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Review

Systematic review with meta-analysis of intraoperative neuromonitoring during thyroidectomy

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HIGHLIGHTS

- The meta-analysis and systematic review including latest and most literature about utilities of IONM in thyroid surgeries.
- The first systematic review with thyroid cancer focused discussion.
- First introduced comparison with CIONM and IIONM in meta-analysis.
- The most comprehensive discussion about RLNP reducing rate and Predictive Power.

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ABSTRACT

Introduction: Intraoperative neuromonitoring (IONM) has been a commonly used technology during thyroid surgery aimed at reducing the incidence of recurrent laryngeal nerve palsy (RLNP), which is a severe complication and leads to significant impacts on a patient's life. In order to give a comprehensive assessment for potential benefits and disadvantage of IONM, this meta-analysis and systematic review discusses RLNP rate, predictive power, continuous intraoperative neuromonitoring (CIONM), and emphasises application during thyroid cancer surgeries.
Methods: A literature search was performed in the following electronic databases: PubMed, Embase, and the Cochrane library from January 1, 2004 to July 30, 2016. After applying inclusion and exclusion criteria, 24 studies, including four prospective randomised trials, were selected. Heterogeneity of studies was checked by the Cochran Q test. Publication bias was assessed by funnel plots with Egger's linear regression test of asymmetry. Odds ratio (OR) was calculated by random effects model.
Results: Overall, 9203 patients and 17,203 nerves at risk (NAR) were included. Incidence of overall, transient, and persistent RLNP in IONM group were, respectively, 3.15%, 1.82%, and 0.67%, whereas for the ID group, they were 4.37%, 2.58%, and 1.07%. The summary OR of overall, transient, and persistent RLNP compared using IONM and ID were, respectively, 0.81 (95%CI 0.66–0.99), 0.76 (95%CI 0.61–0.94), and 0.78 (95%CI 0.55–1.09).
Conclusions: The presented data showed benefits of reducing RLNP rate by using IONM, but without statistical significance for persistent RLNP rate. For patients with thyroid cancer who undergo total thyroidectomy, using IONM may improve the outcome by reducing amount of residual thyroid tissue. However, no benefits were found for thyroid reoperation; visual identification and careful dissection remain standard for this challenging procedure. In addition, the relative low positive predictive power indicated intermittent intraoperative neuromonitoring (IIONM) may not be reliable; but CIONM was showed to be a more promising method, with prudent approach.

1. Introduction

With increasing numbers of thyroid surgery conducted in recent years, recurrent laryngeal nerve palsy (RLNP) has received more

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and more attention. Although the incidence of RLNP is relatively low, persistent hoarseness due to this condition has significant negative impact on a patient's quality of life [1]. In addition, RLNP has become the leading cause of litigation in a thyroidectomy [2]. Since being first introduced in 1966 as an adjunct to conventional visual identification of the RLNP during thyroid surgery [3], intraoperative neuromonitoring (IONM) has developed for 50 years. Although the use of IONM is widespread, and even considered to be the standard of care in some cancer centres, the effectiveness of this prevalent technology is still debatable.

The prevalence of using IONM during thyroidectomy is attributed to its two benefits: to verify the functional integrity of RLN during thyroid surgery, and to aid the surgeon in RLN localisation before visualisation during operations, especially for high-risk situations—reoperative settings and malignant disease surgery. The efficacy of the first purpose can be measured by predictive power (sensitivity, specificity, PPV, and NPV), and the utility of secondary purpose can be identified by reduction of RLNP's incidence (overall, transient, and persistent). It is critically important to develop a clearer understanding of the real impact of IONM. For this reason, the primary purpose of this study was to use the meta-analytic approach to assess the role of IONM in aiding thyroid surgery.

2. Methods

This systematic review was reported in accordance with the Primary Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [4] and the Cochrane Handbook for Systematic Reviews of Intervention. For performing the literature search, the following electronic databases were used: web-based PubMed database, Embase, and the Cochrane Library. Publication data were selected from January 1, 2004 to July 30, 2016. The following keywords and key terms with Boolean operators were used in electronic searching: thyroid, thyroidectomy, RLN, recurrent laryngeal nerve, IONM, intraoperative neuromonitoring, neuro, monitoring. Hand-searching of the reference list was performed in previously conducted meta-analysis and relevant articles.

2.1. Literature review

The exclusion criteria used in this study were the following: 1. No distinction between the results of the IONM group from the ID (control) group. 2. No specified value for number of nerves at risk (NAR) or patients. 3. No separate record of overall RLNP incidence by INOM versus visual identification alone; however, if only transient/persistent RLNP rate record was missed, the study was still eligible for inclusion. 4. The data were not collected by conducting head/neck surgeries. Two investigators, working independently, scanned and assessed the title, abstract, and full text; if the eligibility could not be determined from the title and abstract, of all searched studies against the inclusion and exclusion criteria. Any uncertainties and disagreements as to eligibility were referred to a third investigator and resolved by consensus. After obtaining the eligible publications, data were extracted into a predefined Excel table by one investigator and reviewed by another.

2.2. Data collection

The data items collected included the following: demographics characteristic of operations and patients, such as study type [i.e., prospective/retrospective comparative study (PCS/RCS), randomised controlled trial (RCT)]; country of study and dates; patients' average ages and genders; and the data for calculating primary outcome separately by with and without IONM: number of patients, number of nerves at risk (NAR), overall RLNP, transient RLNP, and persistent RLNP. Primary outcomes of interest were focusing on utility of IONM and predictive power of neuromonitoring technology. In order to assess the utility of using IONM, the incidence of overall, transient, and persistent RLNP was calculated between using IONM and visual identification alone. The predictive power of IONM was measured by sensitivity, specificity, and positive/negative predictive values.

2.3. Statistical analysis

Limited to the primary outcome of interest, risk of bias assessment was conducted for all included studies using the Cochrane Collaboration tool [5]. Specifically, assessments were made relative to: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, and (5) incomplete outcome data [6]. The data collected were analyzed using Stata statistical software. The Mantel–Haenszel method was used to calculate odds ratio (OR) and 95% confidence interval (CI). The Cochran Q test was used to test heterogeneity. Funnel plots with Egger's linear regression test of asymmetry were conducted for publication bias assessment in this systematic review.

3. Results

A flow chart of the literature selection process, including criteria for selected and excluded studies, is shown in Fig. 1. After being screened by authors independently, 24 studies were included in this systematic review [1,7–28], four of them are RCTs [10,15,20,28]. All of them were published in English from 2004 to 2016, and conducted in the US, Germany, China, France, Italy, Poland, Brazil, and Turkey (Table 1). In total, 9203 patients, with a median age of 47.5 years (range 21–68 years) and mean sex ratio of 7.3. Of this group, 4682 patients had IONM during thyroid surgery, and 4521 had visual identification alone and served as the control group. The total number of NAR was 17,203, of which 8668 were in the IONM group and 8535 were in the RLN control group. The overall RLNP rates were 3.15% ($n = 273$) with IONM and 4.37% ($n = 373$) in the control group. Transient RLNP rates were 1.82% ($n = 158$) for IONM and 2.58% ($n = 220$) in the control group. The persistent RLNP rates for IONM and ID were, respectively, 0.67% ($n = 58$) and 1.07% ($n = 91$). The present data, Table 2, showed reduced overall, transient, and persistent incidence of RLNP using IONM compared with using visual identification.

The summary OR of total RLN palsy, transient RLN palsy, and persistent RLN palsy for all included data for using IONM in comparison to visual identification alone on thyroidectomy in 24 studies, respectively, were 0.81 with 95% CI = 0.66 to 0.99, 0.76 with 95% CI = 0.61 to 0.94, and 0.78 with 95% CI = 0.55 to 1.09 (Figs. 2–4). The presented data demonstrated a statistically significant difference between using INOM and ID alone for decreasing overall and transient and RLN palsy rate. However, no significant difference was demonstrated for persistent RLNP rate between the two groups. The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous and could be combined. The funnel plots, shown in Figs. 2–4, indicate no influence of publication bias for total, transient, and persistent RLN palsy. There was lack of significant asymmetry in the funnel plot for all studies.

The analysis of RLNP incidence at thyroid cancer surgeries was conducted on 4 studies that reported the absolute numbers of RLNP considered at cancer surgeries [11,13,16,25]. The overall, transient and persistent RLNP rate, shown in Table 3, were 3.89%, 3.03% and 0.86% separately in IONM group compared with 6.58%, 5.02% and 1.57% in visual identification group. The differences were

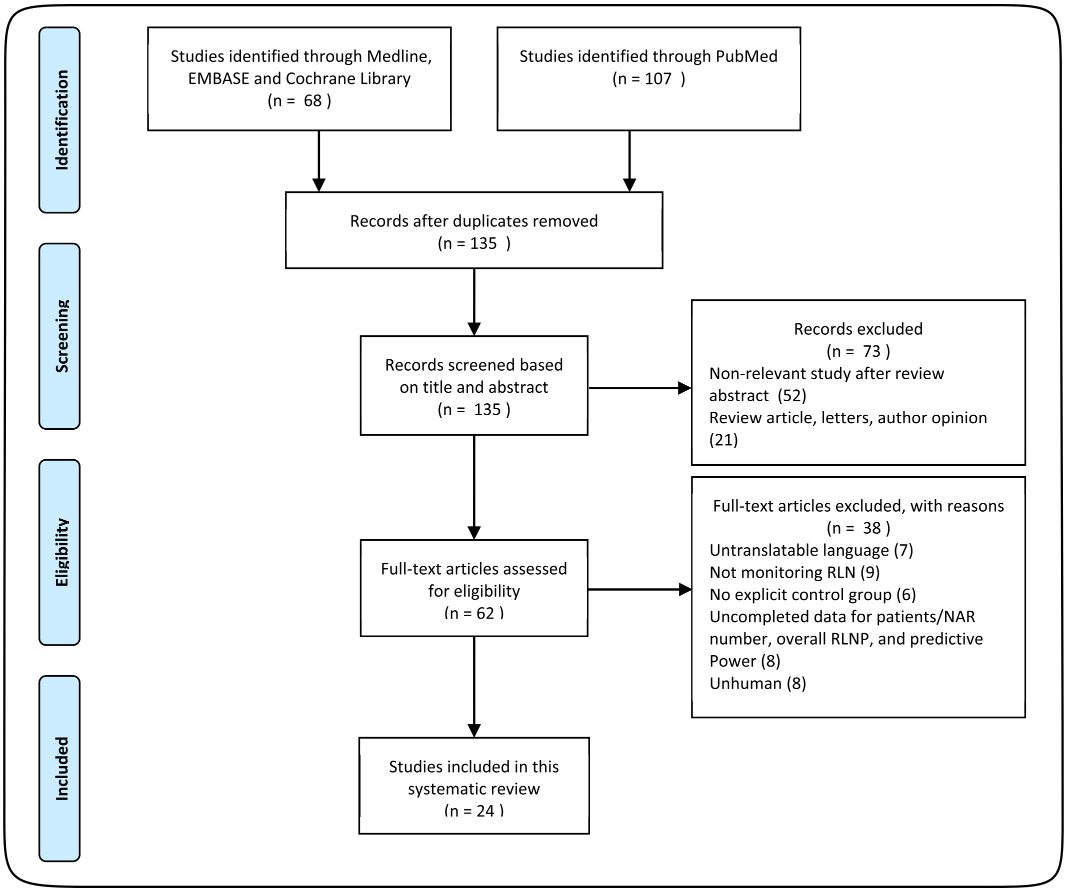

Fig. 1. Flow diagram for the selection of studies. Note: RLNP: Recurrent Laryngeal Nerve Palsy; NAR: Nerves At Risk.

Table 1
Characteristic of operations and patients in included studies. NS: not stated; RCT: randomized controlled trial; RCS: retrospective comparative study; PCS: prospective comparative study.

Study (Year)	Country	Date	Study type	Sample size (Total NAR)	Mean age	Females (%)	Total thyroidectomy (%)
Calò et al., 2016	Italy	2007–2013	RCS	4730	52.2(15–87)	79.20	86.17
Hei et al., 2016	China	2012–2014	RCT	84	47.53 ± 9.87	77.14	4.29
Xie et al., 2016	China	2012–2014	RCS	167	35.01	95.93	35.77
Danschutter et tal. 2015	Netherlands	2009–2012	RCS	170	53 ± 15	86.00	16
Page et al., 2015	France	2001–2010	RCS	1534	53(19–82)	82.14	100
Barczynski et al., 2014	Poland	1993–2012	RCS	1326	54.6 ± 13.2	80.44	38.99
Alesina et al., 2012	Germany	1999–2011	RCS	289	55(25–80)	84.96	26.83
Gremillion et al., 2012	USA	2007–2010	RCS	162	NS	NS	36.13
Stevens et al., 2012	USA	2004–2008	PCS	143	48.1 ± 13.6	59.34	57.14
Duclos et al., 2011	France	2008–2009	PCS	1260	53.3(11.7–90.9)	77.55	83.67
Frattini et al., 2010	Italy	NS	RCS	304	40(19–77)	52.47	100
Sarı et al., 2010	Turkey	2007–2009	RCT	409	47.2 ± 14	82.28	20.68
Barczynski et al., 2009	Poland	2006–2007	RCT	2000	51.9 ± 14.7	91.23	74.9
Dionigi et al., 2009	Italy	2007–2009	RCT	112	39.8(19–77)	86.11	55.56
Agha et al., 2008	Germany	1992–2005	RCS	118	65(39–87)	61.02	28.8
Chiang et al., 2008	Taiwan	2006–2007	PCS	851	47(24–78)	56.20	59.46
Netto et al., 2007	Brazil	2003–2006	PCS	327	43(19–84)	92.30	60.29
Shindo et al., 2007	USA	1998–2005	RCS	1043	NS	NS	52.49
Terris et al., 2007	USA	2004–2006	PCS	176	NS	NS	28.47
Chan et al., 2006	China	2002–2005	PCS	1000	49(8–93)	79.19	55.4
Witt et al., 2005	USA	1998–2003	RCS	190	NS	NS	NS
Robertson et al., 2004	USA	1999–2002	RCS	236	46.5	77.12	NS
Yarbrough et al., 2004	USA	1998–2003	RCS	151	50.4(5–85)	62.50	4.5

statistically significant for overall and transient but not for persistent RLNP rate, which were shown in Fig. 5. Another 4 studies [8,26,28,29] were selected and analyzed for reoperation procedures. The overall, transient and persistent RLNP incidence, shown in Table 4, were 6.21%, 4.72% and 1.48% separately in IONM group compared with 8.30%, 6.04% and 2.25% in control group. The forest plot, shown in Fig. 6, revealed that RLNP rate differences were not statistically significant between the two groups.

Table 2
Overall, transient and persistent recurrent laryngeal nerve palsy (RLNP) rate for employing Intraoperative neuromonitoring (IONM) and visual identification (ID) during thyroid surgeries.

Study (Year)	IONM	ID	IONM	ID	IONM	ID	IONM	ID	IONM	ID
	Nerves at Risk		Patients		Overall		Transient		Persistent	
Calò et al., 2016	2712	2018	1356	1009	29	26	23	20	6	6
Hei et al., 2016	41	43	33	37	7	4	5	3	2	1
Xie et al., 2016	98	69	–	–	6	9	5	7	1	2
Danschutter et tal. 2015	85	85	74	73	2	8	2	2	0	6
Page et al., 2015	612	922	306	461	6	6	–	–	6	6
Barczynski et al., 2014	500	826	306	548	20	72	13	52	7	20
Alesina et al., 2012	128	161	89	157	8	5	8	4	0	1
Gremillion et al., 2012	41	121	31	88	2	4	2	3	0	1
Stevens et al., 2012	62	81	39	52	5	5	4	3	1	2
Duclos et al., 2011	878	382	475	211	36	10	–	–	–	–
Frattini et al., 2010	152	152	76	76	6	14	4	10	2	4
Sarı et al., 2010	210	199	123	114	3	3	3	3	0	0
Atallah et al., 2009	181	240	112	149	16	22	9	13	7	9
Barczynski et al., 2009	1000	1000	500	500	27	50	19	38	8	12
Dionigi et al., 2009	55	57	36	36	1	3	1	3	0	0
Agha et al., 2008	36	82	18	41	1	4	0	2	1	2
Chiang et al., 2008	173	678	–	–	11	40	–	–	–	–
Netto et al., 2007	169	158	104	100	12	12	6	7	6	5
Shindo et al., 2007	671	372	427	257	28	22	16	9	2	1
Terris et al., 2007	92	84	73	64	4	5	4	5	0	0
Chan et al., 2006	501	499	316	323	21	26	17	20	4	6
Witt et al., 2005	83	107	54	83	6	4	4	3	2	1
Robertson et al., 2004	116	120	82	83	5	8	4	5	1	3
Yarbrough et al., 2004	72	79	52	59	11	11	9	8	2	3
Total	**8668**	**8535**	**4682**	**4521**	**273**	**373**	**158**	**220**	**58**	**91**
Incidence per NAR	–	–	–	–	**3.15%**	**4.37%**	**1.82%**	**2.58%**	**0.67%**	**1.07%**

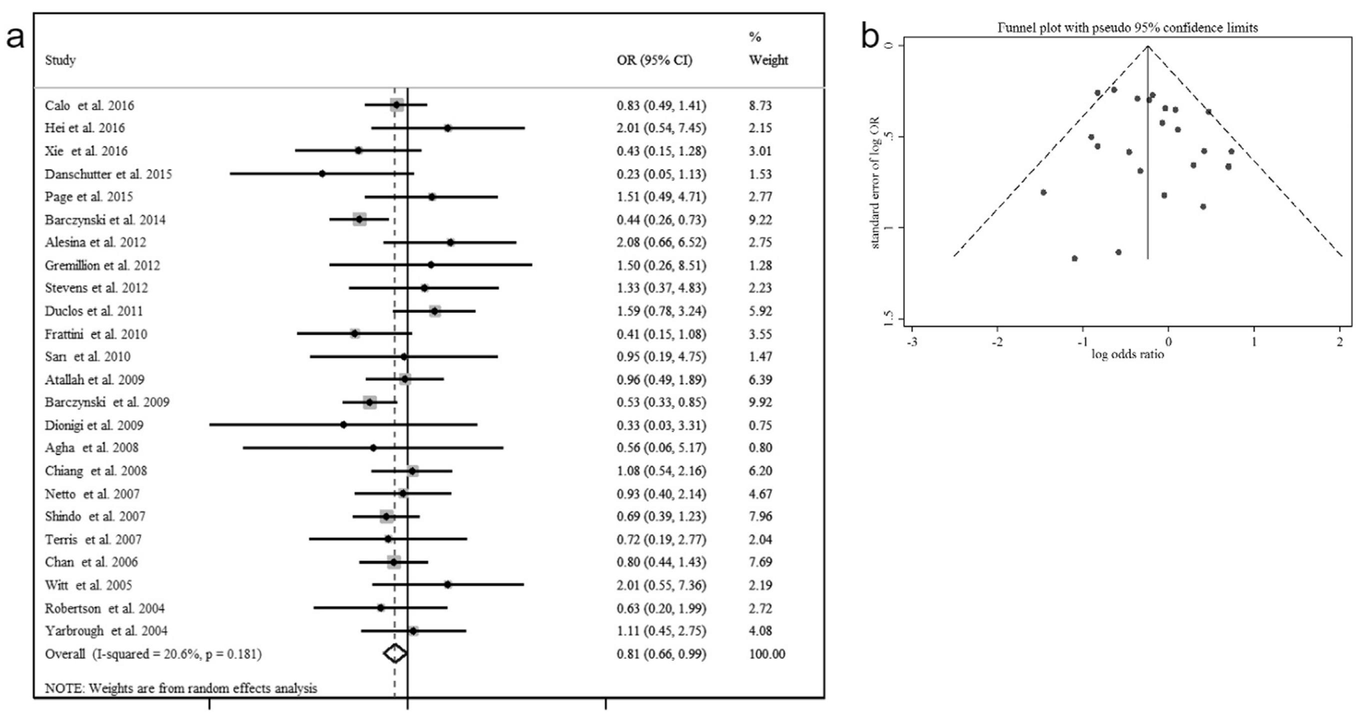

Fig. 2. a) Forest Plot of overall recurrent laryngeal nerve palsy (RLNP) incidence by using Intraoperative neuromonitoring (IONM) compare with visual identification (ID) Heterogeneity: $\tau^2 = 0.0484$ $\chi^2 = 28.99$ $DF = 23$ $P = 0.181$ $I^2 = 20.6\%$ Test for overall effect: Z = 2.05 P = 0.041. **b**) Funnel plot of the log odds ratio (OR) with 95% confidence internals (95% CI) and standard error (SE) for incidence of overall RLNP.

The ability of predicting postoperative vocal cord function is another primary metric for the benefits of using IONM. In clinical nerve monitoring, a missing signal was considered positive, predicting postoperative nerve injury. The test result was regarded as true positive when RLNP was confirmed on postoperative laryngoscopic examination and false positive when normal nerve function was found [10]. Predictive power of selected studies was shown in Table 5. Mean value of sensitivity, specificity, positive

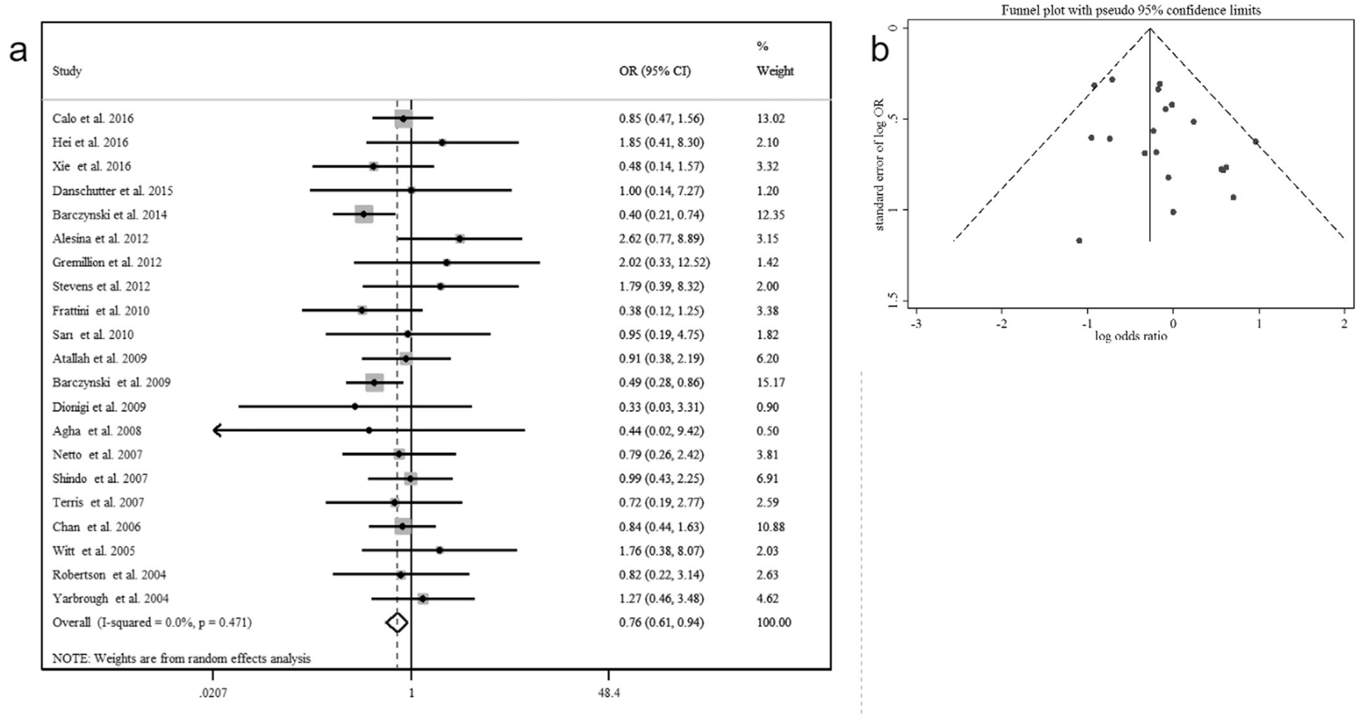

Fig. 3. **a**) Forest Plot of transient recurrent laryngeal nerve palsy (RLNP) incidence by using Intraoperative neuromonitoring (IONM) compare with visual identification (ID) Heterogeneity: $\tau^2 = 0.0000$ $\chi^2 = 19.79$ $DF = 20$ $P = 0.471$ $I^2 = 0.0\%$ Test for overall effect: Z = 2.48 P = 0.013. **b**) Funnel plot of the log odds ratio (OR) with 95% confidence internals (95% CI) and standard error (SE) for incidence of transient RLNP.

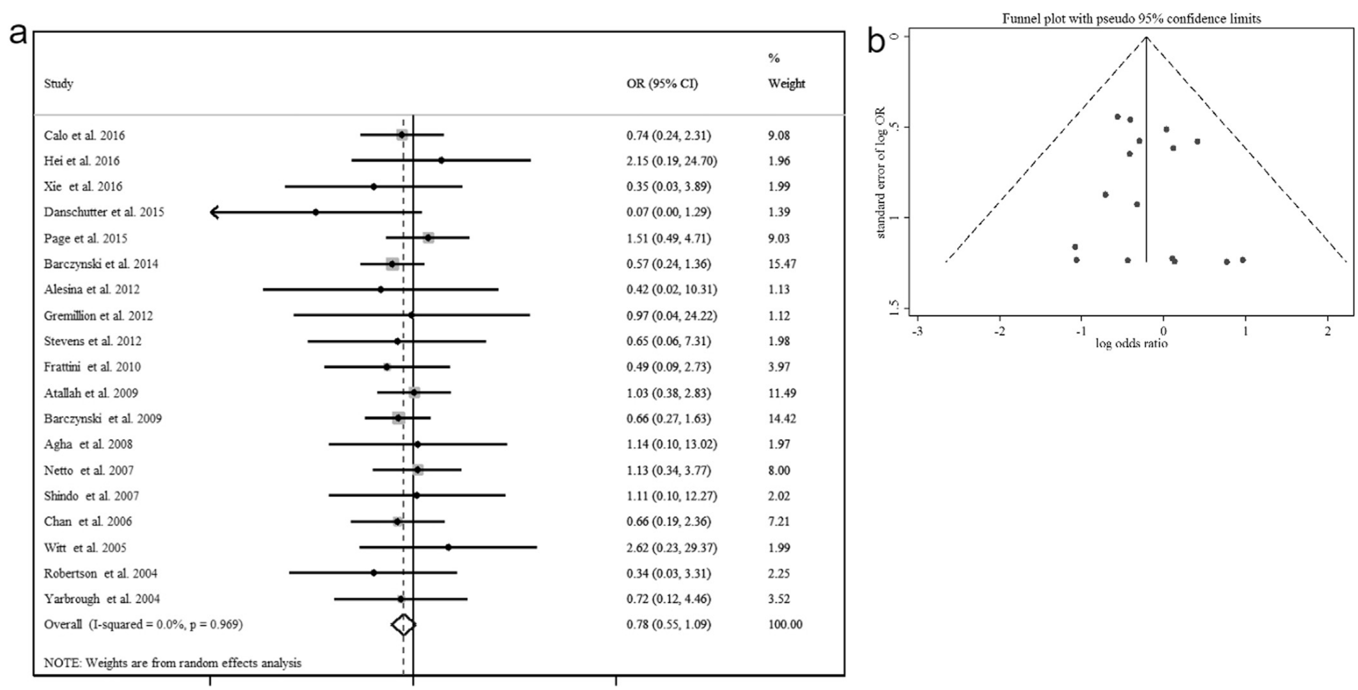

Fig. 4. **a**) Forest Plot of persistent recurrent laryngeal nerve palsy (RLNP) incidence by using Intraoperative neuromonitoring (IONM) compare with visual identification (ID) Heterogeneity: $\tau^2 = 0.0000$ $\chi^2 = 8.56$ $DF = 18$ $P = 0.969$ $I^2 = 0.0\%$ Test for overall effect: Z = 1.45 P = 0.146. **b**) Funnel plot of the log odds ratio (OR) with 95% confidence internals (95% CI) and standard error (SE) for incidence of persistent RLNP.

predictive value (PPV), and negative predictive value (NPV) were, respectively, 66.8%, 97.8%, 63.4%, and 97.4%. The low value of sensitivity and PPV indicated neuromonitoring was not reliable in predicting vocal cord palsy, but can reliably demonstrate intact nerve function, according to high NPV. The sensitivity had a mean value 66.8% (range 36.4%–93.5%), and PPV had a mean value of

Table 3
Overall, transient and persistent recurrent laryngeal nerve palsy (RLNP) rate for employing Intraoperative neuromonitoring (IONM) and visual identification (ID) during thyroid cancer surgeries.

Study (Year)	IONM	ID	IONM	ID	IONM	ID	IONM	ID	IONM	ID
	Nerves at Risk		Patients		Overall		Transient		Persistent	
Xie et al., 2016	98	69	–	–	6	9	5	7	1	2
Barczynski et al., 2011	302	302	151	151	5	10	3	8	2	2
Frattini et al., 2010	152	152	76	76	6	14	4	10	2	4
Chan et al., 2006 (cancer)	142	115	78	63	10	9	9	7	1	2
Total	**694**	**638**	**305**	**290**	**27**	**42**	**21**	**32**	**6**	**10**
Incidence per NAR					**3.89%**	**6.58%**	**3.03%**	**5.02%**	**0.86%**	**1.57%**

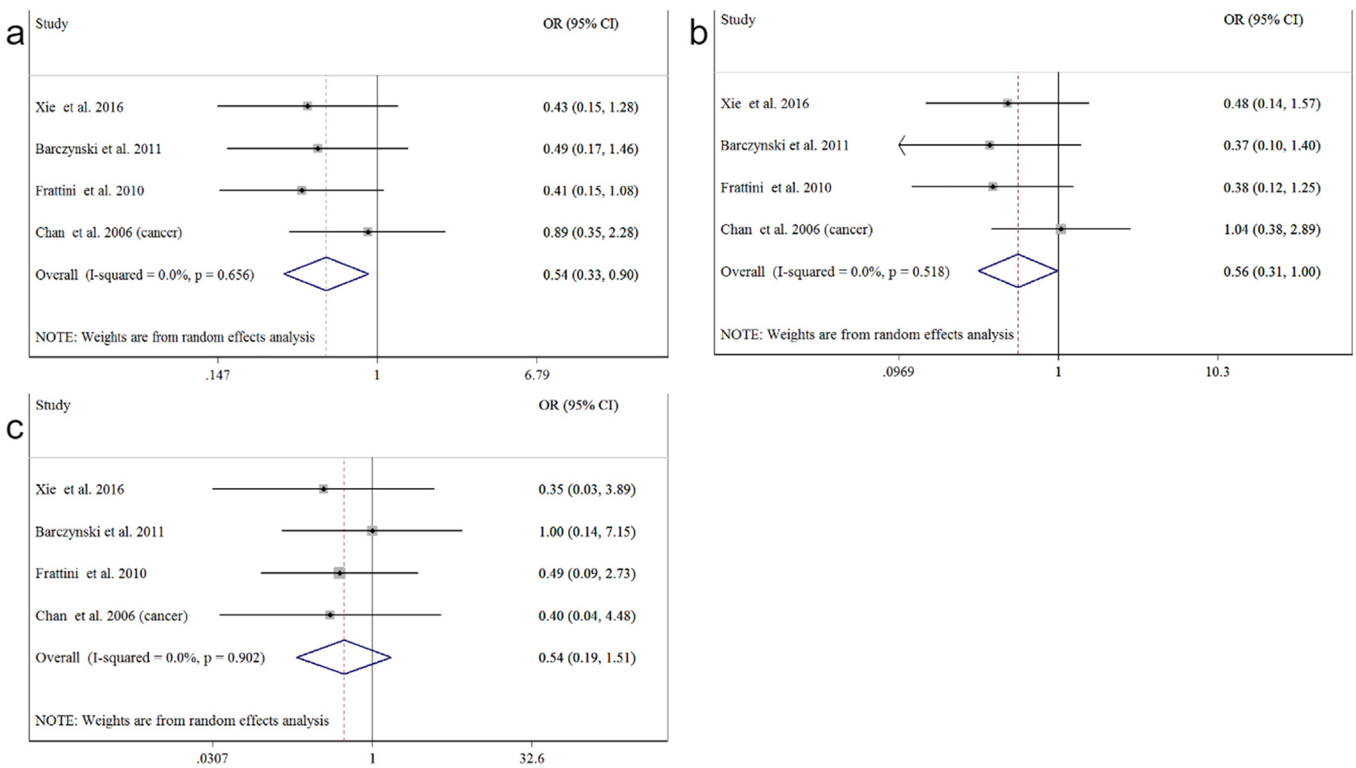

Fig. 5. Forest plots of overall (a), transient (b) and persistent (c) RLNP rate by using Intraoperative neuromonitoring compare with visual identification during thyroid cancer surgeries.

Table 4
Overall, transient and persistent recurrent laryngeal nerve palsy (RLNP) rate for employing Intraoperative neuromonitoring (IONM) and visual identification (ID) during thyroid reoperation procedures.

Study (Year)	IONM	ID	IONM	ID	IONM	ID	IONM	ID	IONM	ID
	Nerves at Risk		Patients		Overall		Transient		Persistent	
Hei et al., 2016	41	43	33	37	7	4	5	3	2	1
Barczynski et al., 2014	500	826	306	548	20	72	13	52	7	20
Alesina et al., 2012	128	161	89	157	8	5	8	4	0	1
Yarbrough et al., 2004	72	79	52	59	11	11	9	8	2	3
Total	**741**	**1109**	**480**	**801**	**46**	**92**	**35**	**67**	**11**	**25**
Incidence per NAR					**6.21%**	**8.30%**	**4.72%**	**6.04%**	**1.48%**	**2.25%**

63.4% (range 35%–92.1%). These findings show significant fluctuation between different studies. Barczynski et al., in 2009, supported these, and in addition noted direct stimulation (through an electrode placed on the ipsilateral RLN nerve) was not as accurate as indirect stimulation (through an electrode placed on the ipsilateral vagus nerve) [10]. Neuromonitoring predictive power was slightly higher for malignant disease (high-risk) situations than benign disease (low-risk) situations.

4. Discussion

Intraoperative electrophysiological neuromonitoring of recurrent laryngeal nerves during thyroid surgery has been employed worldwide as an adjunct to visual identification and to predict postoperative nerve function before concluding the procedure [30,31]. This technique, which is more prevalent in thyroid surgery referral centres and commonly used by surgeons under 40 years of

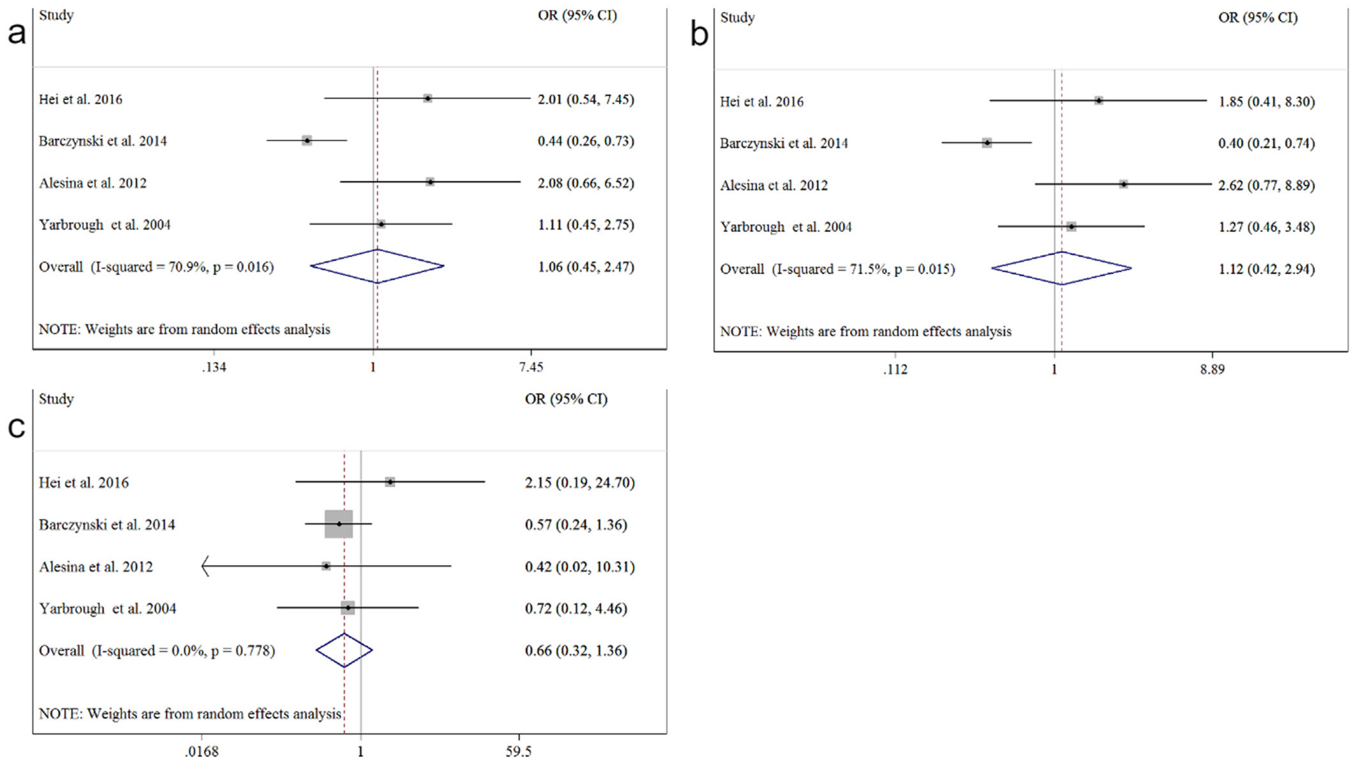

Fig. 6. Forest plots of overall (a), transient (b) and persistent (c) RLNP rate by using Intraoperative neuromonitoring compare with visual identification during reoperation procedures.

Table 5
Review of the literature on prediction of postoperative recurrent laryngeal nerve palsy and the comparison between continuous intraoperative neuromonitoring (CIONM) and intermittent intraoperative neuromonitoring (IIONM) in thyroid surgery. Note: NAR: Nerves at Risk; PPV: Positive Predictive Value; NPV: Negative Predictive Value.

Authors	Year	NAR	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
IIONM						
Yarbrough et al.	2004	151	36.4	96.7	66.7	89.3
Chan et al.	2006	271	53.0	94.0	35.0	97.0
Tomoda et al.	2006	2197	69.3	99.7	92.1	98.5
Barczynski et al.	2009	1000	63.0	97.1	37.8	98.9
Alesina et al.	2012	289	37.5	95.0	43.0	94.0
De Falco et al.	2014	600	83.3	99.5	62.5	99.8
Calò et al.	2014	2068	91.3	99.4	77.8	99.8
Schneider et al.	2015	965	73.9	99.5	77.3	99.4
Calò et al.	2016	4730	93.5	99.4	78.4	99.8
Mean value	–	–	**66.8**	**97.8**	**63.4**	**97.4**
CIONM						
Schneider et al.	2015	1314	90.9	99.7	88.2	99.8
Barczynski et al.	2009	1000				
Indirect stimulation			63.0	97.1	37.8	98.9
Low risk			53.8	97.1	33.3	98.5
High risk			71.4	97.1	35.7	99.1
Direct stimulation			44.4	96.4	25.5	98.4

age [32–34], has been estimated to be used during approximately 40% of thyroid surgeries in US and close to 90% in Germany. However, given the increased cost, comprehensive assessment of the advantages and disadvantage for this technique is imperative.

In this meta-analysis and systematic review, total NAR number of IONM and ID (control) group were relatively large and very closely matched, at 8668 and 8535, respectively. The primary outcome showed reduced RLNP incidence in all of the three categories: overall, transient RLNP, and persistent RLNP. At the same time, the overall and transient RLNP rate decreasing data showed a statistically significant difference between employing IONM and visual identification alone. However, although the presented data showed a benefit of reducing persistent RLNP incidence with employing IONM (reducing from 1.07% to 0.67%), the difference of the data did not reach statistical significance. The reason for this may be that currently included patients and NAR number were inadequate to reflect a statistically significant difference due to the relatively low RLNP rate of persistent RLNP. A larger sample size is needed if we want to make a solid conclusion.

This conclusion was supported by an overwhelming majority of pooled studies [1,3,10,13,14,18,23,26,35–37]. Three single-centre, prospective, RCTs performed by Hei et al. (2016) [28], Barczynski et al. (2009) [10], Dionigi et al. (2009) [3], and Sari et al. (2010) were included. However, because of inherent bias, these sample sizes were not large enough to indicate a statistically significant difference for RLNP rate. In order to prove the benefits of using IONM over visual ID alone with regard to the small difference of RLNP prevalence, an estimated sample size of 9000 NAR was calculated as being required to reliably assess in a prospective randomised trial [38]. Nevertheless, the largest sample size of RCT study conducted by far was 2000 NAR. Thus, achieving an adequate sample size in an RCT setting, particularly in a single centre study may prove impossible. Until RCT with adequate patient numbers can be performed, the use of nonrandomised pooled studies, which have demonstrated fairly accurate results and been advocated for rare conditions for which RCTs are difficult to perform [19], could also be justified for systematic review. Before conducting RLNP rate calculation for pooled randomised and nonrandomised studies, the Cochrane Q test was conducted, and no significant heterogeneity was shown. However, because of inherent bias, such as allocation, performance, and selection, of the current studies, we need to approach with caution.

4.1. Thyroid cancer surgery and reoperation

To date, there are rarely prospective, randomized, large sample size trials focusing on thyroid cancer surgeries and reoperations. Of the 24 studies initially pooled, only 4 were eligible, 3 studies [11,16,25] with entire data and another one [13] with partial relevant data, to be included in quantitative synthesis (Table 3) for thyroid cancer surgeries with total 1332 NAR and 595 patients. From the overall incidence of RLNP difference between Table 2 and Table 3, it is obviously to find out that the RLNP rate (6.58%) in surgeries of thyroid cancer was much larger than average (4.37%) of all 24 pooled studies. However, in the experience groups of using IONM, the average overall RLNP rate of cancer surgeries and entire data decreased to 3.89% and 3.15% separately. Thus, due to the identification of the laryngeal nerves can be difficult in patients undergoing operations for thyroid cancer [39], adoption of IONM to identify and locate the correct position of RLN before visual confirmation might be able to provide benefits and guide surgeons during cancer surgeries. However, since lack of sufficient sample size, this analysis did not reveal statistically significant for persistent RLNP, further studies may needed to confirm it.

For thyroid cancer surgeries, especially when total thyroidectomies are indicated, the surgeon may have to leave some residual thyroid tissue at the site, because it is technically difficult to perform radical excision of thyroid tissue in the area of Berry's ligament. However, with the help of IONM, which was indicated to increase the accuracy of macroscopic identification of RLN bifurcation, surgeons can reduce the volume of residual thyroid tissue in the post-surgical bed in the neck, and prevent restricting the scope of resection to the so-called “near total thyroidectomy” [11]. Thus, potential advantages of employing IONM for thyroid cancer surgery are not only limited to reducing the transient RLNP rate, but also improving the outcomes in patients by increasing the totality of total thyroidectomies.

Compared with primary operation, reoperation represents a greater challenge during thyroid surgery and may lead to increased danger for RLN. With the objective to find whether IONM could provide potential benefits for thyroid reoperation, four studies were performed [8,26,28,29], including one RCT [28], during the past 10 years. However, the pooled data, showed in Fig. 6, did not indicate using IONM to reduce RLNP incidence in repeat thyroid operations compared to using visual identification alone. Many reasons may point to why IONM has been shown beneficial for overall thyroid surgeries but not for reoperation. Because redo procedures are relatively rare due to the wide application of total thyroidectomy, relatively low sample size is not adequate to demonstrate statistical significance, especially for the already very low frequency of RLNP rate. In addition, avoiding RLN injuries may become more difficult, even impossible in certain circumstances during thyroid reoperation, such as dissection of scar tissue adhered by RLNs or invaded by tumours. Thus, nerve visualisation and careful dissection would remain the standard of care to avoid RLNP.

4.2. CIONM and predictive power

Although IONM has not been demonstrated to have significant benefit in all thyroid surgeries, this technique has not stopped developing. Needle electrodes, which were widely employed, have been replaced by less invasive, optimised endotracheal tube electrodes. Real-time continuous intraoperative neuromonitoring (CIONM), which would alert surgeons to halt the suspected causative manoeuvre when impending RLNP is detected prior to ending the procedure and modify the intraoperative strategy, could be employed to replace IIONM, which usually identified RLNP after it occurred. An observational study by Schneider et al. [40] supported this, noting a higher sensitivity of transient RLNP for CIONM compared with IIONM, but not statistically significant, and reduced persistent RLNP rate, shown in Table 5. These benefits could be because recognising impending RLNP helped surgeons to employ a new operational strategy before irreversible damage to the RLN occurred. However, this improved technique still has a false positive rate that cannot be overlooked, and leads to unnecessary procedures (e.g., two-stage thyroidectomy). Furthermore, Terris reported that continuous vagal nerve monitoring might cause serious patient harm (i.e., haemodynamic instability and reversible vagal neuropraxia attributable to the monitoring apparatus) [41], and widespread adoption needs to be prudent.

Although IONM may have a positive contribution to reduce incidence of RLNP [42,43], the added value has yet to be statistically proven [5,18,23,35,36], and has been questioned by many studies [44,45]. As incidence of RLNP using visual identification alone has already been very low in experienced surgeons, margin of improvement by using IONM may be limited. The relatively low positive predictive value (PPV), which is approximately 33–37.8% [10,35], and specificity are additional concerns for the value of employing IONM. However, low PPV may not aggravate the risk of using IONM, because the negative predictive value (NPV) of IONM is as high as 97–99%. This means we could be confident with the result if the signal was indicated to be intact after surgery.

4.3. Limitations

Several limitations should be acknowledged when interpreting the findings from this review. First, we must clarify that only the results of pooled studies, but not the accuracy of them, were systematically reviewed. Because we can only acquire existing information in the published articles, we cannot guarantee that their approaches, data and conclusions are accurate. Second, although over 9000 cases were synthesized, this review was limited to published English language studies. Excluding non-English literatures and unpublished data may introduce potential bias to our conclusion.

5. Conclusion

This current systematic review demonstrated benefits of using IONM in reducing overall and transient RLNP incidence, but no statistically significant difference was indicated for reducing persistent RLNP rate. CIONM was showed as a more feasible and promising method than IIONM, but it need to be approached prudently. Positive contributions of IONM had be observed from studies, but given the additional cost, low PPV, and high false positives, it is not recommended as the standard of care for thyroid surgery before solid confirmation is provided by further studies. However, due to higher predictive power during high-risk procedures and increasing accuracy of macroscopic identification, it may able to guide surgeons and provide additional benefits depending on the surgeon's comfort level and familiarity with this technology. Future studies may include larger patient number, and multicentre, prospective, randomised trials. PPV of IONM should be improved through the establishment of standardised criteria for RLNP diagnosis.

Ethical approval

The protocol for the study was approved by the ethics committee of Fudan University Shanghai Cancer Center.

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Author contribution

Yu Wang designed this meta-analysis and systematic review. Shuwen Yang and Li Zhou extracted key data from the identified publications. All authors screened a portion of the titles and abstracts, and participated in discussion regarding inclusion and exclusion of papers. Shuwen Yang wrote the manuscript and all authors reviewed and approved this prior to submission.

Conflict of interest

The authors declare that there are no conflicts of interest.

Trial registry number

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