Reply to Mikulska et al

To the Editor—We appreciate Mikulska and colleagues’ response [1] to our article [2]. The authors analyzed the effect of the serum galactomannan index (GMI) level on mortality in allogeneic hematopoietic cell transplant (HCT) recipients that were monitored using twice-weekly GMI screening, in contrast to our clinical sign and symptom–based approach. We were pleased to note that the analysis by Mikulska et al was consistent with our finding that a positive serum GMI is associated with higher mortality in patients with invasive aspergillosis (IA). Their analysis suggests that the link between GMI levels and mortality may extend to screening.
strategies based on clinical risk, in addition to those based on clinical signs and symptoms. However, we do not believe that the data presented in our study and in the letter by Mikulska et al support a specific GMI screening strategy over the other.

Extrapolating from the association between higher serum GMI levels and higher mortality, Mikulska and colleagues postulate that a screening strategy that results in lower serum GMI levels at the time of IA diagnosis may be superior. The authors suggest that among positive tests, the serum GMI values in their cohort were significantly lower than those found in our study. This comparison is difficult to interpret: While our study had a higher percentage of patients with a GMI $\geq 1.5$ (36% vs 16%), the median serum GMI value for all patients was similar in our cohort and the cohort studied by Mikulska et al (0.97 vs 1.03). As patient samples were not tested independently at both institutions, potential differences in assay lots and testing procedure were not accounted for in the comparison. Many confounding factors exist in comparing patient cohorts from different institutions, including different underlying morbidities, incidence rates of IA, and use of fungal prophylaxis.

Mikulska and colleagues identified 57 patients with probable IA, with 50 (88%) of these identified using serum GMI; the remaining 12% were identified by an undisclosed method. To identify these 50 patients, however, 439 patients were screened and an unknown number of serum GMI tests were carried out. The mortality analysis uses 7 patients as the comparison group, which limits the power and ability to perform a multivariable analysis. Because patients may have had multiple serum GMIs prior to meeting a probable IA diagnosis, the analysis would have been strengthened if the full history of longitudinal GMI results were included in the analysis in a time-dependent manner.

The practice of using serum GMI testing in asymptomatic allogeneic HCT recipients or in allogeneic HCT recipients with clinical signs and symptoms compatible with IA varies based on institution. Although galactomannanemia can precede clinical symptoms [3, 4], the impact of false-positive tests, of additional costs and risks (eg, imaging), and of patient inconvenience and distress associated with systematic testing has not been studied, nor has it been shown that detecting serum GMI at this stage leads to better clinical outcomes.

Although there are advantages and disadvantages to both IA detection strategies, neither study was designed to discern a preferred screening method. Additional, larger studies utilizing a time-varying approach and incorporating important covariates are needed to fully investigate this issue. Ultimately, a randomized prospective screening study would provide the most robust answer to this question.

**Note**

**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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