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# In Reply: Fine and Gray or Cox model?

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**Abstract:**

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Running head**:** In Reply: Fine and Gray or Cox model?

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I appreciate Arcuri LJ et al. for the opportunity to address this important issue in our study of CMV reactivation on leukemia relapse [1]. They have raised a concern regarding the potential spurious and secondary nature of the protective effect of CMV reactivation in relapse due to our statistical approach using the Fine and Gray method [2]. Through simulation results, they advocated for the use of a cause-specific Cox model, treating competing events as censoring, to demonstrate our findings.

First of all, I would like to clarify that we employed cause-specific Cox models with CMV reactivation and acute GVHD treated as time-dependent covariates in our original paper [1]. We found a protective effect of CMV reactivation on relapse using the Cox models (Table S2 in the original paper). While I initially considered these data sufficient for sensitivity analysis, I followed the suggestions by Arcuri LJ et al. and performed additional analysis. As a result, I also observed a significant association between CMV reactivation and decreased risk of subsequent relapse from the landmark point using the cause-specific Cox regression model (HR 0.85; 95% CI 0.75-0.96; $P = 0.010$).

Understanding the discrepancy in how these approaches handle competing events is important in selecting a statistical method. In the Fine and Gray model, patients who experience death without relapse are retained in the number at risk and are considered to have zero risk of relapse. The cause-specific Cox proportional hazard regression model treats deaths without relapse as censored observations, assuming that they have the potential to experience relapse at a

comparable rate to other individuals still at risk. The simulations by Arcuri LJ et al assume that relapse risk in patients with nonrelapse death is the same as others. However, the graft-versus-leukemia (GVL) effect is proportional to the severity of acute GVHD [3-5], and patients with severe acute GVHD often experience early mortality before relapse [6]. Given the strong association between GVHD and CMV reactivation [7], patients who develop nonrelapse death with concurrent CMV reactivation could potentially exhibit a more robust GVHD-related GVL effect if they survive. Additionally, in cases of high CMV viral load reactivation, donor immune cells might effectively eliminate CMV-infected leukemia cells, and the risk of nonrelapse death is higher in patients with a high CMV viral load and CMV end-organ disease [8, 9]. Consequently, we believe that the true risk of relapse lies between the estimated values derived from the two statistical models. Taken together, it is important to validate the protective effect of CMV reactivation on relapse using both statistical approaches, aligning with the viewpoint of Arcuri LJ et al.

Finally, I would like to comment on their simulation because the relapse and NRM rates differed significantly from our cohort, despite similar HR for NRM. I adjusted the annual relapse and NRM risks to 6% and 5%, respectively, which resulted in observed 4-year relapse and NRM rates of 19.1% (in actual cohort: 19.6%) and 18.9% (in actual cohort: 17.9%), respectively. I used the code provided by Arcuri LJ et al., with the exception of this adjustment [2]. As a result, both the Fine and Gray model and the cause-specific Cox model detected a protective effect of CMV reactivation on relapse in 6.8% and 4.2% of 1,000 simulations, respectively, which did not indicate a large difference among models (close to the alpha error at 5%). On the other hand, 99.2% of the simulations detected significant differences in NRM. I then adjusted the annual

relapse and NRM risks to 10% and 20%, respectively. In this scenario, the median 4-year relapse and NRM rates were calculated to be 22.0% and 51.8%, respectively. Notably, CMV reactivation demonstrated a significant reduction in the risk of relapse using Fine and Gray model and Cox model in 49.4% and 3.9% of the set of 1,000 runs, respectively. These simulations used identical HR for NRM, highlighting that the discrepancy between the two statistical approaches becomes more pronounced when the absolute difference of competing events between groups is high and it needs caution in such a scenario unlike in our cohort.


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## Authorship Contributions:

Y. A. designed the study, analyzed the data, and wrote the manuscript.

## Competing interests:

The author declares no conflict of interest.

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