Cell-Free DNA: Proceed, but with Caution

As the interest in telehealth and remote monitoring increases,1 many transplant practitioners have turned to donor-derived cell-free DNA (dd-cfDNA) to noninvasively monitor the immunologic status of allografts. As use of this testing grows, it is important to highlight limitations in its predictive value. There are several available dd-cfDNA tests. In kidney transplantation, one of the earliest to market was AlloSure (CareDx, Inc.), the results of which were published in JASN in 2017.2 Two features of the original Circulating Donor-Derived Cell-Free DNA in Blood for Diagnosing Acute Rejection in Kidney Transplant Recipients (DART) trial2 analysis may lead to confusion when interpreting dd-cfDNA testing. First, borderline rejections with allograft dysfunction were considered “no active rejection,” even though many centers treat these findings as acute rejection.3 Table 1 is adapted from figure 1 of the DART publication.2 When the study data are reanalyzed to reclassify patients with borderline rejection associated with graft dysfunction, there were 46 patients (43%) with rejection and 61 (57%) without rejection. The assay’s sensitivity for all rejection decreases to only 41%, with specificity of 82% and negative likelihood ratio of 0.72. As a result, the test will only have a reasonable negative predictive value when the pretest probability of rejection is very low.

Second, acute cellular rejections were grouped together with antibody-mediated rejection (AMR), implying that the excellent performance of the dd-cfDNA assay in AMR also applies to acute cellular rejection. When excluding mixed rejections, only five of 30 purely cellular rejections test positive, including only half of patients with severe rejections (1B or worse). Because most kidney allograft rejections are cellular, using this test to rule out rejection will miss a significant proportion of patients.4 In our center, we diagnosed 187 kidney rejections from January 2016 to December 2019 (borderline: 82 [44%]; 1A: 33 [18%]; 1B: 28 [15%]; grade 2/3: 28 [15%]; AMR: 23 [12%]). If dd-cfDNA testing had been used to screen for immunologically quiescent patients, an overall sensitivity of 41% would have led to 110 missed rejections.

All tests have limitations. Kidney allograft biopsy, the gold standard, is invasive, uncomfortable, and subject to its own difficulties with interpretation. The dd-cfDNA assay has a role in transplantation, particularly when following AMR and microvascular inflammation. However, clinicians must recognize that many patients with rejection will have reassuring dd-cfDNA results, so negative tests must be received with caution. On the basis of currently available data, negative dd-cfDNA alone should not be considered to “rule out” rejection in cases where the pretest probability of rejection is not already low.

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REFERENCES


Table 1. Reassignment of DART trial cohort status, classifying patients with borderline changes and graft dysfunction as having T cell-mediated rejection

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total</th>
<th>dd-cfDNA&lt;1%</th>
<th>dd-cfDNA&gt;1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No rejection</td>
<td>61</td>
<td>50 (82%)</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>All rejection</td>
<td>46</td>
<td>27 (59%)</td>
<td>19 (41%)</td>
</tr>
<tr>
<td>Borderline</td>
<td>19</td>
<td>17 (89%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>1A</td>
<td>5</td>
<td>5 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>1B</td>
<td>5</td>
<td>2 (40%)</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>2A</td>
<td>1</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>AMR</td>
<td>8</td>
<td>0 (0%)</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>Mixed ACR/AMR</td>
<td>8</td>
<td>2 (25%)a</td>
<td>6 (75%)b</td>
</tr>
</tbody>
</table>

ACR, acute cellular rejection. aOne patient had mixed 1A and AMR, and one patient had mixed 2A and AMR. bThree patients had mixed borderline and AMR, two patients had mixed 1B and AMR, and one patient had mixed 2A and AMR.
Critically Ill Patients with CKD Deserve Better Mortality Prediction Scores

To the Editor,

I sincerely appreciate the article by Silberzweig et al.,1 which addresses the potential effect of health care resource rationing on patients with CKD. The authors discuss the ethical principles underpinning the scarce resource allocation systems considered in the throes of the coronavirus disease 2019 pandemic. They specifically call attention to the use of strict exclusion criteria, including ESKD, as a reason to deny a patient other life-saving treatments, such as mechanical ventilation, in the setting of crisis standards of care.1

The authors recommend that in the event that all contingency plans have been exhausted, tools such as the Sequential Organ Failure Assessment (SOFA) score should be used to determine eligibility for scarce resources.1 Although the SOFA score provides an objective estimate of mortality and is therefore a step forward from exclusion criteria, I feel it is important to point out its flaws in patients with CKD and ESKD.

The SOFA score assigns points on the basis of the absolute creatinine value at a single point in time. Because the goal of the scoring system is to assess organ dysfunction resulting from severe illness, the change in creatinine would be a much more useful metric. It is known that AKI carries an increased risk of mortality in critically ill patients,2 but the presence of CKD may modify this association. Critically ill patients with preexisting CKD who develop AKI have lower mortality than those without.3 The Acute Physiology and Chronic Health Evaluation (APACHE) score differentiates between AKI and CKD in assigning points and may be more equitable. However, because the APACHE score includes electrolyte abnormalities, its performance among patients with ESKD is moderate at best, with a tendency to overestimate mortality.4

Illness severity scores were never intended to be interpreted as a snapshot or used to allocate scarce resources. However, as noted by the authors, objective and quantitative metrics are integral to ethical triage decision making. Therefore, to provide just treatment for our patient population, we must recognize the biases in these scores and investigate better methods of assessing mortality.

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REFERENCES


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Authors’ Reply

We agree that there are limitations to the use of Sequential Organ Failure Assessment (SOFA) scores for stratification of mortality risk of patients with CKD and ESKD.1 Using a single creatinine (or daily urine volume) measurement to assess the kidney...