Recurrent Laryngeal Nerve Palsy Is More Frequent After Secondary than After Primary Anterior Cervical Discectomy and Fusion: Insights from a Registry of 525 Patients

Victor E. Staartjes1,2, Marlies P. de Wispelaere3, Marc L. Schröder1

BACKGROUND: Recurrent laryngeal nerve (RLN) palsy is a common complication after anterior cervical discectomy and fusion (ACDF) and usually manifests with dysphagia, hoarseness, and respiratory difficulties. Next to proven risk factors, such as age and multilevel procedures, RLN palsy has been speculated to occur more frequently after secondary ACDF procedures.

METHODS: We analyzed a prospective registry of all consecutive patients undergoing zero-profile ACDF for disc herniation, myelopathy, or stenosis. RLN palsy was defined as persistent patient self-reported dysphagia, hoarseness, or respiratory problems without other identifiable causes. RLN palsy was assessed at scheduled 6-week telephone interviews.

RESULTS: Among 525 included patients, 511 primary and 40 secondary ACDF procedures were performed. Hoarseness was present in 12 (2.2%) cases, whereas dysphagia and respiratory difficulties both occurred in 3 (0.5%) cases. Overall incidence of RLN palsy was 2% after primary procedures and 8% after secondary procedures ($P = 0.017$). These rates are in line with the peer-reviewed literature, and the difference remained significant after controlling for confounders in a multivariate model ($P = 0.033$). Other reported risk factors, such as age, sex, surgical time, and multilevel procedures, had no relevant effect ($P > 0.05$).

CONCLUSIONS: Based on our data and other published series in the literature, RLN palsy may occur more frequently after secondary ACDF procedures with a clinically relevant effect size. There is a striking lack of uniformity in methods and reporting in research on RLN injury.

INTRODUCTION

Recurrent laryngeal nerve (RLN) palsy is a common complication of anterior cervical discectomy and fusion (ACDF). Injury to the RLN can lead to hoarseness, dysphagia, and respiratory problems. These symptoms may be transient and frequently improve throughout the first postoperative year, but they can also be persistent. Validated questionnaires, patient-reported symptoms, or objective measurements performed by otolaryngologists can be used to determine RLN palsy. In primary procedures, the incidence of RLN palsy after ACDF is between 1% and 11%. Patient-reported hoarseness or dysphagia occurs in 1%–70% and is a good marker of RLN palsy. If vocal cord paresis is determined by videolaryngostroboscopy, which aims to provide a more objective assessment, lower rates are reported. Risk factors for RLN palsy include multilevel procedures, age, and plating, among others.

It has been hypothesized that the rate of RLN palsy may be higher in secondary ACDF procedures, possibly owing to scarring involving the RLN caused by the primary procedure. Small retrospective studies form the majority of the literature on RLN palsy after ACDF. There is only limited evidence on the incidence of RLN palsy in secondary procedures. Only a few studies report comparative rates of RLN palsy stratified into primary and secondary procedures. An adequate sample size is crucial to reliably determine the incidence of RLN palsy.

Key words
- Cervical
- Complication
- Discectomy
- Dysphagia
- Fusion
- Recurrent laryngeal nerve
- Reoperation

Abbreviations and Acronyms
- ACDF: Anterior cervical discectomy and fusion
- PROM: Patient-reported outcome measures
- RLN: Recurrent laryngeal nerve

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determine an intergroup difference in RLN palsy between primary and the rarer secondary procedures. In the present study, we analyzed an institutional registry of patients who underwent ACDF to determine if RLN palsy, as determined by patient-reported dysphagia, hoarseness, and respiratory problems, was more frequent in secondary procedures.

**MATERIALS AND METHODS**

**Study Design**

This study was carried out according to the ethical principles of the Declaration of Helsinki and was approved by the local institutional review board (Medical Ethics Committees United, Registration Number W17.068). Informed consent was obtained from all participants. Prospectively collected data from an institutional registry of all consecutive ACDF procedures performed between January 2011 and January 2018 were analyzed. Indications for surgery were disc herniation, stenosis, and degenerative myelopathy. All procedures were performed by 2 senior neurosurgeons at a specialized spine center using standalone cages without plating. Patients who already showed signs of RLN palsy preoperatively were excluded. ACDF procedures were classified as “primary” if a patient had not undergone prior anterior cervical spine surgery. If a patient was referred to our center and had undergone prior anterior cervical spine surgery or if a patient required a second procedure at our center, this was classified as a “secondary” ACDF. Briefly, we compared clinical and patient-reported outcomes of primary ACDF versus secondary ACDF with a focus on RLN palsy.

**Outcome Measures**

Complete clinical data were available from all included patients. Adverse events were systematically registered in a separate database. At 6 weeks after surgery, patients were interviewed by telephone and asked about clinical as well as voice and swallowing outcomes. Our primary endpoint was incidence of RLN palsy. We defined RLN palsy as patient-reported transient or persistent 1) hoarseness, 2) dysphagia, 3) or respiratory problems that 4) newly occurred postoperatively and that were 5) not explicable by other causes. Persistent RLN palsy was further assessed by an otolaryngologist. Persistent RLN palsy was defined as duration of clinical symptoms ≥12 months. All patients with RLN palsy were regularly followed up for the duration of their symptoms. Secondary endpoints were other complications as well as patient-reported outcome measures (PROM). In a subset of patients, complete data on PROM were available, including validated Dutch versions of the Neck Disability Index, numeric rating scale for neck pain, and EQ-5D-3L index and visual analog scale.

**Surgical Technique**

After fluoroscopically identifying the correct disc level, a transverse incision measuring 5 cm was made. One surgeon always operated from the right side, whereas the other surgeon always operated from the left side. Revisions were always performed on the same side as the primary procedure. Apart from sitedness, there was no difference in operative techniques and tools among the 2 senior surgeons. Steroids were not used. The platysma was sharply dissected. After reaching the anterior cervical spine by blunt dissection, a retractor was inserted. Distraction pins were drilled into the vertebral bodies, the anterior longitudinal ligament was cut, and the disc space was debulked under microscopic vision. The posterior longitudinal ligament and dorsal osteophytes were removed by use of a punch, and the endplates were prepared for fusion using a high-speed burr. After foraminal decompression, a CORNERSTONE cage (Medtronic plc., Dublin, Ireland) was placed. Meticulous hemostasis was achieved. Distraction pins were removed, and a Redon drain (Braun, Sempach, Switzerland) was introduced. The subcutis and skin were closed in layers using Vicryl (Ethicon Inc., Somerville, New Jersey, USA) and Prolene (Ethicon Inc.), respectively.

**Statistical Analysis**

We reported continuous data as mean ± SD and categorical data as numbers (percentages). Intergroup differences were univariately assessed by Mann-Whitney U and χ² tests with continuity correction. Longitudinal data were analyzed using Wilcoxon signed rank tests. To adjust for baseline confounders, a multivariate binomial logistic regression model was trained. Odds ratios and 95% confidence intervals for RLN palsy were reported, and overall model accuracy was evaluated in area under the receiver operating curve space. We performed a post hoc power analysis on our primary endpoint as assessed by contingency table analysis using as test criteria a minimum detectable difference of 5% and α = 0.05. All analyses were carried out using R Version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). All P ≤ 0.05 on a 2-tailed test was considered statistically significant.

**RESULTS**

Figure 1 demonstrates the flow of patients throughout this analysis. Our power analysis revealed that this sample resulted in a statistical power of 1 − β = 0.867 for the analysis of our primary endpoint. Of the 551 included cases in 525 patients, 511 (93%) were primary ACDF procedures, and 40 (7%) were secondary ACDF procedures (Table 1). Prior ACDF was performed elsewhere in 14 (3%) patients, and these patients were thus handled as secondary cases. Most patients received ACDF for disc herniation (8%) vs. 75%) or foraminal stenosis (13% vs. 23%). In 7 (1%) cases versus 1 (3%) case, medial disc herniation caused symptomatic myelopathy. The most commonly affected levels were C5-6 (48% vs. 43%) and C6-7 (40% vs. 48%), with only a small number of multilevel procedures (5% vs. 3%). The mean length of clinical follow-up in this registry was 31.0 ± 12.2 months. A subset of 94 patients (18%) had complete data on PROM questionnaires with a minimum follow-up of 12 months (Table 2). All PROMs improved significantly from baseline to the 12-month and 24-month follow-ups (all P < 0.001).

**Surgical Characteristics**

Average surgical time was 50.2 ± 18.5 minutes versus 47.1 ± 14.0 minutes, and hospital length of stay was 1.2 ± 0.4 days and 1.3 ± 0.9 days for primary and secondary procedures, respectively. The overall rate of complications was higher in secondary ACDF procedures (5% vs. 20%, P = 0.008) (Table 3). Of the 40 secondary procedures, 38 (95%) were at an adjacent level. Only 2 patients had to undergo a third ACDF procedure for disc herniation and stenosis at a new vertebral level.
New postoperative RLN palsy was recorded in 12 (2%) patients. Nine patients (2%) experienced RLN palsy after primary ACDF, and 3 (8%) patients experienced RLN palsy after secondary ACDF. Pronounced and persisting hoarseness (2% vs. 8%) was the most common indicator of RLN palsy. Patient-reported severe dysphagia (0% vs. 3%) and respiratory difficulties (0% vs. 3%) attributable to RLN injury were also observed. In the primary ACDF group, 3 (33%) patients had persistent RLN palsy, defined as duration of symptoms ≥12 months. Of these patients, 5 (56%) were seen by an otolaryngologist. One (33%) patient in the secondary ACDF group had persistent RLN palsy, and 2 (67%) were assessed by an otolaryngologist. For 1 patient in the secondary ACDF group with RLN injury, the otolaryngologist attributed hoarseness to local damage to the vocal cords owing to endotracheal intubation. The incidence hoarseness attributable to vocal cord injury owing to intubation is extremely low compared with the relatively high incidence of such cases attributable to RLN injury.11 Coupled with the fact that asymptomatic vocal cord injury after intubation probably occurs on a more regular basis, the likelihood of hoarseness owing to isolated vocal cord injury is very low.11 RLN palsy did not have a significant effect on 12-month (P = 0.243) or 24-month (P = 0.182) Neck Disability Index scores.

Univariate Analysis

Table 4 reports the univariate analysis for factors associated with RLN palsy. Secondary ACDF was the only significant univariate predictor of RLN palsy (P = 0.017). Age, body mass index, surgical time, sex, smoking status, and multilevel procedures did not affect RLN palsy in any significant way.

Multivariate Model

A logistic regression model was trained and evaluated to assess the influence of secondary ACDF procedures on the incidence of RLN palsy while controlling for possible confounders (Table 5). Even after adjustment for sex, smoking status, age, body mass index, surgical time, and multilevel procedures in a logistic regression model, secondary ACDF procedures remained an independent predictor of RLN palsy (odds ratio = 4.42; 95% confidence interval, 1.11–15.87; P = 0.0329). The model scored an area under the receiver operating curve of 0.349, indicating limited discriminative ability for this event.

Table 1. Demographic and Perioperative Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Primary ACDF (n = 511)</th>
<th>Secondary ACDF (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>48.2 ± 9.0</td>
<td>49.9 ± 9.2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.8 ± 3.5</td>
<td>25.9 ± 3.4</td>
</tr>
<tr>
<td>Male sex</td>
<td>253 (50)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>Active smoker</td>
<td>154 (30)</td>
<td>13 (33)</td>
</tr>
<tr>
<td>ASA grade I</td>
<td>321 (63)</td>
<td>23 (58)</td>
</tr>
<tr>
<td>Surgical parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertebral level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3-4</td>
<td>10 (2)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>C4-5</td>
<td>74 (14)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>C5-6</td>
<td>247 (48)</td>
<td>17 (43)</td>
</tr>
<tr>
<td>C6-7</td>
<td>206 (40)</td>
<td>19 (48)</td>
</tr>
<tr>
<td>C7-T1</td>
<td>11 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Indication for surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disc herniation</td>
<td>446 (87)</td>
<td>30 (75)</td>
</tr>
<tr>
<td>Foraminal stenosis</td>
<td>65 (13)</td>
<td>9 (23)</td>
</tr>
<tr>
<td>Exploration</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Bilateral pathology</td>
<td>151 (30)</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Multilevel procedure</td>
<td>28 (5)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Surgical time, minutes</td>
<td>50.2 ± 18.5</td>
<td>47.1 ± 14.0</td>
</tr>
<tr>
<td>Length of stay, days</td>
<td>1.2 ± 0.4</td>
<td>1.3 ± 0.9</td>
</tr>
</tbody>
</table>

Values are reported as mean ± SD or number (%).

ACDF, anterior cervical discectomy and fusion; BMI, body mass index; ASA, American Society of Anesthesiologists.
few report incidences stratified by primary and secondary procedures, and still less have systematically assessed this potential risk factor.14 In a meta-analysis, Erwood et al.7 modeled the rate of dysphagia after secondary ACDF in the literature and reported an estimate of 14.1%. They also concluded that because all previous estimates of dysphagia rates for primary ACDF are lower, it is conceivable that there may be a true difference in dysphagia rates among primary and secondary procedures. However, no comparative statistical analysis was performed. In a comparative study of 348 procedures, Lee et al.13 found a higher prevalence of postoperative dysphagia after revision surgery. Similarly, Gerling et al.14 reported that prior surgery was the only independent risk factor for overall complications in ACDF. However, in an analysis of a nationwide registry of >150,000 ACDF procedures, Singh et al.15 did not find an influence of prior surgery on dysphagia rates.

Multiple other risk factors have proven independent predictive value for RLN palsy after ACDF. Multilevel procedures are commonly reported as a risk factor with rigid effect size.1,4,12,13,15 We were unable to replicate these effects, possibly owing to the low proportion of multilevel procedures in our series leading to insufficient power for this analysis. Other recognized risk factors for postoperative RLN palsy are the use of anterior plating compared with standalone constructs,5,6,8 use of recombinant human bone morphogenetic protein,19,20 older age,12,21 and circumferential

DISCUSSION
In an analysis of a registry of prospectively collected data from 525 patients, RLN palsy was found to occur significantly more frequently after secondary ACDF procedures than after primary ACDF procedures. This association remained significant after adjusting for potential confounders. The influence of age, body mass index, sex, and multilevel procedures as risk factors in the published literature was not confirmed by our data.

This cohort represents 1 of the largest single-center studies on ACDF in the peer-reviewed literature. To reliably capture an event such as RLN palsy, which occurs in 1%–11% of patients after primary procedures,17 a comparatively large sample size of >500 is needed. For inferential statistical analysis of risk factors, sample size and power become even more crucial. Based on data from our institutional registry, there was a significant increase in the risk of persisting postoperative RLN palsy after secondary ACDF. At an odds ratio of 4.4, the difference was not only statistically but also clinically relevant. This means that RLN palsy does not remain an occasional complication but instead becomes a regularly occurring complication in almost every 10th patient undergoing secondary ACDF. Although numerous studies in the peer-reviewed literature report the incidence of RLN injury in ACDF cohorts, only a very
fusion.\textsuperscript{22} No plating, recombinant human bone morphogenetic protein use, or circumferential fusion was performed at our center. Higher surgeon volumes have been linked as a protective factor for complications such as dysphagia after ACDF.\textsuperscript{23}

One particular difficulty in research on RLN palsy is the lack of uniformity regarding the methods of capturing RLN injury. Dysphagia is often used as a single marker of RLN palsy in clinical studies. We not only looked at RLN palsy as defined by dysphagia but also addressed the occurrence of persistent hoarseness and respiratory problems inexplicable by other causes. Our study is the first to capture RLN palsy in this way, as we believe that this is a more complete assessment.

Mostly owing to the multitude of tools for assessment, rates of dysphagia and hoarseness after ACDF in the literature range from 1\% to 70\%.\textsuperscript{1} This is mostly explained by the strong variation in dysphagia and hoarseness rates depending on the time of assessment. Early assessment after 1 or 2 weeks consistently produces higher rates than at 3 or 6 months.\textsuperscript{13,15,21,24} Furthermore, prospective studies report relatively higher incidences than retrospective studies, mainly owing to reporting bias.\textsuperscript{1,25} Similarly, studies that use objective markers of RLN injury, such as video-laryngostroboscopy or radiologic methods (e.g., pharyngeal magnetic resonance imaging), or that look at persisting patient-reported symptoms, report lower rates than studies using questionnaires, such as the M.D. Anderson Dysphagia Inventory.\textsuperscript{1,3} Lastly, even when such standardized questionnaires are applied, multiple different thresholds have been implemented to define the presence of dysphagia. The combination of these confounders makes a comparison between studies in the literature exceedingly difficult.

Injury to the RLN can have various causes, including direct sectioning or retraction injury as well as esophageal retraction with reduced perfusion\textsuperscript{26} or direct pharyngeal or esophageal pressure.\textsuperscript{27} Injury to the hypoglossal\textsuperscript{28} or superior laryngeal nerves\textsuperscript{29} as well as intraoperative changes of the C2-7 angle can also cause dysphagia or vocal cord paralysis.\textsuperscript{1} Additionally, the anatomic variation of the RLN along with the presence of scar tissue in secondary procedures can make identification and dissection difficult.\textsuperscript{30} It has recently been shown that multidisciplinary ACDF procedures in which head and neck surgeons perform the approach and protect the RLN potentially reduce dysphagia rates.\textsuperscript{1,29} Although head and neck surgeons may have never performed ACDF themselves, cross-training in thyroid surgery, laryngectomy, and other anterior neck procedures prepares surgeons for difficult dissections that include scar tissue, prior radiation, and tumor. This unique experience may explain why incorporating multidisciplinary care in ACDF seems to reduce the incidence of RLN palsy.\textsuperscript{1,29}

Although many studies report dysphagia as a single marker, the question of whether RLN palsy is more frequent after secondary ACDF has not been answered systematically. Other than this registry study, the published data that deal specifically with this question are scarce.\textsuperscript{7,13} Owing to its clinical relevance, a systematic review and meta-analysis of the literature is warranted. This meta-analysis could include a large amount of cohorts and be based on pooled models or look only at the few studies that comparatively report incidence of RLN palsy in primary and secondary ACDF.

The primary limitation of this study was its retrospective nature. Although all data were collected in a prospective registry, events were captured systematically, and all consecutive patients undergoing ACDF were included, capture and reporting bias cannot be ruled out. Furthermore, all data were obtained from a single center and only 2 senior surgeons, possibly creating center bias. All ACDF procedures were performed in a minimally invasive fashion, possibly limiting the generalizability of results in comparison with the literature. RLN palsy, the primary endpoint of this study, occurred in 12 patients. Although post hoc power analysis determined that the analysis of our primary endpoint reached sufficient statistical power, a larger cohort would have provided for a more secure analysis with narrower confidence intervals. Finally, although patient-reported symptoms of RLN palsy are the most objective clinical indicators of symptomatic RLN injury, our study could additionally have applied hoarseness and dysphagia questionnaires or videolaryngostroboscopy for a more standardized assessment.\textsuperscript{1} Finally, the cases that were captured as RLN palsy with our clinical definition may include

### Table 4. Analysis of Factors Univariately Associated with Anterior Cervical Discectomy and Fusion Procedures That Led to Recurrent Laryngeal Nerve Palsy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RLN Palsy (n = 12)</th>
<th>No RLN Palsy (n = 539)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>47.2 ± 5.4</td>
<td>48.3 ± 9.1</td>
<td>0.85</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.2 ± 2.2</td>
<td>25.9 ± 3.5</td>
<td>0.50</td>
</tr>
<tr>
<td>Surgical time, minutes</td>
<td>49.8 ± 17.8</td>
<td>49.9 ± 18.3</td>
<td>0.91</td>
</tr>
<tr>
<td>Male sex</td>
<td>5 (42)</td>
<td>268 (50)</td>
<td>0.58</td>
</tr>
<tr>
<td>Active smoker</td>
<td>4 (33)</td>
<td>163 (30)</td>
<td>0.82</td>
</tr>
<tr>
<td>Secondary ACDF</td>
<td>3 (25)</td>
<td>37 (7)</td>
<td>0.017*</td>
</tr>
<tr>
<td>Multilevel procedure</td>
<td>1 (8)</td>
<td>28 (5)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Values are reported as mean ± SD or number (%).

RLN, recurrent laryngeal nerve; BMI, body mass index; ACDF, anterior cervical discectomy and fusion.

*P ≤ 0.05.

### Table 5. Multivariate Logistic Regression Analysis of Independent Predictive Effect of Secondary Anterior Cervical Discectomy and Fusion Procedures on Recurrent Laryngeal Nerve Palsy

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
<th>Model AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary ACDF</td>
<td>4.42</td>
<td>1.11–15.87</td>
<td>0.0329*</td>
<td>0.349</td>
</tr>
</tbody>
</table>

Adjustment for sex, smoking status, age, body mass index, surgical time, and multilevel procedures as possible confounders was applied.

ACDF, anterior cervical discectomy and fusion; AUC, area under the receiver operating curve.

*P ≤ 0.05.
superior laryngeal nerve palsy, which is unlikely, as there were only a few procedures at C3-4. Still, there were more procedures at C3-4 in the secondary ACDF group, which may have confounded our results. However, of the 3 symptomatic patients in the secondary ACDF group, 2 were operated at C6-7 and 1 was operated at C5-6, which effectively rules out superior laryngeal nerve injury. Similarly, some cases in the secondary ACDF group may be attributable to asymptomatic RLN palsy after the primary procedure, which was then aggravated and became symptomatic as a result of the secondary procedure.

CONCLUSIONS

Based on our data and other published series in the literature, it can be suggested that RLN palsy occurs more frequently after secondary ACDF procedures. The effect size of secondary procedures as a risk factor for RLN palsy was not only statistically but also clinically relevant. There is a striking lack of uniformity in methods and reporting on RLN injury. To increase the level of evidence on this topic and to further guide clinical risk assessment, a comparative systematic review and meta-analysis of the literature may be warranted.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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