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Authors’ Reply

We thank Matas et al. for their interest in our algorithm for reclassification of acute kidney transplant rejection.1 We agree that data-driven approaches may add value to the iteratively developed Banff classification.2 Moreover, our approach not only provides an easily accessible system for reclassification, it also overcomes the limitations of intermediate and mixed phenotypes, and adds information on disease severity, which is potentially relevant for clinical decision making.

In contrast to what Matas et al. conclude, we do not think that our algorithm’s value is diminished by the similarities between our clusters1 and Banff categories.2 On the contrary, our clusters and visual presentation1 mathematically support the validity of the Banff classification, because both the Banff system and our approach distinguish rejection subtypes primarily on the basis of tubulointerstitial versus microcirculation inflammation, and donor-specific HLA antibodies (HLA-DSA). Furthermore, the similarities between our clusters and the Banff phenotypes enable clinical interpretation of our clusters (clusters 1 and 4 representing no rejection, cluster 3 representing T cell–mediated rejection, cluster 5 representing antibody-mediated rejection). The main, and clinically interesting, differences between our clusters and Banff are (1) the elimination of the disputed borderline category; (2) the addition of “mixed rejection” cluster 6; and (3) the addition of the novel cluster 2, representing the intriguing phenotype of HLA-DSA–negative microcirculation inflammation.3

How our clusters relate to the unvalidated clusters of the Deterioration of Kidney Allograft Function (DeKAF) study4 is more difficult to assess. In contrast to our k-mean clusters, specifically intended for reclassification of acute rejection on the basis of acute lesion scores,1 DeKAF hierarchical clusters were essentially developed for differentiation of chronic injuries, mostly on the basis of features of chronicity.4 Moreover, we neither have access to the exact DeKAF algorithm nor data on the TATR (t-IFTA) lesion, which seems necessary for the DeKAF clustering.

Therefore, we concur that our algorithm, as any other, is not purely data driven but is dependent on the following human choices: (1) the clinical use, i.e., reclassification of acute rejection1 (versus chronic injury4); (2) the method, i.e., k-means clustering, which allows reclassifying new biopsy specimens without the need for retraining1 (versus hierarchic clustering,4 which is often unstable and leads to larger numbers of smaller clusters that are difficult to reproduce); (3) the included features, i.e., acute lesions and HLA-DSA1 (versus selected, mainly chronic,4 lesions but not HLA-DSA4); and (4) the biopsy specimens included in training, i.e., early and late protocol and indication biopsy specimens2 (versus later indication biopsy specimens5).

Additionally, and importantly, we chose semisupervised clustering. In our first unsupervised approach, only two main parameters contributed: (1) presence of HLA-DSA, and (2) the extent of tubulointerstitial inflammation (Supplemental Figure 1 and Supplemental Table 1).1 In unsupervised clustering, the importance of microcirculation inflammation thus seemed underestimated, as compared with extensive literature. By weakly informing the clustering on the relation between individual lesions and graft outcome, which was our final semisupervised approach, we further improved cluster stability and predictive performance and clinical interpretability. We derived the number of clusters from the proportion of ambiguous clustering; we also did not interfere with the features or their weights to compute the clusters.1

Obviously, our semisupervised approach led to some circular argument in the association between the clusters and outcome in our training cohort (Leuven); it was therefore essential to demonstrate the validity of our locked clustering algorithm, the visual presentation, and the added value beyond Banff, on totally independent cases (Paris and Lyon, in total 3835 biopsy specimens from 1989 patients; see detailed...
Supplemental Material). Additional validation on non-European cohorts, using our online tool (https://rejectclass.pythonanywhere.com), would be very valuable to further strengthen confidence in the utility of our algorithm for reclassification of kidney transplant rejection.

**DISCLOSURES**

M. Naesens reports serving as an advisor for the European Medicines Agency and on the editorial boards of several journals. O. Thaunat reports receiving research funding from bioMérieux, Bristol Myers Squibb, Immucor, and Novartis; receiving honoraria from Biotest and Novartis; serving as a scientific advisor for, or member of, the European Society for Organ Transplantation; and having consultancy agreements with Novartis. The remaining author has nothing to disclose.

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**REFERENCES**


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**Addressing Transplant Candidacy When Evaluating Safety of Direct Oral Anticoagulant Agents in Patients on Hemodialysis**

In their analysis of the subgroup of patients on hemodialysis in the Valkyrie study, De Vriese et al. do not directly address the risks and benefits of rivaroxaban in patients on dialysis who are candidates for kidney transplantation. Direct oral anticoagulant agents (DOACs) may affect transplantation because some surgeons will not proceed with transplant due to the risk of bleeding.

Although the timely discontinuation of DOACs is easily arranged before living-donor kidney transplantation, transplants from deceased donors, which account for two thirds of transplants in the United States, are nonelective procedures that do not accommodate advanced planning. The optimal time of DOAC discontinuation before surgery has not been established, particularly in patients with kidney failure. Reversal agents for DOACs remain expensive and rare and, as with DOACs, the safety and efficacy of these agents in the kidney failure population is lacking. Although table 2 of the De Vriese et al. manuscript notes one trial participant who discontinued rivaroxaban prematurely due to “registration on the transplant list,” the authors do not report how many other subjects were already on a transplant waiting list. In some transplant programs, patients may be inactivated on the waiting list when a DOAC is initiated, or sent home in the event they are called in unexpectedly for a deceased-donor kidney. The risk of a patient on DOACs being turned away for transplant increases if the organ offer comes late after recovery, when further delay in transplant would add unacceptably to the cold ischemia time. Organ offers made early, before deceased-donor organ recovery, may allow for discontinuation of the DOACs in sufficient time for the transplantation to proceed. A recent survey of transplant pharmacists emphasized the lack of evidence-based data and the variability in practice across centers and organ programs.

Patients on dialysis who have atrial fibrillation face many competing risks. Over the 18 months of follow-up in the Valkyrie study, 15 of 46 (32%) and 13 of 42 (31%) patients in the two respective rivaroxaban arms died (figure 1). Although no optimal treatment strategy exists for these complex patients, kidney transplantation is generally associated with lower