

Clinical trials are still needed to test transfusion thresholds for African children with severe malaria.

An analysis of 26,106 patients admitted to six hospitals in five sub-Saharan African countries revealed transfusion to be associated with decreased odds of death in site- and severity-adjusted analysis (OR=0.50; 95%CI 0.42-0.60). (1) This association could be subject to immortal time bias (ITB) (2) if many patients died before having an opportunity to receive transfusion – a possibility we explicitly stated in (1). ITB can be addressed by modeling treatment as a time-dependent variable (3); however, time of transfusion was not available in our study nor was it available in Leopold, Watson, et al (4). At issue is whether to exclude early deaths in the analysis when time of transfusion is unknown. While including early deaths could lead to overestimation of the protective effect of transfusion in some scenarios, excluding early deaths could introduce new biases that lead to over- or under-estimation of the true effect depending on the probability of death, the probability of transfusion, and the true effect of transfusion on death which can vary over time. With this caveat in mind, here we provide an alternative estimate of the association of transfusion on death after excluding deaths that occurred in the first four hours for comparison with the analysis in (4).

We calculated times of death or discharge on 22,626 patients with available data (5) and excluded 176 patients (29 of which had been transfused) who died within 4 hours of hospital admission. In analysis adjusted by site and severity as in (1), transfusion remained associated with protection from death (OR=0.64; 0.52-0.78). The low proportion of deaths (16.5%) and high rate of transfusion (16.5%) in the first four hours limited this potential source of bias in our study. The exclusion of early deaths did not substantially change the estimated association of transfusion on death, suggesting that our original result should not be attributed to bias from early deaths that occurred before transfusion could be given. We stand by the original result and subsequent analysis which we interpreted cautiously within the limitations of the observational study design and available data.

In contrast, the association of transfusion on death estimated in (4) changed substantially after exclusion of deaths in the first four hours, suggesting ITB may have impacted their results. Given the potential for exclusion to introduce new and unpredictable biases, their clinically implausible conclusion that transfusion is not associated with severe malaria outcomes should be viewed with caution. There are several reasons why our estimate might differ from theirs. We enrolled African children only, but they pooled two studies of Vietnamese adults with one study of African children, despite important differences in epidemiology and pathophysiology of which they are well aware. We included all sites in the analysis, but they excluded the African site with the highest rate of transfusion. We measured lactate directly and modeled its effect on transfusion while they imputed lactate values for 80% of patients and yet retained lactate as a central node in their pathogenesis model.

Our analysis supports current transfusion guidelines and goes further to highlight the importance of physiological signs of inadequate perfusion, such as impaired consciousness and elevated blood lactate, in modulating the response to transfusion at varying hemoglobin levels. Our observations raise the question of whether children with severe malaria complicated by impaired consciousness or elevated blood lactate would benefit from transfusion when the anemia is of moderate severity. This question deserves a rigorous, empirical examination.

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