Summary

Background

Mortality from severe acute malnutrition (SAM) continues to be high among hospitalized children in developing countries. Due to their impaired immunity, these children experience a high burden of infections which contributes to this mortality. This calls for more studies to further understand their immune functions. It is known that children with SAM experience severe thymus atrophy as a sign of immune impairment which is reversible during nutritional rehabilitation. The delay in immune recovery compared to nutritional recovery may keep nutritionally recovered children still at risk of infections. Hence, the correlates to thymus size at admission as well as predictors of recovery need to be described so that clinicians taking care of them can identify those who have more severe effects on their immunity and those who experience slower immune recovery. Similarly, since mortality from SAM among hospitalized children remains unacceptable in most resource limited settings, studying the predictors of mortality may identify those at highest risk who need to be targeted.

The purpose of this thesis was to describe the correlates of thymus size at admission and its correlation with T cell receptor excision circles (TRECs) among children with SAM. In addition, we determined predictors of thymus gland recovery during nutritional rehabilitation as well as the predictors of mortality among children admitted with SAM.

Methods

The studies were nested in a randomized controlled study. Paper 1 was a cross sectional study among children aged 6-59 months admitted with SAM and healthy controls. At admission, thymus size was determined using ultrasound scan and linear regression was used to identify clinical and laboratory correlates of thymus size. Real time PCR was used for quantification of TRECs. Pearson correlation was used to determine correlation between thymus size and TRECs. Paper 2 was a prospective design in which all the study participants in paper 1 received standard of care and either probiotics or placebo during hospitalization until 8-12 weeks post-discharge. They were followed up and their thymus size was measured again at discharge and at 8 weeks post-discharge. Clinical and laboratory predictors of recovery of the thymus were determined using linear regression during inpatient therapeutic care (ITC) and outpatient therapeutic care (OTC) separately. All children were monitored daily until discharge or death during
hospitalization. Paper 3 determined the predictors of death during inpatient therapeutic care using Cox regression analysis.

**Results**

The mean thymus area was significantly lower among the 388 children with SAM compared to the 27 healthy controls. Thymus size was positively correlated with all anthropometric measurements at admission, current breastfeeding and suspected tuberculosis but negatively correlated with duration of illness ≥2 weeks before admission. Our study found no correlation between thymus size and TREC measurements but the interpretation of these results is limited since a high proportion of TREC measurements were below detection limit.

Our study found a significant increase in thymus size throughout nutritional rehabilitation but there was a higher recovery rate during OTC. Probiotics did not affect thymus recovery neither during ITC nor OTC. During both ITC and OTC, weight gain and increase in mid-upper arm circumference (MUAC) positively predicted thymus recovery while more severe caregiver-perceived illness and anaemia (haemoglobin <8g/dl) at admission were negative predictors. Negative predictors of thymus recovery in the ITC period included grade 3 oedema, dermatosis, C-reactive protein (CRP) >15mg/L and higher neutrophils. During OTC alone, weight-for-height z scores and MUAC at discharge were positive predictors of thymus recovery while HIV infection was a negative predictor.

The mortality rate during the inpatient period was 9.8%. Predictors of mortality included HIV infection, signs of bacterial infections like high neutrophil blood counts, suspected sepsis as well as diarrhoea at admission. In addition, signs of pneumonia like tachypnoea, chest indrawing, and oxygen saturation below 94% predicted mortality. Children with severe dermatosis manifesting with skin ulcers, lack of appetite and females also predicted mortality.

**Conclusion**

Thymus size is markedly reduced among children with SAM, but anthropometric measurements and breastfeeding at admission were associated with a bigger thymus. Thymus size improved during nutritional rehabilitation but had not attained the size of healthy controls by 8 weeks post-discharge. This delay in immune recovery suggests that anthropometric recovery alone may not be enough to discharge them from OTC as is the current practice. Our study identified children
whose immune recovery is slower and may require closer monitoring during nutritional rehabilitation. Since diarrhoea, pneumonia, suspected septicaemia and HIV were major predictors of mortality, there is a need for improved prevention and management of these conditions among children with SAM. We are unable to make conclusions on TREC's due to methodological issues and therefore recommend another study using a different technique to study TREC's at admission and their trends during nutritional rehabilitation in order to understand the effect of thymus gland size on function.