DOI: 10.1111/ajt.15820

AJT

LETTER TO THE EDITOR

CMV merits further evolutionary and biological view

To the Editor:

We read enthusiastically the article by Nadales et al[1] that aims to validate and modify improving the predictive capacity of a prognostic score used in transplanted patients with carbapenem-producing Enterobacterales bloodstream infection (CPE-BSI) with the new variables (cytomegalovirus [CMV] disease status, lymphopenia, no source control, inappropriate empirical therapy, and interaction old score with CMV disease status in 30 days before the bacteremia). In this critique, we are focusing on evaluating the attributed risk for CPE-BSI–related mortality of CMV infection/disease along with the statistical concepts and aiming to question the biological significance of its role in the process.

The authors thought that CMV disease does not increase the death rate in their high underlying risk patients according to the unmodified mortality score but only in patients with lower underlying risk. Yet, it is not meaningful to argue how a variable can be associated with adverse outcomes among patients with a low probability of adverse outcome and disregard patients who already have a high probability of the adverse outcome. We believe that the cause of this problem is the inappropriate use of the interaction term in the score. Additionally, the authors' analysis of an adjusted Cox-regression model that does not include CMV disease variable (generally or cause-specific hazard) associated treatment regimens with all-cause mortality in the different strata of risk. After this, the authors developed an algorithm that illustrates that CMV disease status is first partitioned among low score patients. In the simplest terms, it can be defined as a situation in which biological significance is underestimated for the sake of reaching a statistical winner.

The authors presented the model in a table with the interaction term along with the interacting variables. Interaction effects indicate that a third variable influences the association between the independent and dependent variables. The literature in this field advises that the terms along with the interaction term in the model be included in order to display the significance of an interaction term. At this point, the problem that we would like to underline is the authors' inclusion of both the terms and their interaction in the new score they proposed. Including 2 terms along with their interaction to a score means counting the interaction twice: one is explicit as an interaction term and the other is implicit as the sum of the scores attributed to terms individually. To cover this methodologic problem, the authors attributed a reformative value arbitrarily to the interaction term. To be more precise, let us give an example: We may find an interaction between age and sex in a model. Yet, in this model, we do not put age, sex, and the interaction term (age*sex) together in the score. We must first explore the nature of the interaction by appropriate statistical plots and find out the implicit meaning of the interaction. To illustrate further, if we say that that men above the age of 70 might behave differently than the rest, then we need to put age as <70 and ≥70 in the score along with sex.

In addition to CMV serostatus (donor, recipients), prophylaxis, or preemptive prevention approach, CMV disease details (organ involvement and ganciclovir treatment) are not available in the article. That ganciclovir and other immunosuppressive drugs, as well as underlying chronical organ failures, are generally associated with lymphopenia (one of the score predictors) becomes another "Achilles heel" of the developed score in the article. Concisely, we think that to show CMV as an indirect additional risk factor for combination therapy preference is not the right approach.

On the other hand, we would like to point out the attributed risk of CMV infection/disease for CPE-BSI–related mortality and to question the biological significance of its role in the process, as well. CMV interacts with the hematopoietic progenitor cells in terms of immune cell differentiation and has cytokine homology[2,3] and whether CMV replication is beneficial in transplanted patients is a controversial issue.[4,5] On the other hand, CMV viremia has been observed in nontransplant and bacteremic patients regardless of the causative agent, but its effect on mortality is unknown.[6,7] Studies show that clearance of bacteremia caused by different pathogens can be made stronger in CMV-infected mice.[8] In this sense, it is highly probable that CMV is a marker of extensive stimulation of human immunity. We would like to emphasize that examining evolutionary, cellular, and functional interactions with CMV is more essential than statistical concepts.

Finally, we believe that CMV deserves more evolutionary and biological perspectives rather than being confined to statistical variables.

KEYWORDS

clinical decision-making, clinical research/practice, infection and infectious agents—viral: Cytomegalovirus (CMV), infectious disease

Ferhat Arslan

Department of Infectious Diseases and Clinical Microbiology, İstanbul Medeniyet University, Istanbul, Turkey

Correspondence
Ferhat Arslan
Email: ferhatarslandr@hotmail.com

ORCID

Ferhat Arslan https://orcid.org/0000-0001-8554-7651

REFERENCES

1. Pérez-Nadales E, Gutiérrez-Gutiérrez B, Natera AM, et al. Predictors of mortality in solid-organ transplant recipients with bloodstream infections due to carbapenemase-producing Enterobacterales: the impact of cytomegalovirus disease and lymphopenia [published online ahead of print 2019]. *Am J Transplant*. https://doi.org/10.1111/ajt.15769.
2. Zhu D, Pan C, Sheng J, et al. Human cytomegalovirus reprogrammes haematopoietic progenitor cells into immunosuppressive monocytes to achieve latency. *Nat Microbiol*. 2018;3(4):503-513.
3. Scarborough JA, Paul JR, Spencer JV. Evolution of the ability to modulate host chemokine networks via gene duplication in human cytomegalovirus (HCMV). *Infect Genet Evol*. 2017;51:46-53.
4. Schmidt-Hieber M, Tridello G, Ljungman P, et al. The prognostic impact of the cytomegalovirus serostatus in patients with chronic hematological malignancies after allogeneic hematopoietic stem cell transplantation: a report from the Infectious Diseases Working Party of EBMT. *Ann Hematol*. 2019;98(7):1755-1763.
5. Koldehoff M, Ross SR, Dührsen U, Beelen DW, Elmaagacli AH. Early CMV-replication after allogeneic stem cell transplantation is associated with a reduced relapse risk in lymphoma. *Leuk Lymphoma*. 2017;58(4):822-833.
6. Osawa R, Wagener M, Singh N. Cytomegalovirus infection in patients with sepsis due to bloodstream infections: lower risk and better outcomes in new versus already hospitalised intensive care unit admissions. *Anaesth Intensive Care*. 2016;44(5):571-580.
7. Singh N, Inoue M, Osawa R, Wagener MM, Shinohara ML. Inflammasome expression and cytomegalovirus viremia in critically ill patients with sepsis. *J Clin Virol*. 2017;93:8-14.
8. Smithey MJ, Venturi V, Davenport MP, et al. Lifelong CMV infection improves immune defense in old mice by broadening the mobilized TCR repertoire against third-party infection. *Proc Natl Acad Sci USA*. 2018;115(29):E6817-E6825.