cholesterol levels even below 1.0 mmol·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

(0.122 ± 0.099 g·L^{-1} for the group with severe lymphocytopenia *versus* 0.078 ± 0.085 g·L^{-1} for the group without severe lymphocytopaenia; p=0.101) or the presence of hypocholesterolaemia (0.122 ± 0.086 g·L^{-1} for the group with hypocholesterolaemia *versus* 0.091 ± 0.0941 g·L^{-1} for the group without hypocholesterolaemia; p=0.417). These findings may suggest that severe lymphocytopaenia and hypocholesterolaemia have reflected the status of malnutrition in our study population and that the effect of systemic inflammation to the lymphocytopenia and hypocholesterolaemia was expected to be minimal, even if it may be present.

GIOVANNINI, CHIARLA and colleagues [4–6] have presented the outstanding articles about the nutritional effects on the various situations, especially postoperative conditions. Hypocholestrolaemia in patients undergoing surgical interventions and in those with multiorgan failure and sepsis was well described and it has been explained by the down-regulation of hepatic synthesis and metabolic utilisation [4]. Hypocholesterolaemia after surgery or severe traumatic injury could be partly explained by dilutional effects with resuscitation [7]. In our study population, patients with a postoperative condition or undergoing hepatectomy were not included and hypocholesterolaemia in our study group could be explained by metabolic utilisation rather than other hypotheses. The inflammatory response is mediated by interleukin-6 and tumour necrosis factor-α negatively regulates the lipoprotein metabolism [8]. These factors are also increased in TB [9]. In the report by KUZUAY *et al.* [10], which showed the lack of correlation between TLC and nutritional status in the elderly, the mean age of elderly subjects was 78.6 ± 7.6 yrs (65–95 yrs) and their BMI was 21.8, 21.2 and 22.6 kg·m^{-2} in each subgroup [10]. In our study, only 21 (37.5%) out of 56 patients were elderly subjects and their BMI was 19.7 kg·m^{-2}. The mean value of BMI (19.3 ± 2.8 *versus* 19.7 ± 2.2 kg·m^{-2}; p=0.589), TLC (12.9 ± 12.8 *versus* $8.5 \pm 5.6 \times 10^5$ cells·L^{-1}; p=0.082), cholesterol (3.3 ± 1.2 *versus* 3.6 ± 1.3 mmol·L^{-1}; p=0.485) and albumin (31.0 ± 7.3 *versus* 30.1 ± 6.2 g·L^{-1}; p=0.639) were not different between the younger and elderly group, although as a trend the TLC was lower in the elderly group. Therefore, the result from the study by KUZUAY *et al.* [10] could not be directly extrapolated to our study population.

Nevertheless, we have acknowledged that our retrospective study has the limitation in finding the direct causal relationship between nutritional deficit and outcome of MTB and that surrogate markers for malnutrition including hypocholesterolaemia and lymphocytopaenia might have roles in monitoring other conditions such as systemic inflammatory response or severe infection.

We appreciate the valuable three letters and we hope that our retrospective study can provide momentum to recruit further prospective randomised studies to explain the roles of malnutrition including hypocholesterolaemia and severe lymphocytopenia and the nutritional intervention in the course of tuberculosis.

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STATEMENT OF INTEREST

None declared.

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