senior microscopist. The peripheral blood parasitemia was quantified by counting the number of malaria parasites

per 200 leukocytes assuming a peripheral blood leukocyte count of 8,000/ μL . After parasite DNA extraction (QIAamp 96 DNA Blood Mini Kit; QIAGEN, Valencia, CA), nPCR was performed to detect the presence of *Plasmodium* DNA and infecting *Plasmodium* species.¹⁷ These data were used to categorize all children as having 1) confirmed severe malaria (asexual parasitemia by light microscopy [LM+] and *Plasmodium* species identified by nPCR [PCR+]), 2) indeterminate or submicroscopic infection (LM–, PCR+), or 3) non-malarial severe disease (LM–, PCR–).

Plasma samples were transported frozen and then thawed for assay of concentrations of electrolytes, urea and creatinine, bicarbonate, liver function, and C-reactive protein (CRP) using a COBAS INTEGRA[®] 800 platform (Roche Diagnostics, Mannheim, Germany) with reagents supplied by the manufacturer. Metabolic acidosis was defined as a plasma bicarbonate < 12.2 mmol/L,¹⁰ hyperbilirubinemia as a plasma bilirubin > 35 $\mu\text{mol/L}$, an acute inflammatory response as a plasma CRP > 64 mg/L, and significant liver inflammation as a plasma alanine aminotransferase (ALT) > 90 IU/mL (twice the upper limit of the reference interval). Schwartz's formula was used to estimate creatinine clearance (CrCl), with impaired renal function defined as a CrCl < 75 mL/minute.¹⁸

Inpatient care was coordinated by attending ward clinicians under PNG national guidelines.¹⁹

Data analysis. The statistical program R²⁰ (Vienna, Austria) was used for statistical analyses. Descriptive data are presented as median and IQR. Univariate comparisons of variables between groups were by nonparametric tests for continuous data or Chi-squared tests for categorical data. Backward stepwise logistic regression was applied for multivariate analyses. Candidate variables were included based on biological plausibility or $P < 0.10$ on bivariate regression analysis. We chose the most parsimonious logistic regression model using the minimum Akaike's Information Criterion, after the removal of each variable. A two-tailed significance level of $P < 0.05$ was used throughout. To retain individuals with missing data for at least one variable in multivariate analyses, missing data were imputed using a multivariate imputation method (R package: AMELIA).²¹ Logistic regression modeling was then performed on each of the five imputed datasets and the final adjusted odds ratios (aORs) determined by calculating the mean from each model.²²

RESULTS

Patient characteristics. Of the 4,360 children admitted during the study period, we screened 3,019 children aged between 0.5 and 10 years for inclusion in the study. Of the eligible children with severe illness, the parents or guardians refused consent for 85 (9%) children (Figure 1). A total of 843 children had at least one clinical feature indicative of severe illness and were successfully recruited. Twenty-three and 33 children did not have PCR results or discharge outcome data available, respectively, and could not be categorized in terms of malaria status and survival status. As a result, 787 children had evaluable malaria status and outcome for inclusion in the analysis. This included 336, 145, and 306 children with confirmed malaria, indeterminate, or non-malarial severe illness, respectively (Figure 1).

Clinical course. A total of 79 (2.6%) children screened for the study died during hospitalization. This included 58 (6.6%)

FIGURE 1. Consort diagram of children presenting to Modilon Hospital according to malaria status.

of the 787 children included in the current analysis. One child died without malaria status available and 20 children, who were screened and not enrolled, also died (Figure 1). Of this latter group, four children died on arrival at Modilon Hospital before consent could be obtained and five had no signs of severity on admission but died during the admission. Of the remaining 11 children (all of whom fulfilled the criteria for severe illness), three were excluded because venepuncture could not be performed, the parents of one child declined participation in the study, and seven were not recruited because of other logistical reasons.

The 33 children without an evaluable outcome were not included in the final analysis because the parents left the ward with their child before the planned discharge date (Figure 1). These children had a higher rate of malnutrition (11 [33%]) than the children who survived until discharge (101 [14%]; $P = 0.005$). Children with severe malnutrition (MUAC < 11.5 cm) were even more likely to leave the ward before the planned discharge date (9 [26.4%]) than those without any or moderate malnutrition (41 [5.5%]; $P = 0.0001$).

Predictors of mortality. The demographic, clinical, and laboratory features according survival and malaria status are shown (Table 1). Six (1.8%) children with confirmed malaria infection died. This included four children with mixed *P. falciparum*/*P. vivax* infection, and one each in whom *P. falciparum* and *P. vivax* was identified as the only infecting *Plasmodium* species. The characteristics of these children are described in detail elsewhere.²⁴ Of the patients with severe non-malarial or indeterminate severe illness, 37 (12.1%) and 15 (10.3%) died, respectively.

Common clinical or syndromic diagnoses among children with severe non-malarial disease included lower respiratory tract infection (LRTI; 35%), encephalopathy (13%), tuberculosis (12%), acute bacterial meningitis (ABM; 9%) and gastroenteritis (9%). In children with an indeterminate malaria status, the most common clinical diagnoses included LRTI (19%), severe malaria (16%), ABM (15%), gastroenteritis (12%), and encephalopathy (9%).

The most parsimonious logistic regression model comprised six variables that were independently associated with mortality. Hyperlactatemia (OR [95% CI]: 2.85 [1.24–6.41], $P = 0.01$), malnutrition (2.92 [1.36–6.23], $P = 0.005$), and renal impairment (3.85 [1.53–9.24], $P = 0.002$) were binary variables associated with mortality. Plasma albumin concentration was also an independent inverse predictor (0.93 [0.88–0.98], $P = 0.004$), with a 7% increase in risk of death for every 1 g/L decrease in plasma albumin. Deep coma (BCS ≤ 2) was also an independent predictor (10.3 [4.77–23.0] versus a normal BCS, $P < 0.0001$) but not impaired consciousness (BCS 3 or 4; 1.45 [0.50–3.80]). Confirmed malaria was inversely associated with death (0.11 [0.03–0.30] versus non-malarial severe illness, $P < 0.0001$), whereas indeterminate malaria was not (0.79 [0.33–1.77]).

There were a number of variables associated with mortality on univariate analyses but not in the multivariate analysis (Table 1). These included (unadjusted ORs [95% CI]) respiratory distress (2.09 [1.22–3.58], $P = 0.007$), neck stiffness (4.10 [2.15–7.52], $P < 0.0001$), hemoglobin level (0.99 [0.98–1.00], $P = 0.04$), platelet count (1.002 [1.000–1.003], $P = 0.004$), and abnormal leukocyte count (3.33 [1.61–6.51], $P = 0.003$).

There was no difference in case fatality rate between children with moderate malnutrition (MUAC 11.5–12.4 cm) or severe malnutrition (MUAC < 11.5 cm; 13% versus 19%, respectively, $P = 0.32$).

After multiple imputations, we repeated logistic regression modeling on each of the five complete datasets to determine mortality risk factors. Deep coma (average OR [AOR] 11.28), hyperlactatemia (AOR 3.59), renal impairment (AOR 3.88), malnutrition (AOR 2.38), albumin (AOR 0.90), and malaria status (AOR for malaria versus non-malarial severe illness 0.14) were independently associated with mortality consistently in each case (see Table 1). In each analysis, an increase in platelet count of $1 \times 10^{12}/L$ was associated with a 0.2% increase in mortality. Metabolic acidosis, glucose, hemoglobin, and respiratory distress were associated with mortality in at least one imputed dataset, but not consistently across all

TABLE 1

Demographic, clinical, and laboratory features of Melanesian children presenting to Modilon Hospital with severe illness according to survival and malaria status

	Survived (<i>n</i> = 729)	Died (<i>n</i> = 58)	Univariate OR	Univariate <i>P</i> -value	aOR (95% CI)	<i>P</i> -value	aOR for multiple imputation†
Demographic features							
Age (months), median (IQR)	38 (21–63)	39 (15–71–67)	1.00 (0.99–1.01)	0.80	–	–	–
Male gender, <i>n</i> (%)	415 (57.1)	27 (47.3)	0.68 (0.39–1.16)	0.15	–	–	–
Ethnicity	–	–	1.33 (0.64–2.80)	–	–	–	–
Madang or Sepik, <i>n</i> (%)	601 (82.4)	50 (86.2)	–	0.47	–	–	–
Other, <i>n</i> (%)	128 (17.6)	8 (13.8)	–	–	–	–	–
Maternal education							
No education or elementary, <i>n</i> (%)	224 (31.8)	22 (41.5)	1	0.34	–	–	–
Primary, <i>n</i> (%)	368 (52.2)	24 (45.3)	0.66 (0.37–1.20)	–	–	–	–
Secondary or tertiary, <i>n</i> (%)	113 (16.0)	7 (13.2)	0.63 (0.24–1.49)	–	–	–	–
Adopted, <i>n</i> (%)	57 (7.8)	5 (8.6)	1.1 (0.46–2.68)	0.84	–	–	–
Reported bednet use, <i>n</i> (%)	590 (80.1)	43 (74.1)	0.89 (0.45–1.77)	0.75	–	–	–
Completed vaccination schedule, <i>n</i> (%)	332 (45.5)	19 (32.8)	0.58 (0.33–1.01)	0.06	–	–	–
Malnourished, <i>n</i> (%)	103 (14.3)	20 (38.4)	3.74 (2.05–6.69)	< 0.0001	2.92 (1.36–6.23)	0.005	2.38
Clinical and laboratory features							
Axillary temperature (°C), median (IQR)	37.6 (37.0–38.4)	37.8 (37.0–38.8)	1.01 (0.64–1.08)	0.18	–	–	–
Respiratory distress, <i>n</i> (%)	184 (25.2)	24 (41.4)	2.09 (1.22–3.58)	0.007	–	–	–
Splenomegaly							
None (spleen not palpable)	409 (56.1)	39 (67.2)	1	–	–	–	–
Moderate (spleen palpable and < 10 cm below the costal margin)	302 (41.4)	17 (29.3)	0.59 (0.33–1.06)	0.19	–	–	–
Massive (≥ 10 cm below the costal margin)	18 (2.5)	2 (3.4)	1.17 (0.26–4.94)	–	–	–	–
BCS							
Normal (BCS 5), <i>n</i> (%)	510 (70.0)	22 (37.9)	1	–	1	–	1
Impaired consciousness (BCS 3–4), <i>n</i> (%)	141 (19.3)	10 (17.2)	1.64 (0.80–3.56)	< 0.0001	1.45 (0.50–3.80)	< 0.0001	1.49
Deep coma (BCS ≤ 2), <i>n</i> (%)	78 (10.7)	26 (44.8)	7.73 (4.27–14.29)	–	10.3 (4.77–23.0)	–	11.28
Neck stiffness present, <i>n</i> (%)	74 (11.8)	17 (35.4)	4.10 (2.15–7.52)	< 0.0001	–	–	–
Hemoglobin (g/L), median (IQR)	86 (64–102)	92 (76–108)	0.99 (0.98–1.00)	0.04	–	–	–
Platelet count (×10 ¹² /L), median (IQR)	198 (88–318)	244 (118–403)	1.002 (1.000–1.003)	0.004	–	–	1.002†
Abnormal leukocyte count (< 4 or > 30 × 10 ⁹ /L), <i>n</i> (%)	53 (9.4)	13 (25)	3.33 (1.61–6.51)	0.003	–	–	–
Blood glucose (mmol/L), median (IQR)	7.1 (6.1–8.6)	6.6 (5.3–7.8)	1.00 (0.90–1.08)	0.94	–	–	–
Blood lactate (mmol/L), median (IQR)	2.4 (1.7–3.4)	4.2 (1.9–7.2)	1.25 (1.15–1.35)	0.0001	–	–	–
Hyperlactatemia (> 5.0 mmol/L), <i>n</i> (%)	93 (13.2)	20 (35.7)	3.66 (2.03–6.49)	< 0.0001	2.85 (1.24–6.41)	0.01	3.59
Plasma bicarbonate (mmol/L), median (IQR)	16.4 (14.3–18.5)	16.2 (10.6–17.9)	0.90 (0.84–0.98)	0.01	–	–	–
Metabolic acidosis (< 12.2 mmol/L), <i>n</i> (%)	73 (10.4)	16 (30.7)	3.83 (1.99–7.25)	< 0.0001	–	–	–
Plasma sodium (mmol/L), median (IQR)	130 (127–133)	128 (122–131)	0.98 (0.96–1.01)	0.11	–	–	–
Plasma potassium (mmol/L), median (IQR)	3.6 (3.3–4.0)	3.7 (3.4–4.3)	0.83 (0.69–1.00)	0.03	–	–	–
Plasma C-reactive protein (g/L), median (IQR)	49 (14–119)	45 (12–100)	1.00 (1.00–1.00)	0.61	–	–	–
Plasma albumin (g/L), median (IQR)	34 (30–38)	29 (24–36)	0.90 (0.86–0.94)	< 0.0001	0.93 (0.88–0.98)	0.004	0.90
Alanine aminotransferase (IU/mL), median (IQR)	14 (10–23)	17 (11–29)	1.002 (1.000–1.005)	0.03	–	–	–
CrCL (mL/minute), median (IQR)	1,640 (131–193)	136 (91–167)	0.99 (0.98–1.00)	0.0006	–	–	–
Renal impairment (CrCL < 75 mL/minute), <i>n</i> (%)	45 (6.4)	12 (24.5)	4.74 (2.36–9.80)	< 0.0001	3.85 (1.53–9.24)	0.002	3.88
Malaria status							
Non-malarial illness	269 (35.9)	37 (62.7)	1	–	1	–	1
Indeterminate	130 (17.3)	15 (25.4)	0.84 (0.44–1.57)	< 0.0001	0.79 (0.33–1.77)	< 0.0001	0.89
Severe malaria	330 (44.0)	6 (10.2)	0.13 (0.06–0.31)	–	0.11 (0.03–0.30)	–	0.14

aOR = adjusted odds ratio; BCS = Blantyre coma score; CrCL = creatinine clearance; IQR = interquartile range; OR = odds ratio.

* The aOR from multiple imputations are the mean aOR from logistic regression analyses from five complete imputed datasets.

† aOR for platelet count (per increase of 1×10^{12} /L).

five. These variables were, therefore, excluded from further analysis.

DISCUSSION

The most important finding of the present study is that malaria is not the major cause of childhood mortality in hospitalized PNG children, despite previous evidence to the contrary.⁴ Indeed, although children with confirmed malaria accounted for 43% of presentations with severe illness, they were much less likely to die than children with other severe illnesses after adjustment for potential confounding variables. This provides strong justification for the requirement for a parasitological diagnosis before a death is attributed to malaria in PNG.⁶ Without such routine testing, epidemiological data will continue to give disproportionate weighting to the

burden of malaria and diminish the importance of potentially lethal consequences of alternative diagnoses in severely ill PNG children. The other independent predictors of death were deep coma, hyperlactatemia, hypoalbuminemia, malnutrition, and renal impairment. Although these are all recognized adverse prognostic indicators in a number of childhood illnesses in developing countries,^{4,5,7,24–26} the robust identification of malaria infection in our large sample of unselected severely ill children strengthens their pathophysiological significance.

The overall mortality in the present sample of children aged 0.5–10 years was 2.6%. The WHO 2000 criteria that were developed for severe malaria correctly predicted 94% of all deaths in this age group. Severe confirmed malaria was, however, not an adverse prognostic indicator. This contrasts with studies from Africa where malaria-associated mortality rates are up to 50%^{27–30} and may explain why the rate in the

present study was approximately half that in a cohort of African children (5%) admitted to a provincial hospital for non-trauma or elective indications.⁷ We have postulated previously that the difference between PNG and African mortality rates in severe malaria could reflect protective genetic factors, including the high prevalence of the alpha-thalassemia trait in the present cohort,³¹ relatively infrequent hypoglycemia and bacteremia in PNG children, and/or better access to quality health care in PNG compared with Africa.²³

We used blood film microscopy supported by RDTs and PCR to categorize malaria status. This was important because the children with submicroscopic or indeterminate infections comprised a heterogeneous group with clinical and laboratory characteristics spanning malaria and non-malarial disease, but with a relatively high mortality suggesting a predominant non-malarial etiology. Even if microscopy, RDT, and PCR are not available at the time of presentation to guide clinical management, including risk stratification by malaria status, they are now widely available in developing countries and could be performed *post mortem* to inform the cause of death.

Most studies exploring risk factors for pediatric mortality in developing countries have focused on selected patient groups such as children with pneumonia,^{25,26} diarrhea,^{24,32} or malnutrition as well as malaria.²⁸ However, the clinical presentation of many severely ill children could indicate a number of diagnoses, many of which have overlapping clinical features.³³ This can make diagnostic categorization, and thus identification of disease-specific mortality, difficult. There are no published studies that have examined readily available simple prognostic clinical and laboratory variables, as opposed to specific diagnoses that predict mortality. This includes point-of-care tests such as malaria RDTs³⁴ and lactate which are becoming more widely available and affordable.

The strongest risk factor for mortality in the present study was deep coma. In a comparable study in hospitalized Kenyan children, impaired consciousness as defined by inability to localize pain was also the most important risk factor for mortality and, consistent with this, a major variable in a multivariable prediction score developed by the investigators.⁷ The degree of coma is an adverse prognostic indicator in severe pediatric infections in general,^{35–37} as well as in severe malaria.³⁸ We have found previously that PNG children with severe malaria had lower proportions of cerebral malaria and hypoglycemia than African children,³⁹ but that severe malaria due to mixed *P. falciparum*/*P. vivax* infections appeared to have a poorer prognosis.²³

Malnutrition is consistently identified as a risk factor for mortality in pediatric studies of severe pneumonia,²⁶ diarrhea,^{32,40} and malaria.²⁸ We assessed malnutrition as a MUAC < 12.5 cm, a simpler method than calculating Z-scores for body mass index-for-age or weight-for-age as has been done elsewhere.⁷ Using this metric, malnutrition was present in 16% of the present children, and it was independently associated with mortality. Of note, there was no statistically significant difference between case fatality rates between those children with moderate or severe malnutrition (MUAC < 11.5 cm) in the present study. Nevertheless, the impact of malnutrition may have been underestimated in the present study because of the nine children with severe malnutrition who left the ward before planned discharge and were, thus, not included in analysis. In PNG, it is culturally appropriate and common for families to take children back to die in their villages rather than in a hospital.

A low plasma albumin level was a risk factor for death that was independent of malnutrition. Its etiology is likely to be complex and could include developing multiple organ failure with hepatic dysfunction;⁴¹ intestinal protein loss, especially through diarrheal disease;⁴² and/or nephrotic syndrome.⁴³ We did not have the serial laboratory data to examine the presence and severity of these factors. Renal impairment was another independent mortality risk factor that can arise because of a variety of causes including infections, dehydration, and drugs.⁴⁴ Hyperlactatemia is a robust predictor of mortality in studies of severe malaria^{45,46} and sepsis,⁴⁷ but it has not been examined systematically in studies of unselected hospitalized children. Blood lactate is inexpensive and simple to measure with commercially available point-of-care tests and in the present study was independently associated with mortality.

Although we did not examine the relationship between the delay in presentation to the hospital and mortality, we did not find that the distance between the home villages and hospital influenced outcome. However, most children lived relatively close to the hospital and the geographic distribution of those who died reflected that of the sample as a whole. Socio-demographic variables unrelated to mortality included vaccination and adoption status.

This study has limitations. The data collection for this study was completed 9 years ago. As a result, the relative contribution of malaria to mortality may have changed over time and may not necessarily reflect the current situation. These data also cannot be applied to neonates and children younger than 6 months as they were excluded from the present study. Although it is likely that a large burden of infant and under-5 mortality is from the very youngest of children, our previous studies from this site indicate that severe malaria is uncommon in the youngest children.²³

The present study, conducted using readily available clinical and laboratory features in a large cohort of hospitalized Melanesian children with severe illness, confirmed a range of risk factors for mortality found in other geoepidemiological contexts. These included deep coma, malnutrition, hyperlactatemia, hypoalbuminemia, and renal impairment. In this study, Malaria was inversely associated with death in contrast to studies conducted in sub-Saharan Africa, highlighting the importance of accurate diagnosis at the bedside through RDTs or in the laboratory through blood film microscopy and, if available, PCR.

Received September 22, 2018. Accepted for publication December 10, 2018.

Published online February 18, 2019.

Acknowledgments: We thank the children and their parents/guardians for participation in this study. We are also grateful to the medical and nursing staff of the Pediatric Ward and Children's Outpatient Department at Modilon Hospital; the research nurses, microscopists, data management team, and support staff of the Papua New Guinea Institute of Medical Research for clinical and logistic assistance; and the laboratory and research staff of the Fremantle Hospital Biochemistry Department for biochemical testing.

Financial support: This study was funded by a National Health and Medical Research Council (NHMRC) of Australia grant (#513782) and the PNG Institute of Medical Research through the PNG Government. We also acknowledge infrastructure support from the MalariaGen Genomic Epidemiology Network. M. L. was supported by a Fogarty Foundation scholarship; L. M. by a Basser scholarship from the Royal Australasian College of Physicians and an NHMRC scholarship; and T. M. E. D. by an NHMRC Practitioner Fellowship.

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