Reply to Kontoyiannis

To the Editor We thank Dr Kontoyiannis for his interest and we appreciate his useful insights regarding our study. As highlighted by Dr Kontoyiannis, invasive aspergillosis (IA) invariably occurs in a complex clinical setting in which underlying hematologic disease, administered treatment, and concomitant disease processes can all influence the resultant host response.

We had found that a persistence of elevated proinflammatory interleukin-6 and C-reactive protein at 1 week after initiation of antifungal therapy was associated with adverse outcome in a cohort of patients with IA recruited in a clinical trial [1]. While the intricacies of immune pathogenesis in IA remain to be fully understood, we cannot exclude that they are due to the evolution of underlying hematologic disease. One should also appreciate the fact that these cytokines are often associated with an infectious process and, in the context of our study, may reasonably be explained by the clinical course of IA. We have alluded to both aspects of infection and hematologic malignancy by discussing that: (1) the cytokine trends may be indicative of the host's incapacity to effect an appropriate antimicrobial immune response against the pathogen, while also making reference to a recent proposition that an uncurbed proinflammatory response may paradoxically facilitate the pathogenesis of IA [2]; and (2) similar biomarker trends were incidentally also observed in hematopoietic stem cell transplant recipients (HSCT) [3] and patients with sepsis [4]. Likewise, it is certainly plausible that neutrophil levels in the host could have an influence on the distinct results between our study and that of Roillides et al [5], as indicated. We thank Dr Kontoyiannis for highlighting these points as discussed in the article.

The significance of these findings, however, lies in that these distinct biomarker trends were observed de novo during the course of managing the disease in a sizable cohort of patients with IA who primarily had pulmonary IA, as would have been encountered by clinicians at the bedside. The underlying diseases in the study cohort leading to IA was diverse: patients recruited had the various types of leukemias and lymphomas, had undergone autologous and allogenic HSCTs requiring appropriate chemotherapeutic regimens, and were at different stages of their hematologic diseases [1]. Approximately one-quarter of the patients had documented coinfections at various points in their illness, although the rate of mortality attributable to non-IA causes was not high. Given these mitigating circumstances, it would not have been easy to correct for all of the aforementioned complex variables during analysis. Nonetheless, to facilitate objective assessment of the utility of these biomarkers, we had depicted both the receiver operating curve diagrams with areas under the curve, as well as sensitivity and specificity values for the various cutoff levels that we deemed appropriate.

We agree that a well-designed, prospective controlled trial examining cytokine and/or chemokine response in a large cohort of patients with IA would be ideal, and we look forward to the challenge of conducting such a study. Until then, it is hoped that our current study has provided the clinical basis for the potential utility of biomarkers, especially C-reactive protein, as surrogate indicators of treatment response and lays the foundation for additional research on understanding host immunes response during IA.

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Louis Y. A. Chai,[1,2] and Mihai G. Netea,[1]
Bart-Jan Kullberg[1]

[1]Department of Medicine, Radboud University Nijmegen Medical Center and Nijmegen Institute for Infection, Inflammation and Immunity (N4i)Nijmegen, the Netherlands; and [2]Department of Medicine, National University Health System, Singapore

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Correspondence: Louis Chai, MD, PhD, Department of Medicine, National University Health System, Singapore, NUHS Tower Block, 1E Kent Ridge Road, Singapore 119228, Singapore (chailouis@hotmail.com).

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