Being underweight is a well known factor that predisposes patients to the development of TB [2, 3]. However, TB may also lead to significant wasting and debilitation [4]. In a large-scale prospective TB treatment trial, being underweight at baseline [5] and the absence of an early gain in weight during chemotherapy have been associated with an increased risk of relapse [6]. As high as 61% of relapsed patients in that trial occurred among those $\geq 10\%$ underweight at diagnosis and in turn 62% of these occurred in those failing to gain $>5\%$ weight in the initial phase of treatment [5, 6]. However, in the absence of randomised intervention targeted on nutritional status, the question still remains whether the weight gain associated with TB chemotherapy just reflects successful control of the disease, or further augments the host defence against the mycobacterial pathogen.

Miliary TB carries a very substantial degree of mortality. If poor nutritional status does predispose patients to major complication(s) and death, specific intervention targeted at improving the nutritional status would be indicated to decrease the associated morbidity and mortality. Unfortunately, systematically collected data are notably scarce in this area. Notwithstanding that, a cholesterol-rich diet has been shown to accelerate bacteriological sterilisation in pulmonary TB [7]. Micronutrients have also been shown to decrease the risk of reversion of sputum culture to positivity after initial conversion in the first month in both HIV-infected and noninfected patients, but there was no significant effect on mortality [8]. Overall, micronutrients benefitted HIV-uninfected subjects the most in that trial, whereas the opposite was the case in a previous trial in the same locality [9]. Although micronutrient deficiencies often occur in the midst of global nutritional deficits, neither of these trials contained specific information on total protein-calorie intake or serial measurements of body weight or body mass index to allow inference to be drawn on the effect of the overall nutritional status.

Systemic inflammatory responses also appear to play an important role in the development of severe complications in tuberculosis. In the study by Kim *et al.* [1], an elevated C-reactive protein level was also shown to be an independent predictor of acute respiratory failure [1]. Poor appetite and decreased food intake may also be associated with advanced tuberculosis disease. Adjunctive corticosteroid administration during tuberculosis treatment has been found to afford earlier and more significant body weight gain, albeit causes no differences in sputum bacteriological conversion and disease relapse rate [10]. Such a form of treatment might also merit reappraisal in clinical situations associated with heightened inflammatory responses, especially when simple dietary manipulation does not appear to result in a significant improvement in nutrition status.

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STATEMENT OF INTEREST

None declared.

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To the Editors:

We have read with great interest the article by Kim *et al.* [1] on the relationship between changes in parameters reflecting nutritional deficit, such as hypocholesterolaemia and prognosis in miliary tuberculosis. We wonder if the value of hypocholesterolaemia in predicting progression to respiratory failure and poor outcome in their patients was not exclusively related to malnutrition (intended as nutritional deficit), but was also related to more severe underlying infection. Indeed, in recent years conventional markers of malnutrition, such as hypocholesterolaemia, have also become recognised as markers of inflammation and severity of illness, for instance in severe infection [2–4]. Curiously, a historical reference for this more recent concept is a 1911 article on febrile tuberculosis [5].

We are involved in using hypocholesterolaemia as a marker of sepsis and severity of illness in critically ill postoperative patients. We often find that sepsis is associated with

cholesterol levels even below $1.0 \text{ mmol}\cdot\text{L}^{-1}$, independently of the underlying nutritional state, and find that persistently severe hypocholesterolaemia is associated with poor outcome [3, 4].

Perhaps a more severe underlying infection might help to explain, at least in part, the poor prognostic implications of hypocholesterolaemia in tuberculosis [1]. It would be interesting to observe the correlation with the level of C-reactive protein.

In sepsis, an unresolved issue is whether acute hypocholesterolaemia merely reflects severity of disease, or it actively contributes to poor outcome. The differences between tubercular infection and surgical sepsis do not allow generalisations, however the article by Kim *et al.* [1] also offers an interesting insight into this problem. Several hypotheses support the view that the low availability of cholesterol in sepsis may impair adequate synthesis of stress hormones, and the adequate synthesis and function of cells taking part in host defence [4]. The latter also seems to be the case with tubercular infection [6, 7] and, interestingly, oral or parenteral cholesterol supplementation has been used or proposed in both conditions [6, 8].

This aspect still deserves satisfactory assessment although, despite the apparent modernity of the issue, a 1920 article on pneumonia patients [9] was already observing that hypocholesterolaemia is a marker of the activity of infection and is associated with prognosis, white blood cells and pus have a high content of cholesterol and that cholesterol might be associated with anti-toxic properties.

Of course, the importance of an adequate nutritional state in tubercular infection [1] remains fundamental, independently of the interpretation of the components of hypocholesterolaemia, and we congratulate again the authors of the Kim *et al.* [1] study for their interesting work.

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STATEMENT OF INTEREST

None declared.

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From the authors:

We would like to thank C.C. Leung, D. Aggarwal, I. Giovannini and their colleagues for their interest and important comments about our recent paper and for giving us the chance to discuss the details in replying to their letters.

In regards to the comment of C. Leung and W. Yew, we totally agree that randomised intervention targeted on nutritional status is essential to explain its role in the morbidity and mortality in patients with tuberculosis (TB).

I. Giovannini and D. Aggarwal and colleagues pointed out that hypocholesterolaemia and severe lymphocytopenia might not be good surrogate markers for malnutrition and these parameters could be confounding factors in determining the outcome of miliary tuberculosis (MTB). This is a very important comment. Because these serum surrogate markers are not specific for any disease or condition and they may be affected with various conditions such as malnutrition [1–2], systemic inflammatory conditions including severe injury and sepsis [3–6], these surrogate markers should be interpreted carefully according to the study population in which the markers were applied.

We have looked into the characteristics of our study population. Total lymphocyte count (TLC) showed significant correlation with the nutritional marker, such as the value of body mass index (BMI; Pearson correlation coefficient 0.305; $p=0.026$) and serum level of albumin (Pearson correlation coefficient 0.366; $p=0.005$) and cholesterol level was significantly correlated with the serum level of albumin (Pearson correlation coefficient 0.425; $p=0.001$).

In addition, the correlation between TLC and C-reactive protein (CRP) presented as a systemic inflammation marker was weak in our study population (Pearson correlation coefficient -0.264; $p=0.064$) and the mean value of CRP didn't show a statistically significant difference between the groups classified with the presence of severe lymphocytopenia