Unilateral Vocal Fold Paralysis and Risk of Pneumonia: A Nationwide Population-Based Cohort Study

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Abstract

Objective. To investigate pneumonia risk among patients with unilateral vocal fold paralysis (UVFP).

Study Design. Retrospective population-based cohort study.

Setting. This study used data from the National Health Insurance Research Database of Taiwan, a nationwide population-based database.

Subjects and Methods. A total of 419 patients newly diagnosed with UVFP between January 1, 1997, and December 31, 2013, were identified from the Longitudinal Health Insurance Database 2000, a nationally representative database of 1 million randomly selected patients. Moreover, 1676 patients without UVFP were matched to patients with UVFP at a 1:4 ratio based on age, sex, socioeconomic status, urbanization level, and site-specific cancers. Patients were followed up until death or the end of the study period (December 31, 2013). The primary outcome was the occurrence of pneumonia.

Results. The cumulative incidence of pneumonia was significantly higher for patients with UVFP than those without UVFP (P < .001). The adjusted Cox proportional hazard model showed that UVFP was significantly associated with a higher incidence of pneumonia (hazard ratio, 1.97; 95% CI, 1.35-2.86; P < .001). Subgroup analyses demonstrated that UVFP was an independent risk factor of pneumonia for 4 subgroups: young (18-50 years), older (>51 years), male, and cancer.

Conclusion. This is the first nationwide population-based cohort study to investigate the association between UVFP and pneumonia. The findings indicate that UVFP is an independent risk factor of pneumonia. Given the study results, physicians should be aware of the potential for pneumonia occurrence following UVFP.

Keywords
unilateral vocal fold paralysis, pneumonia, dysphagia, choking, aspiration, infection, risk factor

Pneumonia is a leading infectious cause of hospitalization and death among adults in the United States and worldwide.1,2 In the United States, the annual incidence of pneumonia has been reported as 24.8 cases per 10,000 adults, with the highest incidence rates observed for adults aged >65 years.1 Approximately 5% to 15% of patients with community-acquired pneumonia (CAP) are in...
the elderly population, and the majority of nursing home–
acquired pneumonia cases are caused by aspiration.3-5
Unilateral vocal fold paralysis (UVFP) occurs when 1
vocal fold is paralyzed in the paramedian or lateral position
with extremely limited movement. UVFP with dysphonia
and dysphagia comorbidity may lead to pneumonia due to
aspiration, which has potentially life-threatening conse-
quences.6,7 Based on the results of fiberoptic endoscopy
and stroboscopy evaluation, previous studies reported that UVFP
increases the odds of aspiration.8-13 To the best of our
knowledge, the long-term risk of pneumonia among patients
with UVFP remains unknown. Therefore, this study investig-
gated whether UVFP is a risk factor of pneumonia.

Methods

Data Source and Study Design

This nationwide cohort study used data from the population-
based National Health Insurance Research Database
(NHIRD). The National Health Insurance (NHI) program,
implemented on March 1, 1995, is a single-payer compul-
sory universal health insurance plan that currently covers all
types of health care services for >99% of all citizens of
Taiwan.14,15 This high coverage rate enables studies based
on the NHIRD to be nationwide population-based studies.
The NHIRD contains comprehensive information on pre-
scription details, clinic visits, surgical procedures, and diag-
nostic codes.16,17 The International Classification of
Diseases, Ninth Revision, Clinical Modification (ICD-9-
CM) and International Classification of Diseases, Ninth
Revision, Procedure Coding System are used to define the
diagnostic and procedure codes in the NHIRD, respec-
tively.18 This database has been used for various scientific
studies, and the information on diagnosis, hospitalization,
and prescription use included in the database has been
proven to be of high quality.19 The present study retrieved
data from the Longitudinal Health Insurance Database 2000
(LHID2000), a representative database of 1 million patients
randomly selected from the 2000 Registry of Beneficiaries
of the NHIRD by using a systematic sampling method; the
LHID2000 contains all claims data recorded from 1996 to
2013.20 According to reports from the Taiwan National
Health Research Institutes, in the LHID2000, no statistically
significant differences were observed for age, sex, socioeco-
nomic status, or urbanization level between the sample
group and all enrollees of the NHI program.21

This study was approved by the Institutional Review Board
of Chang Gung Medical Foundation (No. 201700214B1). To
ensure privacy, the personal information of all patients
included in the NHIRD is deidentified. The NHI Admini-
stration and Institutional Review Board of Chang Gung
Medical Foundation guarantee the confidentiality of the
personal and health information of all patients.

Study and Comparison Cohorts

Figure 1 presents a flowchart of the patient enrollment pro-
cess for the study cohort. Patients aged ≥18 years who were
newly diagnosed with UVFP (ICD-9-CM code 478.32)
between January 1, 1997, and December 31, 2013, were
identified from the NHIRD and included in the study
cohort. We included only patients with UVFP if the ICD-9-
CM codes for this condition occurred in the inpatient setting
or in ≥3 ambulatory care claims. These strict inclusion cri-
tera enabled us to confirm diagnoses of UVFP. The date of
enrollment was defined as the date of initial diagnosis of
UVFP.

Patients without UVFP were randomly selected from the
same data sets and included in the comparison cohort.
These patients were also matched to patients with UVFP at
a 1:4 ratio based on age, sex, socioeconomic status, urbani-
zation level, and site-specific cancers. For the comparison
cohort, the start of follow-up was defined as the date of the
first visit to a medical facility in the year of enrollment. In
both cohorts, patients diagnosed with pneumonia within 1
month before enrollment were excluded from this study to
avoid interference from the antecedent infection.

Outcome and Covariate Measurements

Patients were followed up until death or the end of the
study period (December 31, 2013). Death was defined as
the withdrawal of the patient from the NHI program.14 The
primary outcome was the occurrence of pneumonia (ICD-9-
CM codes 480-486, 507.0-507.8).

Patients’ sociodemographic characteristics, including age,
sex, socioeconomic status, and urbanization level, were obtained
from their initial enrollment data. Cross-checking for dysphagia (ICD-9-CM codes 438.12 and 787.20-787.29) among pneumonia patients was performed. The comorbidities associated with pneumonia were assessed and retrieved from ambulatory and inpatient claims data. The comorbidities were as follows: asthma (ICD-9-CM code 493), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, 496), diabetes mellitus (ICD-9-CM code 250), stroke (ICD-9-CM codes 430-438), heart failure (ICD-9-CM codes 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428), cancer (ICD-9-CM codes 140-208), and chronic kidney disease (CKD) (ICD-9-CM codes 582, 583, 585, 586, 588, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, v45.1). We included these comorbidities in the analysis if they occurred in the inpatient setting or in ≥3 ambulatory care claims. Each comorbidity was analyzed as a binomial variable.

**Statistical Analyses**

To compare the comorbidities between the UVFP and comparison cohorts, descriptive statistics including categorical and continuous data were analyzed with the Pearson chi-square test and independent Student t test, respectively. The Kaplan-Meier method was used to calculate the cumulative incidence rates of pneumonia in both cohorts, and the log-rank test was used to analyze the differences between the curves. The adjusted hazard ratio for matched-pair pneumonia occurrence was estimated with a Cox proportional hazard model by including a matching variable, which accounted for the matching based on age, sex, socioeconomic status, urbanization level, and site-specific cancer. To test the potential effects of modifiers, we conducted subgroup analyses stratified by sex, age, and cancer. All statistical analyses were conducted with SAS 9.4 (SAS Inc, Cary, North Carolina) and statistical significance was set at 2-sided P < .05.

**Results**

This study enrolled 419 patients with UVFP and 1676 patients without UVFP. After matching based on sex, age, socioeconomic status, and site-specific cancer, the results showed that patients in the UVFP cohort were more likely to have pneumonia than were those in the comparison cohort (Table 1). Cross-checking for dysphagia codes among pneumonia patients indicated that 25% (13 of 52) of the patients with pneumonia in the UVFP cohorts had dysphagia and 4.2% (5 of 119) of the patients with pneumonia in non-UVFP cohorts had dysphagia (P < .001). In our study, the mean (SD) observation durations were 3.96 (3.08) and 4.54 (2.98) years for the UVFP and comparison cohorts, respectively.

Based on the Kaplan-Meier method without accounting for competing risk events, the cumulative incidence of pneumonia was significantly higher in the UVFP cohort than the comparison cohort (P < .001; Figure 2). The 1-, 4-, and 8-year cumulative incidence rates of pneumonia were 6.54% and 1.09%, 13.3% and 5.15%, and 18.8% and 12.9% in the UVFP and comparison cohorts, respectively. Specifically, sex-, age-, and cancer-stratified analyses revealed that patients with UVFP had significantly higher risk of pneumonia than patients without UVFP for men but not women (Figure 3A), for the 18- to 50-year and ≥51-year age groups (Figure 3B), and for patients with or without cancer (Figure 3C), respectively.

Table 2 presents the results of multivariate analysis comparing the risk of pneumonia between the UVFP and comparison cohorts. As shown in Table 2, after adjustment for comorbidities, the risk of pneumonia was significantly higher in the UVFP cohort (adjusted hazard ratio, 1.97; 95% CI, 1.35-2.86; P < .001) than in the comparison cohort. In addition, chronic obstructive pulmonary disease, diabetes mellitus, and stroke were the predictors of pneumonia. In Table 3, all subgroup analyses are adjusted for confounders, and the data were stratified according to potential confounders. Moreover, the effects of UVFP remained significant for men but not women, for the 18- to 50-year and ≥51-year age groups, and for patients with cancer but not those without cancer.

| Table 1. Baseline Characteristics of Study Patients. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variables       | UVFP            | Non-UVFP        | P Value         |
| Total           | 419             | 1676            | 1.000           |
| Sex             |                 |                 |                 |
| Male            | 234             | 936             | 55.9            |
| Female          | 185             | 740             | 44.2            |
| Age, y          |                 |                 | 1.000           |
| 18-50           | 191             | 764             | 45.6            |
| ≥51             | 228             | 912             | 54.4            |
| Urbanized level |                 |                 | 1.000           |
| 1 (City)        | 143             | 572             | 34.4            |
| 2               | 168             | 672             | 40.1            |
| 3               | 71              | 284             | 17.0            |
| 4 (Villages)    | 37              | 148             | 8.8             |
| Income (NTD)    |                 |                 | 1.000           |
| 0               | 77              | 308             | 18.4            |
| 1-15,840        | 77              | 308             | 18.4            |
| 15,841-25,000   | 177             | 708             | 42.2            |
| ≥25,001         | 88              | 356             | 21.0            |
| Pneumonia       | 52              | 119             | 12.4            |
| Comorbidities   |                 |                 |                 |
| Asthma          | 60              | 140             | 14.3            |
| CKD             | 52              | 105             | 12.4            |
| COPD            | 104             | 215             | 24.8            |
| Diabetes mellitus| 92              | 287             | 22.0            |
| Heart failure   | 44              | 104             | 10.5            |
| Stroke          | 87              | 227             | 20.8            |
| Cancer          | 112             | 448             | 26.7            |

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; NTD, New Taiwan dollar; UVFP, unilateral vocal fold paralysis.
We found that patients with UVFP had a higher risk of pneumonia than those without UVFP across all subgroups, and this finding was statistically significant for men, for the 18- to 50-year and ≥51-year age groups, and for patients with cancer. Accordingly, our findings support that UVFP is an independent risk factor of pneumonia.

UVFP is related to unilateral 10th nerve palsy and isolated recurrent laryngeal nerve injury. Thus, patients with UVFP exhibit ipsilateral vocal fold paralysis but also supraglottic laryngeal and pharyngeal abnormalities with reduced laryngeal elevation, weak pharyngeal stripping wave, and pharyngeal retention, all of which may cause aspiration. Leder et al reported that individuals with UVFP have 2.5-times higher odds of aspirating that do those without UVFP. Another study reported that dysphagia in patients with UVFP is demonstrated during flexible endoscopic evaluation by pooling, spillage, penetration, and aspiration. Moreover, 1 study reported that patients with UVFP exhibit an alteration of bolus transit through the upper esophageal sphincter and have no adaptation in swallowing timing related to the increase in bolus volume. These studies verify the increased risk of dysphagia among patients with UVFP and provide possible mechanisms.

Aspiration pneumonia, defined as the misdirection of oropharyngeal or gastric contents into the larynx and lower respiratory tract, can be caused by dysphagia, stroke, and neurodegenerative diseases. Previous studies indicated the association between dysphagia and aspiration pneumonia. Park et al reported that aspiration and penetration observed during a videofluoroscopic swallow study and high-resolution manometry were predictors of aspiration pneumonia among patients with dysphagia. Almirall et al reported that oropharyngeal dysphagia is a risk factor for CAP among elderly patients. Moreover, dysphagia related to stroke and Parkinson’s disease is a risk factor of pneumonia. The aforementioned studies verified that dysphagia is associated with a higher risk of pneumonia. However, our study is the first to report the increasing risk of pneumonia after UVFP. Thus, our findings extend existing knowledge about the complications of UVFP.

The 8-year cumulative incidence rate of pneumonia was >12% in the non-UVFP group, suggesting that a considerable portion of pneumonia cases were related to CAP rather than aspiration pneumonia. Information on the etiology of pneumonia was unavailable in the population-based database; thus, we could not confirm the definite etiology of pneumonia (aspiration pneumonia or CAP). We conducted cross-checking for dysphagia codes in the records of patients with pneumonia to determine whether their pneumonia was related to aspiration. The results revealed that although patients with pneumonia in the UVFP group were more likely to have dysphagia than those in the non-UVFP group (25% vs 4.2%, \( P < .001 \)), only 25% of patients with pneumonia in the UVFP group had dysphagia. The aforementioned results suggest that a considerable portion of pneumonia cases in the UVFP and non-UVFP groups may be related to CAP. Nevertheless, the prevalence of
dysphagia in the UVFP group is much lower than that of previous studies, which reported a dysphagia prevalence of 50% to 69% among patients with UVFP.27-29 This discrepancy may be attributed to an underestimation of dysphagia among patients with UVFP in our study; that is, the NHIRD provides only ICD-9 diagnosis codes, not the original medical records containing detailed symptoms and signs. However, we could not confirm this, given the setting and design of our study—a natural limitation of many large-scale databases. Additional prospective studies are required to clarify this critical issue.

The weakened coughing force in patients with UVFP may contribute to the increasing risk of pneumonia. A previous study reported that half of healthy adults aspirate small amounts of oropharyngeal secretions during sleep.3,30 Healthy adults with forceful coughing and normal immune

Figure 3. Cumulative incidence of pneumonia in (A) men and women, (B) 18- to 50-year and ≥51-year age groups, and (C) patients with and without cancer. Stratified analyses revealed a significantly higher risk among patients with unilateral vocal fold paralysis (UVFP) than among those without UVFP for men but not women, 18- to 50-year and ≥51-year age groups, and patients with cancer but not those without cancer.
mechanisms can prevent themselves from pneumonia. However, for patients with UVFP who have an impaired coughing force, the aspiration of even a small amount of secretions without obvious symptoms of dysphagia may lead to pneumonia. *Haemophilus influenzae* and *Streptococcus pneumoniae* colonize the naso- or oropharynx and may cause aspiration pneumonia and CAP. The term *aspiration pneumonia* refers to the presence of radiographically evident pneumonia among patients with an increased risk of aspiration. However, pneumonia occurring among patients with UVFP who have a weakened coughing force but not obvious dysphagia might be diagnosed as having CAP instead of aspiration pneumonia. In this situation, the differential diagnosis of aspiration pneumonia and CAP becomes more difficult for patients with UVFP.

In the present study, the risk of pneumonia was significantly higher in the UVFP cohort than the comparison cohort. Specifically, in subgroup analysis, significantly higher risks were found for men but not women, possibly because of the following reasons. In Taiwan, men are far more likely to smoke (odds ratio, 17.90; 95% CI, 15.40-20.80). Smoking may reduce the innate defense mechanisms in the airways and lead to an increased risk of pneumonia and respiratory tract infection. Once aspiration occurs in patients with UVFP who are smokers, the risk of pneumonia may further increase.

We observed a higher risk of pneumonia in the UVFP cohort than in the comparison cohort across all subgroups. In addition, in subgroup analysis, significantly higher risks were found in the cancer subgroup but not in the noncancer subgroup. Previous studies reported that pneumonia risks are higher for patients with head and neck cancer, esophageal cancer, lung cancer, and hematologic malignancies. Cancer- and cancer treatment–related derangements of lung architecture, mucositis, impaired airway protection or swallow function, disparate mechanisms of neutropenia, and malnutrition all contribute to increased pneumonia risks. Thus, for patients with cancer, UVFP may further increase the risk of pneumonia.

Given the results of the present study, patients with UVFP who are at a high risk of pneumonia should be identified. Physicians should pay closer attention to the potential for pneumonia occurrence among patients with UVFP to enable its early diagnosis; they should also routinely perform chest radiography and laboratory evaluations and regularly monitor patients with UVFP to detect related symptoms and signs of infection. Moreover, our study reported a higher incidence of pneumonia in the UVFP cohort versus the comparison cohort in the first year after

### Table 2. Multivariable Cox Proportional Hazard Model for the Associations of Pneumonia with UVFP and Covariates.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Crude HR (95% CI)</th>
<th>P Value</th>
<th>Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UVFP vs Non-UVFP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non- UVFP</td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>UVFP</td>
<td>2.41 (1.69-3.43)</td>
<td>&lt;.001</td>
<td>1.97 (1.35-2.86)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>1.76 (1.08-2.85)</td>
<td>.022</td>
<td>1.14 (0.65-1.99)</td>
<td>.653</td>
</tr>
<tr>
<td>CKD</td>
<td>1.55 (0.89-2.70)</td>
<td>.125</td>
<td>0.99 (0.53-1.83)</td>
<td>.968</td>
</tr>
<tr>
<td>COPD</td>
<td>2.24 (1.52-3.29)</td>
<td>&lt;.001</td>
<td>1.63 (1.05-2.54)</td>
<td>.029</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.05 (1.38-3.05)</td>
<td>&lt;.001</td>
<td>1.78 (1.16-2.74)</td>
<td>.009</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.99 (1.20-3.30)</td>
<td>.008</td>
<td>1.38 (0.79-2.43)</td>
<td>.263</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.14 (1.44-3.18)</td>
<td>&lt;.001</td>
<td>1.69 (1.11-2.58)</td>
<td>.015</td>
</tr>
</tbody>
</table>

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; UVFP, unilateral vocal fold paralysis.

### Table 3. Subgroup Analysis of the Association of Pneumonia with UVFP according to Potential Confounders.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Crude HR (95% CI)</th>
<th>P Value</th>
<th>Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.52 (1.69-3.77)</td>
<td>&lt;.001</td>
<td>2.18 (1.42-3.35)</td>
<td>&lt;.001</td>
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<tr>
<td>Female</td>
<td>2.08 (0.99-4.38)</td>
<td>.055</td>
<td>1.55 (0.63-3.84)</td>
<td>.340</td>
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<tr>
<td>Age, y</td>
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<td></td>
</tr>
<tr>
<td>18-50</td>
<td>2.76 (1.27-6.02)</td>
<td>.011</td>
<td>2.77 (1.16-6.66)</td>
<td>.023</td>
</tr>
<tr>
<td>≥51</td>
<td>2.33 (1.57-3.46)</td>
<td>&lt;.001</td>
<td>1.82 (1.19-2.78)</td>
<td>.006</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.28 (1.38-3.77)</td>
<td>.001</td>
<td>2.21 (1.31-3.71)</td>
<td>.003</td>
</tr>
<tr>
<td>No</td>
<td>2.37 (1.43-3.92)</td>
<td>&lt;.001</td>
<td>1.46 (0.81-2.62)</td>
<td>.205</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; UVFP, unilateral vocal fold paralysis.
UVFP diagnosis (1-year cumulative incidence: 6.54% vs 1.09%). This finding implies that early treatment of UVFP may serve as a strategy for preventing pneumonia. Bhattacharyya et al reported that early vocal cord medialization for patients with a new onset of UVFP after thoracic surgery can reduce pulmonary complications. A previous study reported that for patients with UVFP and dysphagia, a significant improvement in swallowing was achieved following medialization laryngoplasty. Another study reported that voice therapy had marked benefits for patients with UVFP and dysphagia. However, not all patients with paralysis require immediate medialization. Therefore, fiberoptic endoscopic evaluation of swallowing is a tool that physicians can use to determine which patients most urgently require this procedure. In this study, sufficient evidence was not provided to indicate whether the treatment of UVFP decreased the risk of pneumonia. Thus, additional studies are required to evaluate the treatment outcomes.

Our study had several limitations. First, the diagnoses of UVFP and pneumonia recorded in administrative claims data may not be as accurate as diagnoses made in clinical prospective settings. Second, to clarify their individual roles in pneumonia, the definite etiologies of UVFP (iatrogenic, malignancy, idiopathic, and level of nerve injury) and pneumonia (bacterial, viral, or aspiration) could not be clearly distinguished on the basis of ICD-9-CM codes in the NHIRD. Third, laryngoscopy images and stroboscopy videos are not available in the database; thus, we could not correlate the severity of UVFP with the occurrence of pneumonia. Fourth, chest radiographic, blood culture, and sputum culture data are not available. As such, the methodology of this study cannot distinguish between aspiration pneumonia and CAP. Finally, our study was retrospective. Additional prospective clinical trials are necessary to elucidate the causal relationship between UVFP and pneumonia and the related treatment outcomes.

Conclusion

This is the first nationwide population-based cohort study to investigate the association between UVFP and pneumonia. The findings indicate that UVFP is an independent risk factor of pneumonia. Given the study results, physicians should be aware of the potential for pneumonia occurrence following UVFP. Further studies are required to evaluate the effects of treatment (including medialization laryngoplasty, injection laryngoplasty, voice therapy, and dysphagia therapy) on pneumonia risk.

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Author Contributions

Ming-Shao Tsai, conception and design of the project; acquisition, analysis and interpretation of the data; drafting, critical revision and final approval of the manuscript; Yao-Hsu Yang, acquisition, analysis and interpretation of the data; critical revisions and final approval of the manuscript; Chia-Yen Hsu, conception and design of the project; drafting, critical revision and final approval of the manuscript; Meng-Hung Lin, conception and design of the project; drafting, critical revision and final approval of the manuscript; Hsueh-Yu Li, conception and design of the project; drafting, critical revision and final approval of the manuscript; Cheng-Ming Hsu, conception and design of the project; drafting, critical revision and final approval of the manuscript.

Disclosures

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References