To the Editor:

We read with interest the recent report titled "High short-term mortality following lung biopsy for usual interstitial pneumonia" by Utz et al. [1]. The major implications of this study are that there is a high short-term mortality following surgical lung biopsy for usual interstitial pneumonia (UIP), and that this high risk of death is related to the procedure itself. Given the importance of surgical lung biopsy to the proper management of patients with idiopathic interstitial pneumonia, the conclusions that might be drawn from this article are concerning as they risk discouraging the use of surgical lung biopsy in the very patients who benefit from it the most (i.e., patients with atypical features of idiopathic pulmonary fibrosis who cannot be confidently clinically diagnosed) [2].

In chronically ill outpatients with interstitial lung disease, previous data have supported a low surgical risk (see table 1) [3–15]. In the largest published review, Gaensler and Carrington [15] reviewed over 500 cases (64 of which were patients diagnosed with UIP) and found the 30-day mortality of open thoracotomy to be only 0.3%. Even among patients ≥65 yrs old (the group with the highest incidence of UIP), the 30-day operative mortality for video-assisted thoracic surgery (VATS) was <1% [9]. Further, there were no deaths within the 30 days following open thoracotomy or VATS among 238 patients with UIP prospectively enrolled into a Specialized Center of Research study at the National Jewish Medical and Research Center, between 1982–1996 [16]. Many of the patients that Utz et al. [1] reported on were acutely ill, with accelerated clinical courses. Consequently, the substantially higher 30-day mortality rate reported by Utz et al. [1] (16.7%) appears to be the result of a selection bias, and should not be extrapolated to other patients in which substantial data supports a low surgical risk.

The finding of increased perioperative mortality in acutely ill patients with UIP is useful because it suggests a need for caution in deciding whether or not a surgical lung biopsy should be obtained in similar patients. Why might short-term mortality be higher in acutely ill patients? Thoracotomy and lung resection has been associated with the development of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), and also with the development of a "shock lung" syndrome after cardiopulmonary bypass and other open surgical procedures [17, 18]. These complications may be more frequent in acutely ill patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients n and n (%)</th>
<th>Procedure (n patients)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayed and Raghunathan [3]</td>
<td>61 total</td>
<td>Open thoracotomy (29)</td>
<td>1.6% at 30 days</td>
</tr>
<tr>
<td></td>
<td>20 (33) IIP</td>
<td>or thorascopy (32)</td>
<td></td>
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<tr>
<td>Miller et al. [4]</td>
<td>42 total</td>
<td>Open thoracotomy (22)</td>
<td>0% at 30 days</td>
</tr>
<tr>
<td></td>
<td>22 (52) UIP</td>
<td>or thorascopy (20)</td>
<td></td>
</tr>
<tr>
<td>Rena et al. [5]</td>
<td>58 total</td>
<td>Thorascopy</td>
<td>0% (unspecified time)</td>
</tr>
<tr>
<td></td>
<td>14 (24) IPF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vansteenkiste et al. [6]</td>
<td>24 total</td>
<td>Thorascopy</td>
<td>0% at 30 days (four patients died during follow-up)</td>
</tr>
<tr>
<td></td>
<td>4 (17) UIP</td>
<td></td>
<td>4.7% (unspecified time)</td>
</tr>
<tr>
<td>Zegdi et al. [7]</td>
<td>64 total</td>
<td>Thorascopy</td>
<td>1.9% overall</td>
</tr>
<tr>
<td></td>
<td>19 (30) IPF</td>
<td></td>
<td>5% ILD (unspecified time)</td>
</tr>
<tr>
<td>Allen et al. [8]</td>
<td>771 total</td>
<td>Thorascopy</td>
<td>&lt;1% at 30 days</td>
</tr>
<tr>
<td></td>
<td>147 (33) ILD</td>
<td></td>
<td></td>
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<tr>
<td>Jaklitsch et al. [9]</td>
<td>296 total</td>
<td>Thorascopy</td>
<td>0% (unspecified time)</td>
</tr>
<tr>
<td>Krasna et al. [10]</td>
<td>26 ILD</td>
<td>Thorascopy</td>
<td>0% (unspecified time)</td>
</tr>
<tr>
<td>Carnochan et al. [11]</td>
<td>50 total</td>
<td>Open thoracotomy (25)</td>
<td>0% (unspecified time)</td>
</tr>
<tr>
<td></td>
<td>or thoracotomy (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bensard et al. [12]</td>
<td>43 total</td>
<td>Open thoracotomy (21)</td>
<td>2.3% at 30 days</td>
</tr>
<tr>
<td></td>
<td>4 (9) UIP</td>
<td>or thoracotomy (22)</td>
<td></td>
</tr>
<tr>
<td>Ferson et al. [13]</td>
<td>75 total</td>
<td>Open thoracotomy (28)</td>
<td>12% (unspecified time)</td>
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<tr>
<td></td>
<td>or thoracotomy (47)</td>
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<tr>
<td>Boutin et al. [14]</td>
<td>75 total</td>
<td>Thorascopy</td>
<td>0% (unspecified time)</td>
</tr>
<tr>
<td>Gaensler and Carrington [15]</td>
<td>502 total</td>
<td>Open thoracotomy</td>
<td>0.3% at 30 days</td>
</tr>
<tr>
<td></td>
<td>130 (26) IIP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>64 (13) UIP</td>
<td></td>
<td></td>
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</table>

IIP: idiopathic interstitial pneumonia; UIP: usual interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; ILD: interstitial lung disease.
syndrome (ARDS) [17, 18]. The postoperative mortality when this occurs is high. It has been hypothesized that ischaemia-reperfusion injury associated with single-lung ventilation is a major mechanism of the endothelial damage. As Utz et al. [1] point out, five of the 10 deaths recorded in their study were patients that were biopsied because of accelerated declines in respiratory status, and at least two were in respiratory failure. Moreover, nine of the 10 deaths were attributable to ALI/ARDS. One can speculate that prolonged single-lung ventilation during the operation may have caused the high frequency of postoperative lung injury in this series. A prospective study, with appropriate control subjects, may provide better evidence in support of this hypothesis.

Surgical lung biopsy is important to the diagnosis and management of ~50–75% of patients with idiopathic interstitial pneumonia who do not have the classical clinical, radiological and physiological features of usual interstitial pneumonia [2]. First, such knowledge helps physicians decide the relative risks and benefits of corticosteroid therapy, a highly morbid intervention [19, 20]. The American Thoracic Society/European Respiratory Society also recommend immunomodulatory therapy in patients with idiopathic pulmonary fibrosis/usual interstitial pneumonia, a therapy not recommended for the other histopathological patterns [21]. Secondly, the prognosis for patients with usual interstitial pneumonia is distinctly worse than for other histopathological patterns [20, 22]. Estimation of prognosis is of critical importance to physicians, patients and their families, and allows for early referral to lung transplantation in progressive cases. Lastly, patients with usual interstitial pneumonia may be candidates for promising new therapies aimed at its primarily fibroproliferative pathophysiological process [23]. Given the importance of accurate histopathological diagnosis and the weight of the evidence showing that surgical lung biopsy is a well-tolerated, relatively low-risk procedure in non-acute settings, it should continue to play a prominent role in the evaluation of many patients with suspected idiopathic interstitial pneumonia.

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References
From the authors:

We appreciate the comments of H.R. Collard and T.E. King Jr and agree that surgical lung biopsy should continue to play a significant role in the assessment of patients with diffuse interstitial lung disease, particularly those without "classic" radiographic features of usual interstitial pneumonia (UIP) on high-resolution computed tomography (HRCT). We anticipated that our report would generate controversy, given the surprisingly high 30-day surgical mortality rate in patients with idiopathic UIP (idiopathic pulmonary fibrosis (IPF)) [1].

H.R. Collard and T.E. King Jr indicate that the implication of this study is that there is a high short-term mortality following surgical lung biopsy if UIP is present, and that "conclusions that might be drawn from this article are concerning as they risk discouraging the use of surgical lung biopsy in the very patients who benefit from it the most (i.e. patients with atypical features...)". These conclusions are far broader and stronger than any we expressed in our manuscript. Our data do not support such a conclusion; rather, they only raise the possibility that increased risk may be present in selected patients with UIP. We stressed that our patients, who were found to have UIP by surgical lung biopsy, were highly selected and represented a small proportion of the patients with IPF or connective tissue disease-associated UIP at our institution. These patients were subjected to biopsy because of their atypical features, and may have had more advanced or rapidly progressive disease than other patients with UIP. We indicated that these patients "may be at higher risk" for death following surgical lung biopsy than patients presenting with more typical features or patients with other interstitial lung diseases. This distinction is more than arbitrary, it is important. Additionally, we recognized that our findings may have been the result of small patient numbers and selection bias. However, we also felt that these data were compelling enough to suggest that others should look carefully at their surgical mortality in this group of patients (biopsy demonstrating UIP with presenting clinical features, which are atypical or nondiagnostic) in order to determine whether our findings were based on chance or a true reflection of previously under-appreciated risk in this specific patient group. Understanding the risk of surgical lung biopsy in this group is important when one considers that the recent American Thoracic Society and European Respiratory Society consensus statement recommended performing surgical lung biopsy in patients demonstrating atypical clinical or radiographical features of IPF [2]. This recommendation has also been emphasized by H.R. Collard and T.E. King Jr and is in agreement with our own view and practice.

Surgical mortality rates at our institution are historically low, as indicated in our manuscript [1]. In fact, the mortality rate in 771 cases of video-assisted thoracic surgery reported by Allen et al. [3] from our institution was 1.9%. There was a higher mortality rate in patients with IPF/UIP presenting with atypical or nondiagnostic features suggests that these patients may be at higher risk for death following surgical lung biopsy than patients presenting with more typical features or patients with other interstitial lung diseases. However, these data do not establish this as a universal fact.

H.R. Collard and T.E. King Jr may be correct in their assertion that our experience may have been a statistical "fluke" related to peculiar features of the patients biopsied, but we do not believe that the multiple reports of low "short-term mortality in surgical lung biopsy" outlined in table 1 by H.R. Collard and T.E. King Jr prove their point. Many of these reports are from time periods when IPF encompassed a broader spectrum of disorders, not in keeping with the more limited definition of IPF/UIP now accepted [2, 4]. Even if we accept, by leap of faith, that patients in these prior reports had what we now understand to be UIP (many of whom were described as showing "pulmonary fibrosis", "interstitial fibrosis", and "interstitial pneumonia"), these patients may not have been comparable to the patients in our series (severity of disease at the time of biopsy, the proportion with an "accelerated course" prior to biopsy, and the degree to which they demonstrated "atypical" clinical or HRCT findings). Indeed, many of the prior cases are not from the HRCT era and are unlikely to be precisely relevant to the discussion at hand. In addition, a review of the cited references indicates that the actual proportion of patients with UIP in the series reported by Bouts et al. [5] Bensard et al. [6] Gaensler and Carrington [7], Vansteenkiste et al. [8] Rena et al. [9] and Krassna et al [10] ranged from only 3–27%. Although 52% of patients in the series of Miller et al. [11] were felt to have UIP, this only amounts to 22 patients. The series of Jaklitsch et al. [12] and Carnochan et al. [13] do not provide histopathological details and the proportion of patients with UIP, if any, is unknown. In the series of Zegdi et al. [14], which included 64 patients, the overall mortality rate was 4.7%. On closer review, however, two of the three deaths probably occurred in the 19 patients with IPF, suggesting that the actual surgical mortality in patients with IPF was 11% (two of 19). Only 20 of the 61 patients in the series of Ayed and Raghunathan [15] had "interstitial fibrosis", one of whom died. In the series of Persson et al. [16], which