Response

To the Editor:

We thank Drs A. E. Mirrakhimov and E. M. Mirrakhimov and Drs Nobre and Thomas for their letters in response to our review article on rhabdomyolysis.1 We agree that elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations can be excellent clues for the astute clinician to recognize the possibility of inapparent rhabdomyolysis and to order additional testing.2 Of note, the AST to ALT ratio > 2:1 usually seen in acute rhabdomyolysis may not be present with more indolent forms of muscle breakdown, such as in inflammatory myositis.3 Unexpected elevations of lactate dehydrogenase concentrations may also be another nonspecific clue suggesting rhabdomyolysis.2

Measurement of cardiac-specific troponins is useful for cardiac injury screening, but as Drs Nobre and Thomas point out, there are still limitations of these biomarkers to diagnose acute coronary syndrome. An early study found that troponin I and troponin T levels may be elevated in patients with rhabdomyolysis.4 Other studies have suggested that troponin T level is more commonly elevated than troponin I in rhabdomyolysis due to several different etiologies.5 Interpretation of an elevated troponin concentration in patients with rhabdomyolysis may be difficult because of limitations of the assay itself6 or concomitant risk factors that could predispose to cardiac muscle injury. Further evaluation for acute coronary syndrome in patients with rhabdomyolysis and an elevated troponin concentration is best left to the judgment of the clinician caring for the patient. We strongly agree that exposure to contrast agents for diagnostic testing should be avoided if at all possible in patients with rhabdomyolysis.

Janice L. Zimmerman, MD, FCCP
Michael C. Shen, MD
Houston, TX

References


Interobserver Variability in Grading Acute Rejection After Lung Transplantation

To the Editor:

We read with great interest the article by Bhorade et al1 in CHEST (June 2013) about the interobserver agreement of grading acute rejection after lung transplantation. They indicated that the overall concordance rates for grade A and grade B biopsy specimens were 74% and 89%, respectively, and interobserver discrepancies for acute rejection were lower when pulmonary biopsies were performed earlier (≤ 6 weeks) compared with later time points. However, we would like to add more information after deeper analysis of the data and address some important concerns.

In the Bhorade et al1 study, the interobserver agreement for grade A and grade B readings were presented as the overall concordance rate, as well as that determined by treatment arm and clinical symptoms. The overall concordance rate ranged from 62% to 91%, according to the data from the tables in the article1; however, it should be noted that the interobserver agreement provided by the authors was ambiguous and requires further analysis. Therefore, we conducted k analysis to reevaluate the concordance of interpretations for acute rejection between site pathologist and central pathologist (based on the data presented in tables in the article). The score of Cohen k coefficients ranged from 0 to 1, where k scores ≥ 0.75 represent fair agreement, scores < 0.4 represent poor agreement, and the scale of 0.4 to 0.75 was considered moderate agreement. The McNemar-Bowker test was performed to estimate the diagnostic differences between site pathologist and central pathologist. After thorough statistical analysis of the data from Tables 2 and 3 in the Bhorade et al1 article, we found that...

Correspondence

Affiliations: From Houston Methodist Hospital (Drs Zimmerman and Shen); and Weill Cornell Medical College (Dr Zimmerman), New York, NY.

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site pathologists were more likely to judge the acute rejection at a higher level for both grade A readings and grade B readings (P = .000 and .002, respectively), and the \( \kappa \) scores showed poor interobserver agreement for both grade A and grade B readings (\( \kappa = 0.276 \) and 0.195, respectively).

Also, as we can see from Table 1, when the effect of the immunosuppressant type and symptoms in interobserver agreement for grade A readings were reassessed, moderate agreement for the azathioprine group was achieved (\( \kappa = 0.472 \)), whereas poor agreement for the sirolimus group, surveillance, and clinical biopsy specimens (\( \kappa < 0.4 \)) was found, and more acute rejections at a higher level were diagnosed by site pathologists when compared with central pathologists (\( P < .05 \)). Poor concordance was observed for grade B readings (\( \kappa < 0.4 \) (Table 2), and discrepancy in diagnostic ability existed between the site and central pathologists for the azathioprine group and surveillance biopsy specimens (\( P = .015 \) and .011, respectively); however, there was no difference regarding the diagnostic ability for the sirolimus group and clinical biopsy specimens (\( P = .096 \) and .146, respectively). Hence, it is important to recognize the differences in diagnostic capability for acute rejection between central and site pathologists in the context of the current grading system.

The data analysis as an addition to the article reflects that results may be confused by some factors that complicate clinical decision-making. Identification of risk factors as predictors of acute rejection after lung transplantation may facilitate the diagnosis of acute rejection and reduce morbidity. Some studies reported that patients with human leukocyte antigen (HLA) mismatches at the B and DR loci were more susceptible to acute rejection, implying that bias introduced by mismatches at the HLA-DR and HLA-B loci may affect interobserver agreement for acute rejection after transplant,

\[ 2,3 \]

which should be included in the statistical analysis. Moreover, whether the transplant type influences the interobserver agreement remains undecided.

Bhorade et al mentioned that the concordance rate of scheduled biopsy specimens was higher than that of clinical bronchoscopy.\footnote{Bhorade SM, Husain AN, Liao C, et al. Interobserver variability in grading transbronchial lung biopsy specimens after lung transplantation. Chest. 2013;143(6):1717-1724.}

Not only the blinded analysis, but the complex state of the illness per se often complicated the specimen readings when patients presented with clinical symptoms, with greater deviations made both by the site and central pathologists. Therefore, repeated blinded readings of one slide by the same pathologist as a reliable policy is a promising approach to decrease the interobserver disagreement. In addition, although further education for pathologists to improve concordance in grading acute rejection was recommended by the authors,\footnote{Schulman LL, Weinberg AD, McGregor C, Galantowicz ME, Suciu-Foca NM, Itescu S. Mismatches at the HLA-DR and HLA-B loci are risk factors for acute rejection after lung transplantation. Am J Respir Crit Care Med. 1998;157(6 pt 1): 1833-1837.} optimal modifications to the International Society for Heart and Lung Transplantation grading system for acute rejection after lung transplantation should be made with the accumulation of clinical experience resembling the evolution of TNM classification for non-small-cell lung cancer.\footnote{Correspondence to: Wenjun Mao, MD, Division of Cardiothoracic Surgery, Wuxi People’s Hospital, No. 299, Qing Yang Rd, Wuxi City, Jiangsu, China 214023; e-mail: maowenjun1@126.com © 2014 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details. DOI: 10.1378/chest.13-1788}

### Table 1—\( \kappa \) Analysis and McNemar-Bowker Test for Grade A Readings

<table>
<thead>
<tr>
<th>Type</th>
<th>Group</th>
<th>( \kappa ) Score (Patients, No.)</th>
<th>McNemar-Bowker Test, ( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppressant</td>
<td>Azathioprine</td>
<td>0.472 (251)</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>Sirolimus</td>
<td>0.244 (221)</td>
<td>.002</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Surveillance</td>
<td>0.373 (386)</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>Clinical</td>
<td>0.279 (86)</td>
<td>.000</td>
</tr>
</tbody>
</table>

### Table 2—\( \kappa \) Analysis and McNemar-Bowker Test for Grade B Readings

<table>
<thead>
<tr>
<th>Type</th>
<th>Group</th>
<th>( \kappa ) Score (Patients, No.)</th>
<th>McNemar-Bowker Test, ( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppressant</td>
<td>Azathioprine</td>
<td>0.142 (214)</td>
<td>.015</td>
</tr>
<tr>
<td></td>
<td>Sirolimus</td>
<td>0.313 (198)</td>
<td>.096</td>
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<tr>
<td>Symptoms</td>
<td>Surveillance</td>
<td>0.123 (350)</td>
<td>.011</td>
</tr>
<tr>
<td></td>
<td>Clinical</td>
<td>0.347 (62)</td>
<td>.146</td>
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