The Non-Recurrent Laryngeal Nerve: a meta-analysis and clinical considerations

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Background. The Non-Recurrent Laryngeal Nerve (NRLN) is a rare embryologically-derived variant of the Recurrent Laryngeal Nerve (RLN). The presence of a NRLN significantly increases the risk of iatrogenic injury and operative complications. Our aim was to provide a comprehensive meta-analysis of the overall prevalence of the NRLN, its origin, and its association with an aberrant subclavian artery.

Methods. Through March 2016, a database search was performed of PubMed, CNKI, ScienceDirect, EMBASE, BIOSIS, SciELO, and Web of Science. The references in the included articles were also extensively searched. At least two reviewers judged eligibility and assessed and extracted articles. MetaXL was used for analysis, with all pooled prevalence rates calculated using a random effects model. Heterogeneity among the included studies was assessed using the Chi^2 test and the I^2 statistic.

Results. Fifty-three studies (33,571 right RLNs) reported data on the prevalence of a right NRLN. The pooled prevalence estimate was 0.7% (95%CI: 0.6-0.9). The NRLN was found to originate from the vagus nerve at or above the laryngotracheal junction in 58.3% and below it in 41.7%. A right NRLN was associated with an aberrant subclavian artery in 86.7% of cases.

Conclusion. The NRLN is a rare yet very clinically relevant structure for surgeons and is associated with increased risk of iatrogenic injury, most often leading to temporary or permanent vocal cord paralysis. A thorough understanding of the prevalence, origin, and associated pathologies is vital for preventing injuries and complications.

1   **The Non-Recurrent Laryngeal Nerve: a meta-analysis and clinical considerations**

3   *Running Title: Non-Recurrent Laryngeal Nerve: A Review*

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24   **ABSTRACT**

25   **Background.** The Non-Recurrent Laryngeal Nerve (NRLN) is a rare embryologically-derived

26   variant of the Recurrent Laryngeal Nerve (RLN). The presence of a NRLN significantly increases

27   the risk of iatrogenic injury and operative complications. Our aim was to provide a comprehensive

28   meta-analysis of the overall prevalence of the NRLN, its origin, and its association with an aberrant

29   subclavian artery.

30   **Methods.** Through March 2016, a database search was performed of PubMed, CNKI,

31   ScienceDirect, EMBASE, BIOSIS, SciELO, and Web of Science. The references in the included

32   articles were also extensively searched. At least two reviewers judged eligibility and assessed and

33   extracted articles. MetaXL was used for analysis, with all pooled prevalence rates calculated using

34   a random effects model. Heterogeneity among the included studies was assessed using the Chi^2

35   test and the I^2 statistic.

36   **Results**. Fifty-three studies (33,571 right RLNs) reported data on the prevalence of a right NRLN.

37   The pooled prevalence estimate was 0.7% (95%CI: 0.6-0.9). The NRLN was found to originate

38   from the vagus nerve at or above the laryngotracheal junction in 58.3% and below it in 41.7%. A

39   right NRLN was associated with an aberrant subclavian artery in 86.7% of cases.

40   **Conclusion**. The NRLN is a rare yet very clinically relevant structure for surgeons and is

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42   vocal cord paralysis. A thorough understanding of the prevalence, origin, and associated

43   pathologies is vital for preventing injuries and complications.

44

45

INTRODUCTION

The Non-Recurrent Laryngeal Nerve (NRLN) is a rare variant of the Recurrent Laryngeal Nerve (RLN) that takes an aberrant course, not descending into the thorax as is usual (Figure 1). It was first reported by Stedman in 1823 (Stedman, 1823). It arises almost exclusively on the right side and is closely associated with vascular anomalies of the aortic arch (Wang et al., 2011). On the right side, the NRLN usually results from partial regression of the fourth pharyngeal arch, resulting in an aberrant subclavian artery (arteria lusoria) that runs behind the esophagus (Figure 1B) (Wang et al., 2011). This atypical vascular pattern permits the nerve to migrate freely into the neck as the fetus grows longitudinally (Wang et al., 2011). The existence of a NRLN without the associated vascular anomalies has no clear embryological explanation (Wang et al., 2011). NRLNs on the left side have only been reported a few times, all of them accompanied by other significant pathologies such as situs inversus (Henry et al., 1988; Toniato et al., 2004; Hong, Park & Yang, 2014).

The NRLN variant of the RLN is a major risk factor for iatrogenic injury and can lead to detrimental postoperative complications if its existence is not observed in a timely fashion. As noted by Toniato (2004), patients experienced a nearly six-fold increase in intraoperative nerve injuries if they had an undetected NRLN (Toniato et al., 2004). A thorough dissection in all approaches to thyroidectomy, parathyroidectomy, and endarterectomy is essential for identifying the neurovascular structures and preventing intra- and post-operative nerve complications, the most common of which is vocal cord paralysis (De Luca et al., 2000; Hong, Park & Yang, 2014). It was noted in Iacobone (2015) that preoperative ultrasonography (USG) to assess patients for a NRLN was extremely successful, with an accuracy of more than 98% (Iacobone et al., 2015). It is therefore strongly suggested that measures such as preoperative USG are taken to identify these variant structures because they clearly help to prevent injury. In Iacobone's study nerve palsy did

69   not arise in the ultrasound group yet arose 3 times in the control group, a true testament to the

70   importance of preoperative identification (Iacobone et al., 2015).

71   The prevalence of the NRLN has been reported numerous times with rates ranging from 0% to

72   4.76% (Menck, Grüber & Lierse, 1990; Freschi et al., 1994; Moreau et al., 1998; Sasou, Nakamura

73   & Kurihara, 1998; Sturniolo et al., 1999; Monfared, Gorti & Kim, 2002; Page, Foulon & Strunski,

74   2003; Makay et al., 2008; Lee et al., 2009; Kandil et al., 2011; Benouaich et al., 2012; Ngo Nyeki

75   et al., 2015). It is essential to obtain accurate anatomical data on the NRLN if patients with this

76   anomaly are to be assessed properly for surgical candidacy and operative planning. The aim of our

77   analysis was to provide a comprehensive and evidence-based assessment of the prevalence of the

78   NRLN. We also aimed to investigate the course-related consequences of the different types of

79   NRLN, and the association of this variant nerve with the incidence of an aberrant subclavian artery.

80   Since the RLN, and in particular the NRLN, are particularly susceptible to surgical injury, a

81   complete understanding and assessment of their variant anatomy is essential for preventing injuries

82   and ensuring complication-free procedures.

83

METHODS

Search strategy

Through March 2016, a database search was performed of PubMed, CNKI, ScienceDirect, EMBASE, BIOSIS, SciELO, and Web of Science in order to identify eligible articles for the meta-analysis. The exhaustive search strategy employed for PubMed is presented in Supporting Table 1. No date limits or language restrictions were applied. The references in the included articles were also extensively searched. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were strictly followed throughout this meta-analysis (Supporting Table 2) (Moher et al., 2009). We prospectively registered the meta-analysis in PROSPERO (CRD42015026096).

Criteria for Study Selection

Studies were considered eligible for inclusion in the meta-analysis if they: (1) reported clear, extractable prevalence data on the non-recurrent laryngeal nerve with respect to side and (2) were cadaveric, intraoperative, or imaging studies. The exclusion criteria included: (1) case studies, case reports, conference abstracts, and letters to the editor; (2) studies reporting incomplete data (i.e. not reporting rates with respect to side); and (3) studies on patients with trauma to the head and neck region. The decision to include only articles reporting rates with respect to side was based on the previously-established difference in prevalence rates of the NRLN between the right and the left sides (Henry et al., 1988).

All studies were independently assessed for eligibility by three reviewers (S.S., J.V., and B.S.). Any disparities arising during the assessment were resolved by a consensus among all the reviewers, after consulting with the authors of the original study, if possible. All full-text articles published in languages not spoken fluently by the authors were translated for further eligibility

107   assessment by medical professionals fluent in both English and the original language of the

108   manuscript.

109   **Data extraction**

110   Data were independently extracted from the included articles by two independent reviewers (S.S.

111   and J.V.). These data included demographic information such as year, country, type of study, study

112   design, and number of nerves. The primary outcome, the prevalence of right and left NRLNs was

113   isolated. Secondary outcomes such as the level of origin of the NRLN from the vagus nerve (at or

114   above the level of the laryngotracheal junction OR below that level) (Figure 2), and the prevalence

115   of an aberrant subclavian artery when a NRLN was present were also noted when available. In the

116   event of data inconsistencies, the reviewers attempted to contact the authors of the original study

117   by email for clarification.

118   **Statistical analysis**

119   Statistical analysis was performed by B.M.H. and M.G. using MetaXL version 2.0 by EpiGear

120   International Pty Ltd (Wilston, Queensland, Australia). All pooled prevalence rates were

121   calculated using a random effects model (Henry, Tomaszewski & Walocha, 2016). The Chi^2 test

122   and the I^2 statistic were used to measure the level of heterogeneity among the included studies. For

123   the Chi^2 test, a Cochran's Q p-value of <0.10 indicated significant heterogeneity (Higgins & Green,

124   2011). The values of the I^2 statistic were interpreted as follows: 0-40% might not be important;

125   30-60% could indicate moderate heterogeneity; 50-90% could indicate substantial heterogeneity;

126   and 75-100% indicated considerable heterogeneity (Higgins & Green, 2011).

127   To probe the etiology of heterogeneity, subgroup analysis was performed on the basis of type of

128   study (cadaveric vs. intraoperative), study design (prospective vs. retrospective), and geographical

129   origin of the articles. Significant differences between subgroups were judged from the confidence

130   intervals of the rates, any overlap between groups indicating a lack of statistical significance

131   (Henry, Tomaszewski & Walocha, 2016). Furthermore, a leave-one-out sensitivity analysis was

132   performed to explore the source of heterogeneity.

133

134   **RESULTS**

135   **Study Identification**

136   Figure 3 presents an overview of the flow of studies in the meta-analysis. Through database

137   searching, 2,795 initial articles were identified. A further 84 articles were identified from reference

138   searching. After removing duplicates and primary screening, 328 articles were assessed by full

139   text for eligibility in the meta-analysis. Of these, 53 were deemed eligible and included, while 275

140   were excluded, 21 for not reporting extractable NRLN rates with respect to side.

141

142   **Characteristics of Included Studies**

143   The characteristics of the studies included in the meta-analysis are summarized in Table 1, along

144   with the reported prevalence of a right NRLN. A total of 53 studies (n= 53,577 total nerves;

145   33,571 Right RLNs and 20,006 Left RLNs) were included: 35 intraoperative, 17 cadaveric and 1

146   imaging (CT) (Reed, 1943; Wade, 1955; Hunt, Poole & Reeve, 1968; Stewart, Mountain &

147   Colcock, 1972; Skandalakis et al., 1976; Papadatos, 1978; Proye et al., 1982; Flament, Delattre

148   & Palot, 1983; Henry et al., 1988; Menck, Grüber & Lierse, 1990; Lekacos et al., 1992; Freschi

149   et al., 1994; Moreau et al., 1998; Sasou, Nakamura & Kurihara, 1998; Sturniolo et al., 1999;

150   Campos & Henriques, 2000; Raffaelli, Iacobone & Henry, 2000; Watanabe et al., 2001, 2016a;

151   Monfared, Gorti & Kim, 2002; Page, Foulon & Strunski, 2003; Hermans et al., 2003; Ardito et

152   al., 2004; Toniato et al., 2004; Spartà et al., 2004; Sciumè et al., 2005; Shindo, Wu & Park, 2005;

153   Beneragama & Serpell, 2006; Maranillo et al., 2008; Makay et al., 2008; Serpell, Yeung &

154   Grodski, 2009; Lee et al., 2009; Sunanda, Tilakeratne & De Silva, 2010; Shao et al., 2010; Wang

155   et al., 2011; Kaisha, Wobenjo & Saidi, 2011; Kandil et al., 2011; Pradeep, Jayashree & Harshita,

156   2012; Chiang et al., 2012; Tang et al., 2012; Benouaich et al., 2012; Asgharpour et al., 2012;

157   Silva, Siqueira & Arruda, 2013; Donatini, Carnaille & Dionigi, 2013; Satoh et al., 2013; Cai et

158   al., 2013; Hong, Park & Yang, 2014; Yang et al., 2014; Han, Bai & Lu, 2015; Dolezel et al.,

159   2015; Iacobone et al., 2015; Buła et al., 2015; Ngo Nyeki et al., 2015; Barczyński et al., 2015).

160   The dates of the included studies spanned the period from 1943 to 2016. Their geographical

161   distribution was extremely wide, the most substantial contributions coming from Europe (27

162   studies) and Asia (15 studies).

163

164   **Prevalence of a Right NRLN**

165   A total of 53 studies (33,571 right RLNs) reported data on the prevalence of a right NRLN. The

166   overall pooled prevalence estimate in the general population was 0.7% [95%CI: 0.6-0.9; I^2 =42.5

167   (95%CI: 20.2-58.6); p=0.001] (Figure 4).

168   In subgroup analysis, the pooled prevalence of a right NRLN was significantly higher in cadaveric

169   (1.4%, 95%CI: 0.9-2.0) than intraoperative (0.7%, 95%CI: 0.5-0.8) studies (Table 2). Subgroup

170   analysis by geographical origin revealed no significant differences (Table 3), and no significant

171   differences were detected in the leave-one-out sensitivity analysis.

172

173   **Types of Right NRLN**

174   A total of 14 studies (n=81 right NRLNs) reported extractable data on the type of NRLN with

175   respect to its level of origin from the vagus nerve. In 58.3% (95%CI: 36.1-79.0) of cases, the

176   NRLN originated at or above the level of the laryngotracheal junction, while in 41.7% (95%CI:

177   21.0-63.9) it originated below that level (I^2=67.6%, 95%CI: 43.4-81.4; p< 0.001).

178

179   **Prevalence of an aberrant subclavian artery in cases of Right NRLNs**

180   In 21 studies with right NRLNs (n=136 nerves), an aberrant subclavian artery was reported. An

181   aberrant subclavian artery was present in 89.3% (95%CI: 79.6-96.3) of cases (I^2=49.1%, 95%CI:

182   15.7-69.3; p=0.006).

183

184   **Prevalence of a Left NRLN**

185   A total of 41 studies with left RLNs (n=20,006) reported data on the prevalence of a left NRLN.

186   Only one of the included studies, by Henry in 1988, reported the presence of left NRLNs (two

187   cases, both in patients with situs inversus), which equated to a pooled prevalence estimate of 0%

188   (95%CI: 0-0.1; I^2 =0%, p=1.0) (Henry et al., 1988).

189

DISCUSSION

190

191 The NRLN, a rare, often developmentally-derived variant of the RLN, most often results from

192 partial failure of the pharyngeal apparatus during embryo development (Watanabe et al., 2016b).

193 A NRLN can very easily be injured surgically and this leads to long-term postoperative

194 complications such as vocal cord paralysis. Adequate identification and isolation is most important

195 for preventing injury (Toniato et al., 2004). The frequency of NRLN injury remains poorly

196 reported, vague, and believed to be continually underestimated (Dolezel et al., 2015).

197 The pooled prevalence rates of NRLN were calculated solely from studies that provided

198 information about the rate per side in patients or cadavers. No NRLN has ever been noted on the

199 left side in the absence of rare pathologies such as situs inversus with accompanying aortic arch

200 abnormalities (Toniato et al., 2004; Hong, Park & Yang, 2014). To include studies that mixed right

201 and left sides into one rate would dilute and thereby falsify the overall pooled prevalence rates.

202 We therefore infer that the best representation of overall NRLN prevalence is its existence on the

203 right side. Thus, the pooled prevalence estimate of a right-sided NRLN is a proxy of the pooled

204 prevalence estimate of NRLN per person/cadaver. In support of our decision to include only

205 studies that reported rates per side, we calculated the prevalence of left NRLNs on the basis of

206 literature data. The prevalence was 0% in a sample of 20,006 left nerves examined, indicating that

207 this anomaly occurs in <0.1% of the population.

208 We found an overall pooled prevalence of right NRLN of 0.7% in the general population.

209 Subgroup analysis based on study modality revealed significant differences, NRLNs being found

210 more than twice as often in cadavers as in operative subjects. We should note that because of such

211 limitations in the intraoperative viewing of anatomical structures as equipment obstruction, edema,

212 inflammation, and small caliber of nerve branches, the cadaveric rate (1.4%) could reflect the

213   NRLN's true prevalence better. However, the cadaveric group (1,700 nerves) was limited by its

214   small sample size, dwarfed by the intraoperative group (31,277 nerves). Further subgroup analysis

215   based on geographical origin of the study revealed no notable differences among populations.

216   A subanalysis of variant nerves allowed the types of origin of the NRLN to be assessed on the basis

217   of whether they lay above or below the laryngotracheal junction (LTJ); the prevalence values were

218   58.3% and 41.7%, respectively. Many previous articles have developed classification systems for

219   NRLN origins, but very few have used the same system, the majority just describing the NRLNs

220   identified (Stewart, Mountain & Colcock, 1972; Henry et al., 1988; Toniato et al., 2004; Chiang

221   et al., 2012; Hong, Park & Yang, 2014; Dolezel et al., 2015). However, the nerves differed in their

222   courses despite originating from similar levels on the vagus nerve. Some NRLNs exhibited a

223   course in which the nerve immediately tracks medially and enters the larynx. As described in the

224   study by Toniato et al., most patients with NRLNs who experienced injuries in their series had

225   nerves that originated above the LTJ and coursed with the superior thyroid artery (Toniato et al.,

226   2004). Another subset of patients had NRLNs originating above the LTJ but displaying a looping

227   course, where after originating they descended inferiorly and then reascended superiorly before

228   entering the larynx (Figure 5) (Toniato et al., 2004; Hong, Park & Yang, 2014).

229   The prevalence of a right NRLN was strongly associated with the presence of aberrant subclavian

230   artery, the causative anomaly of Dysphagia Lusoria (Bayford-Autenrieth Dysphagia) (Watanabe

231   et al., 2001). The symptoms associated with an aberrant subclavian artery are very often silent, but

232   if present can include dysphagia, chronic cough, and unexplained ischemia of the right upper limb

233   (Natsis et al., 2015). We noted that 86.7% of right NRLN patients had an aberrant subclavian artery

234   pattern. The embryological pathogenesis of a NRLN with an aberrant subclavian artery is clear

235   and understood, but the presence of the variant nerve without the accompanying vascular anomaly

236   remains a mystery (Dolezel et al., 2015). Wang et al. noted, along with the research by Raffaelli

237   et al., that the origin of the NRLN was never confirmed to be the vagus in these non-aberrant

238   subclavian artery cases (Raffaelli, Iacobone & Henry, 2000; Wang et al., 2011). It is posited that

239   the connecting branches between the sympathetic trunk and normal RLN could be mistaken for a

240   NRLN (Raffaelli, Iacobone & Henry, 2000).

241   Preoperative identification of aberrant subclavian arteries and NRLNs is the best defense for a

242   surgeon. As was noted by Iacobone for USG and Watanabe for Computed Tomography (CT),

243   identification of these variant structures is potentially 100% of the time by using these imaging

244   techniques (Iacobone et al., 2015; Watanabe et al., 2016a). Another option for identification

245   intraoperatively is the use of nerve monitoring (IONM) techniques. Dolezel reports that the use of

246   IONM increased the prevalence of NRLNs yet decreased the incidence of postoperative nerve

247   palsy (Dolezel et al., 2015). The use of IONM is particularly advantageous when patients have an

248   underlying pathology which may restrict surgical dissection and viewability of the neural

249   structures (Barczyński et al., 2014). The IONM technology is continually becoming more

250   advanced and provides a promising tool for use in future procedures.

251   Additional research on this topic is necessary to assess the possible etiologies of the NRLN when

252   it occurs in the absence of an aberrant subclavian artery. Furthermore, morphometric analysis of

253   the NRLN with regard to its origin and course would provide useful insight into its behavior and

254   enable its location to predicted more readily for operative planning. Nonetheless, since the variant

255   occurs in nearly 1% of the population and is associated with a high risk of iatrogenic injury, we

256   recommend preoperative USG examination for all patients undergoing procedures in the anterior

257   neck.

258   This study was limited by several facets, particularly, several studies were omitted from the meta-

259   analysis due to the lack of reported data on the side of occurrence of the NRLN. Moreover,

260   although we performed detailed subgroup investigations, high levels of heterogeneity lingered

261   between the included studies. We suspect that this is because of inherent variability in the

262   occurrence of the NRLN. Lastly, no quality and risk-of-bias assessment of included studies was

263   performed due to a lack of an available tool for the field of anatomy.

264

265

266

267 **CONCLUSIONS**

268 The NRLN is an asymptomatic and most often embryologically-derived variant of the RLN in

269 which the nerve arises directly from the vagus at a cervical level. In healthy patients the anomaly

270 is restricted to the right side and, if present, is a very clinically relevant structure, particularly for

271 surgeons conducting procedures directly or requiring access to the anterior neck. Non-Recurrent

272 Laryngeal Nerves are associated with increased risks for iatrogenic surgical injury, most often

273 leading to either temporary or permanent vocal cord paralysis. While a NRLN occurs in only about

274 1% of the population, the high risk of iatrogenic injury indicates that its possible occurrence in a

275 patient should be screened preoperatively using USG. A thorough and complete understanding of

276 the prevalence, origin, and associated pathologies is vital for preventing injuries and for ensuring

277 patient safety and operative success.

278

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444 **TABLES**

445 **Table 1 - Table of Included Studies**

Study	Country	Type	# of Right RLNs	# of NRLN (Prevalence)
Ardito 2004	Italy	IP	1342	5 (0.37%)
Asgharpour 2012	Spain	C	143	1 (0.70%)
Barczynski 2015	Poland	IP	1250	9 (0.72%)
Beneragama 2006	Australia	IP	114	1 (0.88%)
Benouaich 2012	France	C	10	0 (0%)
Bula 2015	Poland	IP	1710	4 (0.23%)
Cai 2013	China	IP	783	4 (0.51%)
Campos 2000	Brazil	C	71	0 (0%)
Chiang 2012	Taiwan	IP	310	4 (1.29%)
Dolezel 2015	Czech Republic	IR	725	4 (0.55%)
Donatini 2013	France	IR	402	11 (2.74%)
Flament 1983	France	C	100	2 (2%)
Freschi 1994	Italy	IP	42	0 (0%)
Han 2015	China	IR	1056	6 (0.57%)
Henry 1988	France	IR	4921	31 (0.63%)
Hermans 2003	Belgium	IP	484	1 (0.21%)
Hong 2014	Korea	IR	2187	15 (0.69%)
Hunt 1968	Australia	C	77	1 (1.30%)

Iacobone 2015	Italy	IP	1477	17 (1.15%)
Kaisha 2011	Kenya	C	73	1 (1.37%)
Kandil 2011	USA	IP	162	0 (0%)
Lee 2009	Korea	C	70	0 (0%)
Lekacos 1992	Greece	IR	109	1 (0.92%)
Makay 2008	Turkey	IP	250	0 (0%)
Maranillo 2008	Spain	C	137	1 (0.73%)
Menck 1990	Germany	C	101	0 (0%)
Monfared 2002	USA	C	21	1 (4.76%)
Moreau 1998	France	C	17	0 (0%)
Ngo Nyeki 2015	Switzerland	IP	32	0 (0%)
Page 2003	France	IP	205	0 (0%)
Papadatos 1978	France	C	239	2 (0.84%)
Pradeep 2012	India	IR	324	1 (0.31%)
Proye 1982	France	IR	2490	15 (0.60%)
Raffaelli 2000	France	IP	656	3 (0.46%)
Reed 1943	USA	C	253	3 (1.19%)
Sasou 1998	Japan	IR	367	0 (0%)
Satoh 2013	Japan	IR	1561	11 (0.70%)
Sciumè 2005	Italy	IR	263	2 (0.76%)
Serpell 2009	Australia	IP	432	1 (0.23%)

Shao 2010	China	IP	1988	12 (0.60%)
Shindo 2005	USA	IP	149	1 (0.67%)
Silva 2013	Brazil	C	106	1 (0.94%)
Skandalakis 1976	USA	C	102	1 (0.98%)
Sparta 2004	France	IP	274	2 (0.73%)
Stewart 1972	England	IP	1776	6 (0.34%)
Sturniolo 1999	Italy	IR	141	0 (0%)
Sunanda 2010	Sri Lanka	IP	24	1 (4.17%)
Tang 2012	China	C	80	2 (2.50%)
Wade 1955	England	C	100	4 (4%)
Wang 2011	China	IR	290	9 (3.10%)
Watanabe 2001	Japan	Imaging (CT)	594	6 (1.01%)
Watanabe 2016	Japan	IP	730	4 (0.55%)
Yang 2014	China	IR	2251	28 (1.24%)

446 RLN - Recurrent Laryngeal Nerve, NRLN - Non-Recurrent Laryngeal Nerve, C - Cadaveric, IP -
447 Intraoperative Prospective, IR - Intraoperative Retrospective

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454 **Table 2 - Type of Study Subgroup Analysis for Prevalence of a NRLN**

	# of studies (# of nerves)	Prevalence of NRLN: % (95% CI)	I^2: % (95% CI)	Cochrane's Q, p-value
Overall	53 (33571)	0.7 (0.6-0.9)	42.5 (20.2-58.6)	0.001
Cadaveric	17 (1700)	1.4 (0.9-2.0)	0 (0-33.1)	0.761
Intraoperative	35 (31277)	0.7 (0.5-0.8)	50.6 (27.1-66.5)	< 0.001
Intraoperative (Prospective)	21 (14190)	0.5 (0.4-0.7)	22.7 (0-54.6)	0.170
Intraoperative (Retrospective)	14 (17087)	0.8 (0.6-1.1)	64.9 (38.0-80.1)	< 0.001

455 NRLN - Non-Recurrent Laryngeal Nerve

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467 **Table 3 - Geographical Subgroup Analysis for Prevalence of a NRLN**

	# of studies (# of nerves)	Prevalence of NRLN: % (95% CI)	I^2: % (95% CI)	Cochrane's Q, p-value
Overall	53 (33571)	0.7 (0.6-0.9)	42.5 (20.2-58.6)	0.001
Africa	2 (105)	1.5 (0.0-4.3)	0.0 (0.0-0.0)	0.613
Asia	15 (12615)	0.8 (0.6-1.1)	54.2 (18.0-74.4)	0.006
Europe	25 (17588)	0.7 (0.5-0.9)	45.0 (11.9-65.6)	0.008
North America	6 (2463)	0.7 (0.2-1.4)	38.4 (0.0-75.5)	0.149
Oceania	3 (623)	0.6 (0.0-1.5)	14.1 (0-91.1)	0.312
South America	2 (177)	0.9 (0.0-2.5)	0.0 (0.0-0.0)	0.449

468 NRLN - Non-Recurrent Laryngeal Nerve

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479   FIGURES

480   **Figure 1 -** Normal Right Recurrent Laryngeal Nerve (A) and Right Non-Recurrent Laryngeal

481   Nerve in the Presence of an aberrant subclavian artery (B)

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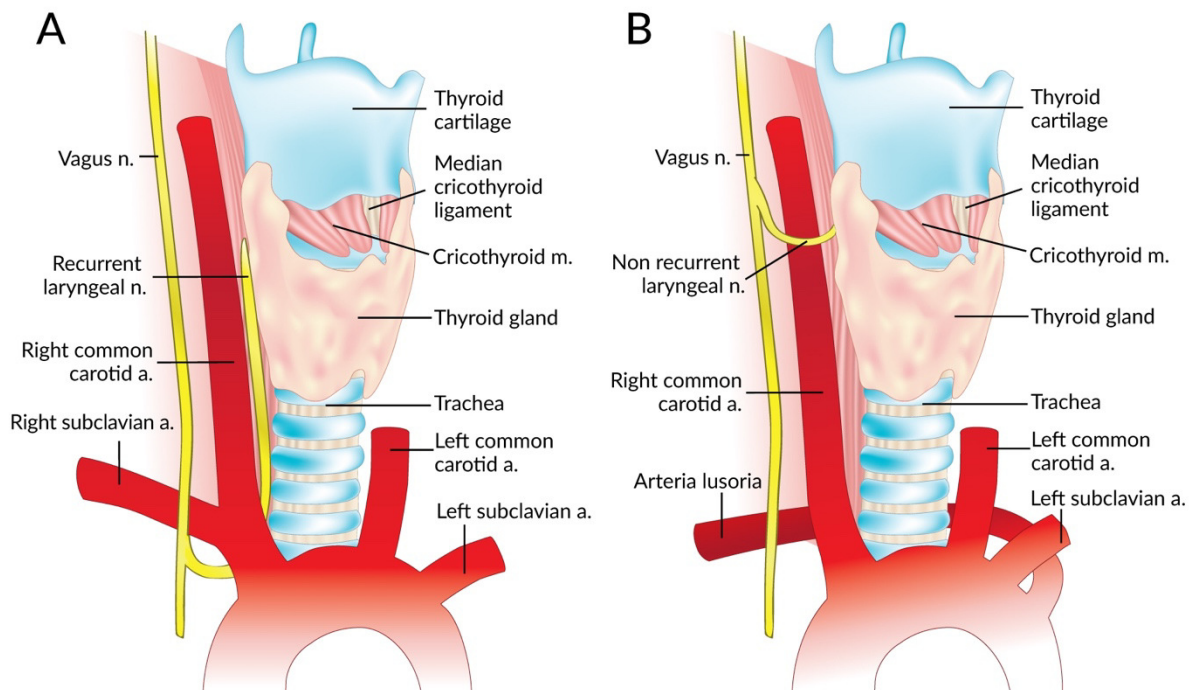
491   **Figure 2 -** A Non-Recurrent Laryngeal Nerve Originating from the Vagus Nerve above (A) and

492   below (B) the Laryngotracheal Junction

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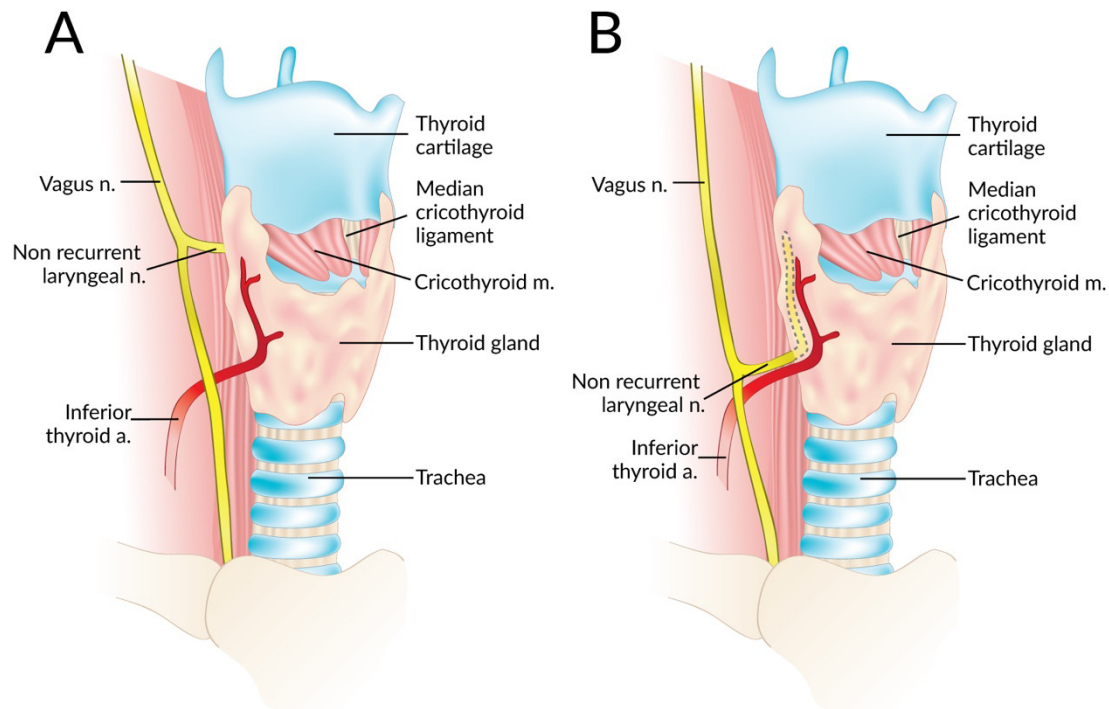
503   **Figure 3 -** Flowchart of Study Search, Eligibility Assessment, and Inclusion

| Records identified through database searching (n = 2,795) | # of additional records identified through reference searching (n = 84) |

Duplicates removed (n = 41)

Records screened (n =2,838) → Records excluded for not meeting inclusion crtieria (n = 2,510)

Full-text articles assessed for eligibility (n = 328) →

Full-text articles excluded, with reasons (n = 275)

Animal study = 1

Case reports or series = 31

Conference abstract = 3

Data not reported by side: 21

Incomplete data = 9

Letter to editor = 13

No relevant data = 172

Overlapping data = 14

Review articles = 11

Studies included in the meta-analysis (n = 53)

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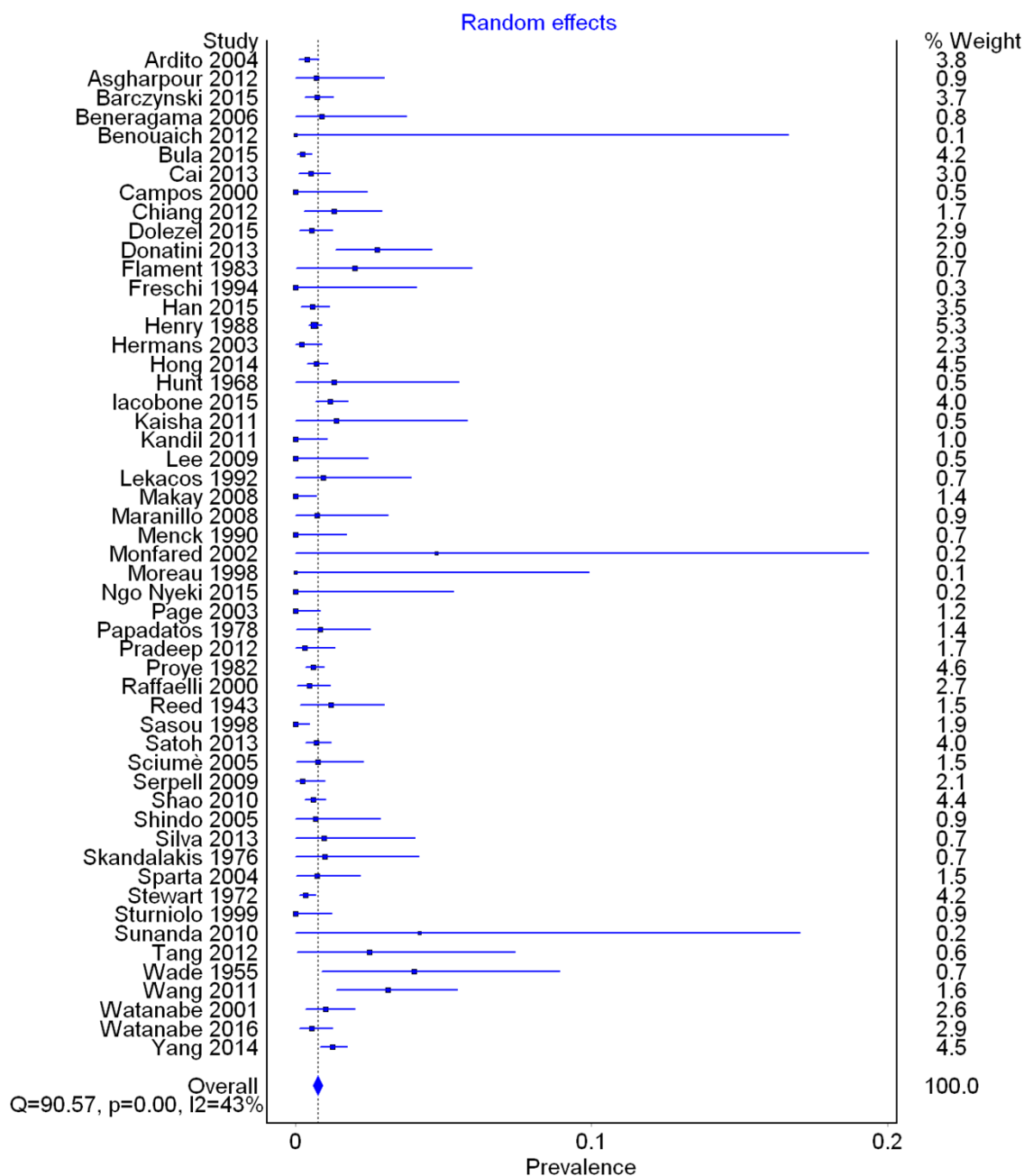
508 **Figure 4 -** Forest Plot for Pooled Prevalence of a Non-Recurrent Laryngeal Nerve

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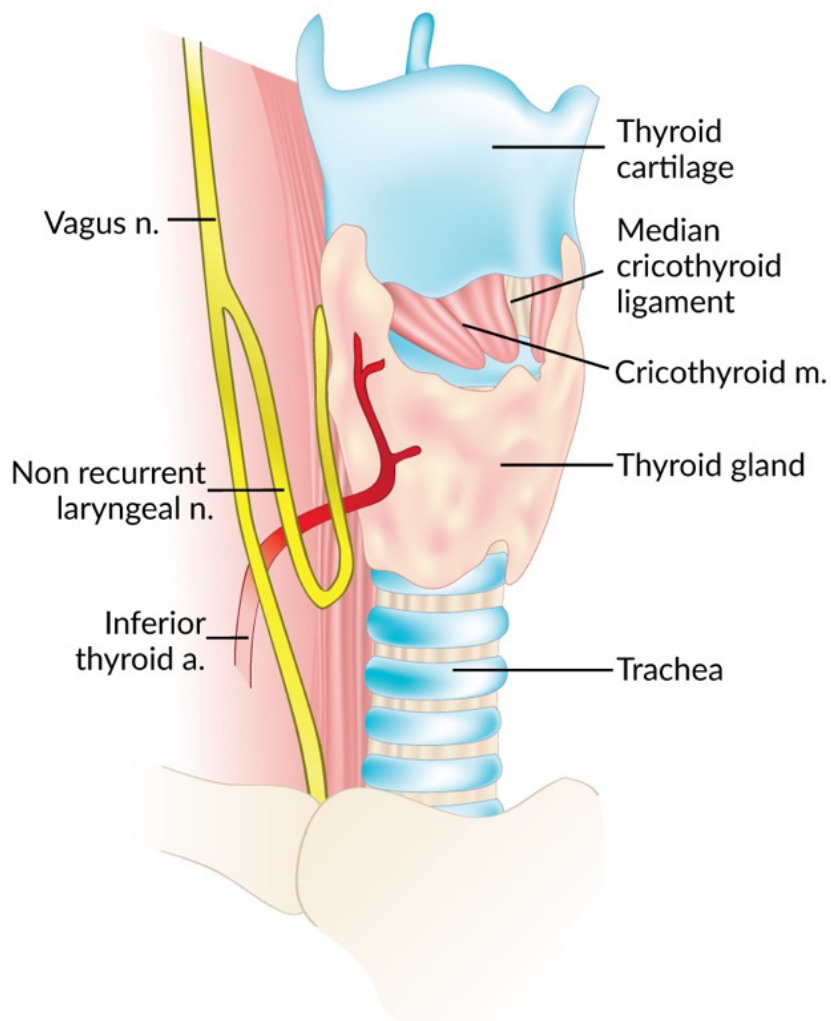
512   **Figure 5 -** Looping Course of a Right Non-Recurrent Laryngeal Nerve

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519   **SUPPPLEMTAL INFORMATION LEGENDS**

520   Supplement Table 1 - Search Strategy for PubMed

521   Supplement Table 2 - PRISMA 2009 Checklist

522   Supplement Table 3 – Complete Study Data

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