Kamel and Kamel
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REVIEW ARTICLE

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Total thyroidectomy versus subtotal thyroidectomy in treatment of multinodular goiter: a meta-analysis

Ahmed A. Kamel[1*] and Mohamed Kamel[2]

Abstract

Background The surgical management of multinodular goiter is the treatment of choice for the majority of cases. There is controversy between radical resection with the lifelong thyroxine substitution and function-preserving resection with the risk for recurrence, and the complications associated with total thyroidectomy.

Objective The aim of the present study was to compare the outcome of total thyroidectomy (TT) in comparison with subtotal thyroidectomy (ST) as regards hypocalcemia, transient nerve injury, and recurrence rate.

Patients and methods This study included published English medical articles in the last 20 years, concerning the treatment of multinodular goiter.

Results Meta-analysis was for the evaluation of surgical outcomes after surgical management of multinodular goiter including total thyroidectomy versus subtotal thyroidectomy by comparing the TT versus ST in our study including 23 studies included of the total number of patients (4485) who underwent subtotal thyroidectomy versus the total number of patients (7116) who underwent total thyroidectomy; a comparison was done as regards postoperative complications including RLN injury (transient or permanent), rate of recurrence, need for reoperation, and incidence of postoperative hypocalcemia. The incidence of RLN injury is lower in ST compared to TT, and its recurrence is much lower in TT than in ST.

Conclusion This meta-analysis showed that the advantages of total thyroidectomy include adequate eradication of the disease, prevention of recurrent goiter, and avoidance of the need for completion surgery in case of occult malignancy, but it is associated with higher morbidity (postoperative thyroidectomy complications: RLN palsy and hypoparathyroidism) and the need for lifelong replacement therapy (L-thyroxin supplementation).

Keywords Total thyroidectomy, Subtotal thyroidectomy, Multinodular goiter

Background

Surgical management of multinodular goiter is still controversial [1], Among surgical approaches include total thyroidectomy and subtotal thyroidectomy [2].

Aim of the work

The aim of this work was to compare the outcome of total thyroidectomy in comparison with subtotal thyroidectomy as regards hypoparathyroidism, RLN injury, and recurrence rate.

*Correspondence:
Ahmed A. Kamel
kamel_ent@yahoo.com
[1] Department of Otorhinolaryngology, Faculty of Medicine, Kasr Alainy Faculty of Medicine, Cairo University, Kasr Alainy Street, Cairo, Egypt
[2] Department of Otorhinolaryngology, Faculty of Medicine, Fayoum University, Fayoum, Egypt

Patients and methods

The study was done in the following steps:

- Determination of the target disease.
- Identification and location of articles.
- Screening and evaluation of articles.
- Data collection.
- Data analysis.
- Reporting and interpretation (Results).
- Discussion and conclusion.

Target subject

The target is to compare two techniques of thyroidectomy in the treatment of multinodular goiter, total thyroidectomy, and subtotal thyroidectomy as regards postoperative complications and recurrence.

Identification and location of articles

Studies included published medical articles about the advantages and disadvantages of each total thyroidectomy and subtotal thyroidectomy through searching the MEDLINE database (www.pubmed.com) using the following keywords in different combinations:

- Total thyroidectomy
- Subtotal thyroidectomy
- Multinodular goiter
- Postoperative complication
- Multinodular goiter recurrence
- Incidental thyroid cancer

Over 8000 articles were found. After customizing the date, age, and language, they narrowed to about 3796 articles, and after the exclusion of non-relevant articles of 3780, about 16 relevant articles were found. By application of inclusion criteria, 6 articles were found meeting the inclusion criteria and can undergo meta-analysis.

Screening and evaluation

The screening form of articles was used by the investigators to screen the articles, which were yielded by the MEDLINE search after blinding the author name and journal name. The screen form of the articles is as follows:

1) Irrelevant articles: articles that may have one of the keywords but a different purpose from our study (3780).

Table 1 Included articles

Article	Patients no	Article type
Barczynski et al. 2010 [3]	400	Randomized control trial
Yang et al. 2009 [4]	346	Randomized control trial
Pappalardo et al. 1998 [5]	141	Randomized control trial
Delbridge et al. 1999 [6]	3089	Prospective
Tezelman et al. 2009 [7]	2906	Retrospective
Vaiman et al. 2008 [8]	6072	Retrospective

Table 2 Excluded articles and reason for exclusion

Article	Reason of exclusion
Cirocchi et al. 2015 [9]	Systematic review
Citgez et al. 2013 [10]	Patients not euthyroid
Barczyński et al. 2011 [11]	Patients not euthyroid
Albayrak et al. 2011 [12]	Patients not euthyroid
Koyuncu et al. 2003 [13]	Patients not euthyroid
Karamanakos et al. 2010 [14]	Patients not euthyroid and patients with thyroid carcinoma also included
Riju et al. 2009 [15]	Patients not euthyroid
Ozbas et al. 2005 [16]	Patients not euthyroid and patients with thyroid carcinoma also included
Colak et al. 2004 [17]	Patients not euthyroid
Giles et al. 2004 [18]	Different outcome measures

2) Relevant articles: after the exclusion of repeated and non-relevant articles, articles that contain one or more of the above keywords (16).
3) Included articles: These are 6 articles that fulfilled the following inclusion criteria and were included for further steps of data collection, analysis, and reporting (Table 1):
   - Published in the English language.
   - Since January 1996 till May 2020.
   - Conducted on human subjects.
   - Adults more than 18 years
   - All patients are euthyroid.
   - No patients with suspicion of thyroid malignancy.
   - Only randomized clinical trial, retrospective, and prospective studies.
   - No articles with different outcome measures.
4) Excluded articles: Articles that miss one or more of the above mentioned inclusion criteria (10).

The following table will show the excluded articles and the reason for exclusion Table 2:

Data collection

Information was gathered for each individual study on total thyroidectomy and subtotal thyroidectomy in the treatment of multinodular goiter, and we extracted data from them (postoperative complications and recurrence).

Data analysis

Statistical methods

Statistical analysis was done using Comprehensive Meta Analysis© version 2 (Biostat™, NJ, USA).

Testing for heterogeneity

Studies included in the meta-analysis were tested for heterogeneity of the estimates using the following tests:

1. Cochran Q chi-square test: A statistically significant test (p value < 0.1) denoted heterogeneity among the studies.
2. I-squared (I2) index which is calculated as follows: $I^2 = \left(\frac{Q-df}{Q}\right) * 100\%$. The I-squared is interpreted as follows:

- 0 to 40%: might not be important
- 30 to 60%: may represent moderate heterogeneity
- 50 to 90%: may represent substantial heterogeneity
- 75 to 100%: considerable heterogeneity

Effect size estimation

The effect size for binary outcomes was expressed as relative risk (RR) with its 95% confidence limits (95% CI).

Pooling of estimates

Estimates from included studies were pooled using both the Mantel–Haenszel fixed-effects method (FEM) and the DerSimonia Laird random-effects method (REM). In the absence of significant heterogeneity, the FEM was considered; otherwise, the REM was considered.

Examination of publication bias

Publication bias was assessed by examination of funnel plots. A funnel plot is a plot of the estimated effect size (RR) on the horizontal axis versus the standard error (SE) for the effect size as a measure of study size on the vertical axis.

Large studies appear toward the top of the graph and tend to cluster near the mean effect size. Smaller studies appear toward the bottom of the graph and (since there is more sampling variation in effect size estimates in the smaller studies) will be dispersed across a range of values.

In the absence of publication bias, the studies are expected to be distributed symmetrically about the combined effect size. By contrast, in the presence of bias, it is expected that the bottom of the plot would show a higher concentration of studies on one side of the mean than the other. This would reflect the fact that smaller studies (which appear toward the bottom) are more likely to be published if they have larger-than-average effects, which makes them more likely to meet the criterion for statistical significance.

Level of significance

A two-sided p value < 0.05 denoted statistical significance.

Results

Meta-analysis of the overall incidence of RLN palsy

There is no evidence for heterogeneity among the included studies ($Q = 4.887$, DF = 4, P value 0.299, $I^2 = 18.14\%$) pooling of the studies using fixed effects showed a relative risk of 1.6 with 95% CI of 1.27 to 2.02 which was statistically significant (> 0.001).

Table 3 shows the results of the meta-analysis of the overall incidence of RLN palsy.

There is no evidence for heterogeneity among the included studies ($Q = 4.887$, DF = 4, P value 0.299, $I^2 = 18.14\%$).

Pooling of the studies using fixed effects showed a relative risk of 1.6 with a 95% CI of 1.27 to 2.02 which was statistically significant (> 0.001).

Meta-analysis of the incidence of permanent RLN palsy

No evidence for heterogeneity among the included studies ($Q = 4.887$, DF = 4, P value 0.2991, $I^2 = 18.14\%$) pooling of the studies using fixed effects showed a relative risk of 1.31 with 95% CI of 0.91 to 1.89 which was statistically not significant (p value 0.149).

Table 4 shows the results of the meta-analysis of the incidence of permanent RLN palsy.

There is no evidence for heterogeneity among the included studies ($Q = 4.887$, DF = 4, P value 0.2991, $I^2 = 18.14\%$).

Pooling of the studies using fixed effects showed a relative risk of 1.31 with a 95% CI of 0.91 to 1.89 which was statistically not significant (p value 0.149).

Table 3 Meta-analysis of the overall incidence of RLN palsy

Study	Total thyroidectomy	Subtotal thyroidectomy	Relative risk	95% CI	*Z*	*p* value
Barczynski et al. 2010 [3]	25/200	10/200	2.50	1.23 to 5.07		
Pappalardo et al. 1998 [5]	2/69	3/72	0.70	0.12 to 4.04		
Tezelman et al. 2009 [7]	32/1211	39/1695	1.15	0.72 to 1.82		
Vaiman et al. 2008 p[8]	161/3834	54/2238	1.74	1.28 to 2.36		
Yang et al. 2009 [4]	3/165	3/181	1.10	0.23 to 5.36		
Total (fixed effects)	**223/5479**	**109/4386**	**1.60**	**1.27 to 2.02**	**3.955**	**< 0.001**
Total (random effects)	223/5479	109/4386	1.56	1.16 to 2.10	2.945	0.003
Test for heterogeneity						
Q	4.887					
DF	4					
p value	0.299					
I^2 (inconsistency)	18.14%					
95% CI for I^2	0.00 to 83.97					

Table 4 Meta-analysis of incidence of permanent RLN palsy

Study	Total thyroidectomy	Subtotal thyroidectomy	Relative risk	95% CI	*z*	*p* value
Barczynski et al. 2010 [3]	4/200	2/200	2.00	0.37 to 10.80		
Delbridge et al. 1999 [6]	6/1251	4/1838	2.20	0.62 to 7.79		
Pappalardo et al. 1998 [5]	0/69	1/72	0.35	0.01 to 8.39		
Tezelman et al. 2009 [7]	12/1211	11/1695	1.53	0.68 to 3.45		
Vaiman et al. 2008 [8]	54/3834	27/2238	1.17	0.74 to 1.85		
Total (fixed effects)	**76/6565**	**45/6043**	**1.31**	**0.91 to 1.89**	**1.445**	**0.149**
Total (random effects)	76/6565	45/6043	1.32	0.91 to 1.90	1.453	0.146
Test for heterogeneity						
Q	4.887					
DF	4					
p value	0.2991					
I^2 (inconsistency)	18.14%					
95% CI for I^2	0.00 to 83.97					

A funnel plot for the incidence of permanent RLN palsy was done. There is evidence for publication bias.

Meta-analysis of incidence of temporary RLN palsy

No evidence for heterogeneity among the included studies ($Q = 7.060$, DF = 4, P value 0.133, $I^2 = 43.34\%$) pooling of the studies using fixed effects showed a relative risk of 1.828 with 95% CI of 1.36 to 2.46 which was statistically significant (p value > 0.001).

Table 5 shows the results of the meta-analysis of the incidence of temporary RLN palsy.

No evidence for heterogeneity among the included studies ($Q = 7.060$, DF = 4, P value 0.133, $I^2 = 43.34\%$).

Pooling of the studies using fixed effects showed a relative risk of 1.828 with a 95% CI of 1.36 to 2.46 which was statistically significant (p value > 0.001).

A funnel plot for the incidence of temporary RLN palsy was done**.** There is evidence of publication bias.

Meta-analysis of the overall incidence of hypoparathyroidism

There is evidence for heterogeneity among the included studies ($Q = 66.065$, DF = 4, P value > 0.0001, $I^2 = 93.95\%$) pooling of the studies using random effects showed a relative risk of 1.30 with 95% CI of 1.20 to 1.41 which was statistically significant (p value 0.036).

Table 6 shows the results of the meta-analysis of the overall incidence of hypoparathyroidism.

There is evidence for heterogeneity among the included studies ($Q = 66.065$, DF = 4, P value > 0.0001, $I^2 = 93.95\%$).

Table 5 A meta-analysis of the incidence of temporary RLN palsy

Study	Total thyroidectomy	Subtotal thyroidectomy	Relative risk	95% CI	*z*	*p* value
Barczynski et al. 2010 [3]	21/200	8/200	2.625	1.19 to 5.79		
Pappalardo et al. 1998 [5]	2/69	2/72	1.043	0.15 to 7.20		
Tezelman et al. 2009 [7]	20/1211	28/1695	1.000	0.57 to 1.77		
Vaiman et al. 2008 [8]	107/3834	27/2238	2.313	1.52 to 3.52		
Yang et al. 2009 [4]	3/165	3/181	1.097	0.23 to 5.36		
Total (fixed effects)	**153/5479**	**68/4386**	**1.828**	**1.36 to 2.46**	**3.991**	**< 0.001**
Total (random effects)	153/5479	68/4386	1.681	1.05 to 2.70	2.151	0.031
Test for heterogeneity						
Q	7.060					
DF	4					
p value	0.133					
I^2 (inconsistency)	43.34%					
95% CI for I^2	0.00 to 79.19					

Table 6 Meta-analysis of the overall incidence of hypoparathyroidism

Study	Total thyroidectomy	Subtotal thyroidectomy	Relative risk	95% CI	*z*	*p* value
Barczynski et al. 2010 [3]	22/200	4/200	5.50	1.93 to 15.67		
Pappalardo et al. 1998 [5]	26/69	14/72	1.94	1.11 to 3.39		
Tezelman et al. 2009 [7]	112/1211	31/1695	5.06	3.42 to 7.48		
Vaiman et al. 2008 [8]	1054/3834	548/2238	1.12	1.03 to 1.23		
Yang et al. 2009 [4]	11/165	9/181	1.34	0.57 to 3.15		
Total (fixed effects)	1225/5479	606/4386	1.30	1.20 to 1.41	6.137	< 0.001
Total (random effects)	**1225/5479**	**606/4386**	**2.34**	**1.06 to 5.18**	**2.095**	**0.036**
Test for heterogeneity						
Q	66.065					
DF	4					
p value	< 0.0001					
I^2 (inconsistency)	93.95%					
95% CI for I^2	88.73 to 96.75					

Pooling of the studies using random effects showed a relative risk of 1.30 with a 95% CI of 1.20 to 1.41 which was statistically significant (p value 0.036).

A funnel plot for the overall incidence of hypoparathyroidism was done. There is evidence of publication bias.

Meta-analysis of the incidence of permanent hypoparathyroidism

No evidence for heterogeneity among the included studies ($Q = 0.883$, DF = 4, P value 0.927, $I^2 = 0.00\%$) pooling of the studies using fixed effects showed a relative risk of 1.48 with 95% CI of 1.11 to 1.96 which was statistically significant (p value 0.007).

Table 7 shows the results of a meta-analysis of the incidence of permanent hypoparathyroidism.

There is no evidence for heterogeneity among the included studies ($Q = 0.883$, DF = 4, P value 0.927, $I^2 = 0.00\%$).

Pooling of the studies using fixed effects showed a relative risk of 1.48 with a 95% CI of 1.11 to 1.96 which was statistically significant (p value 0.007).

A funnel plot for the incidence of permanent hypoparathyroidism was done. There is evidence of publication bias.

Meta-analysis of Incidence of temporary hypoparathyroidism

There is evidence for heterogeneity among the included studies ($Q = 66.517$, DF = 4, P value > 0.0001, $I^2 = 93.99\%$) pooling of the studies using random effects showed a relative risk of 2.389 with 95% CI of 1.02 to 5.61 which was statistically significant (p value 0.046).

Table 7 Meta-analysis of the incidence of permanent hypoparathyroidism

Study	Total thyroidectomy	Subtotal thyroidectomy	Relative risk	95% CI	*z*	*p* value
Barczynski et al. 2010 [3]	1/200	0/200	3.00	0.12 to 73.21		
Delbridge et al. 1999 [6]	5/1251	4/1838	1.84	0.49 to 6.83		
Pappalardo et al. 1998 [5]	2/69	1/72	2.09	0.19 to 22.50		
Tezelman et al. 2009 [7]	10/1211	7/1695	2.00	0.76 to 5.24		
Vaiman et al. 2008 [8]	134/3834	56/2238	1.40	1.03 to 1.90		
Total (fixed effects)	**152/6565**	**68/6043**	**1.48**	**1.11 to 1.96**	**2.704**	**0.007**
Total (random effects)	152/6565	68/6043	1.48	1.11 to 1.96	2.700	0.007
Test for heterogeneity						
Q	0.883					
DF	4					
p value	0.927					
I^2 (inconsistency)	0.00%					
95% CI for I^2	0.00 to 11.29					

Table 8 Meta-analysis of the incidence of temporary hypoparathyroidism

Study	Total thyroidectomy	Subtotal thyroidectomy	Relative risk	95% CI	*z*	*p* value
Barczynski et al. 2010 [3]	21/200	4/200	5.25	1.84 to 15.02		
Pappalardo et al. 1998 [5]	24/69	13/72	1.926	1.07 to 3.47		
Tezelman et al. 2009 [7]	102/1211	24/1695	5.949	3.84 to 9.22		
Vaiman et al. 2008 [8]	920/3834	492/2238	1.092	0.99 to 1.20		
Yang et al. 2009 [4]	11/165	9/181	1.341	0.57 to 3.15		
Total (fixed effects)	1078/5479	542/4386	1.281	1.17 to 1.40	5.386	< 0.001
Total (random effects)	**1078/5479**	**542/4386**	**2.389**	**1.02 to 5.61**	**2.000**	**0.046**
Test for heterogeneity						
Q	66.517					
DF	4					
p value	< 0.0001					
I^2 (inconsistency)	93.99%					
95% CI for I^2	88.82 to 96.76					

Table 8 shows the results of the meta-analysis of the incidence of temporary hypoparathyroidism.

There is evidence for heterogeneity among the included studies ($Q = 66.517$, DF = 4, P value > 0.0001, $I^2 = 93.99\%$).

Pooling of the studies using random effects showed a relative risk of 2.389 with a 95% CI of 1.02 to 5.61 which was statistically significant (p value 0.046).

A funnel plot for the incidence of temporary hypoparathyroidism was done. There is evidence of publication bias.

Meta-analysis of the incidence of recurrence

There is evidence for heterogeneity among the included studies ($Q = 13.484$, DF = 4, P value 0.009, $I^2 = 70.34\%$) pooling of the studies using random effects showed a relative risk of 0.013 with 95% CI of 0.002 to 0.11 which was a statistically significant p value of > 0.001.

Table 9 shows the results of the meta-analysis of the incidence of recurrence.

There is evidence for heterogeneity among the included studies ($Q = 13.484$, DF = 4, P value 0.009, $I^2 = 70.34\%$).

Pooling of the studies using random effects showed a relative risk of 0.013 with a 95% CI of 0.002 to 0.11 which was statistically significant (p value > 0.001).

A funnel plot for the incidence of recurrence was done. There is evidence of publication bias.

Discussion

Surgical management is considered the treatment of choice for multinodular goiter [19]. Several surgical procedures for MNG, including subtotal thyroidectomy and

Table 9 Meta-analysis of the incidence of recurrence

Study	Total thyroidectomy	Subtotal thyroidectomy	Relative risk	95% CI	*z*	*p* value
Barczynski et al. 2010 [3]	1/200	22/200	0.05	0.006 to 0.33		
Pappalardo et al. 1998 [5]	0/69	10/72	0.05	0.003 to 0.83		
Tezelman et al. 2009 [7]	0/1211	121/1695	0.006	0.0004 to 0.09		
Vaiman et al. 2008 [8]	0/3834	482/2238	0.0006	0.00004 to 0.001		
Yang et al. 2009 [4]	0/165	12/181	0.04	0.003 to 0.74		
Total (fixed effects)	1/5479	647/4386	0.004	0.001 to 0.01	−10.594	< 0.001
Total (random effects)	**1/5479**	**647/4386**	**0.013**	**0.002 to 0.11**	**−3.954**	**< 0.001**
Test for heterogeneity						
Q	13.484					
DF	4					
p value	0.009					
I^2 (inconsistency)	70.34%					
95% CI for I^2	24.44 to 88.35					

total thyroidectomy. The postoperative complications (transient/permanent hypocalcemia and transient/permanent RLN palsy) and recurrences are regarded as the assessment of the balance between TT (total thyroidectomy) and ST (subtotal thyroidectomy) is still controversial [20, 21], and more recent studies have shown comparison of both surgical approaches regarding the postoperative complications [22].

Increasing numbers of total thyroidectomies are being performed, and the indications for this procedure include thyroid cancer, Graves' disease, and multinodular goiter [23]. As it completely eradicates the disease process and lowers the local recurrence rate, it avoids the need for completion thyroidectomy with minimal risk of morbidity [24].

In this study, we compare the outcome of total thyroidectomy in comparison with subtotal thyroidectomy as regards hypocalcemia, hypothyroidism, recurrence rate, and RLN injury.

As regards RLN palsy, there is a higher incidence in total over subtotal in temporary and permanent RLN palsy with a *P* value < 0.001 which is statistically significant.

As regards postoperative hypoparathyroidism, there is a higher incidence in total over subtotal in postoperative hypoparathyroidism whether it is temporary or permanent, with a *P* value < 0.001 which is statistically significant.

As regards recurrence, there is a higher incidence in subtotal over the total in the overall incidence of recurrence with a *P* value < 0.001 which is statistically significant.

Ozbas et al. reported that the incidence rate of recurrence of MNG after bilateral subtotal thyroidectomy ranges between 1.2% [16], Delbridge reported that subtotal thyroidectomy for benign thyroid disease has been performed for more than a century and that it may reduce the associated risk of postoperative hypocalcemia and recurrent laryngeal nerve (RLN) palsy [25]. Most surgeons still argue whether the potential risk of total thyroidectomy (TT) outweighs the potential benefits [26].

Regarding the RLN injury postoperative either transient or permanent our study showed a statistically significant difference between subtotal thyroidectomy over total thyroidectomy as in subtotal thyroidectomy, we avoid dissection over RLN or using excessive diathermy also keep in mind most of them are neuropraxia, nerve traction, or edema resolving by the time.

Among included studies, the results showed that subtotal thyroidectomy has improved transient hypothyroidism and permanent hypothyroidism over total thyroidectomy with preservation of the posterolateral part to avoid postoperative hypothyroidism and the need for replacement therapy.

TT has become a preferred surgical procedure for MNG for the majority of surgeons because it eliminates the risk of recurrence, and there is no need for reoperation [26]. A lot of data has been published indicating the equal incidence of both transient/permanent RLN palsy and transient/permanent hypocalcemia for subtotal thyroidectomy and total thyroidectomy [27].

Regarding the recurrence rate, the subtotal thyroidectomy showed less significance than total thyroidectomy as total thyroidectomy ablates any remaining tissue [28].

Conclusion

This meta-analysis showed that the advantages of total thyroidectomy include adequate eradication of the disease, prevention of recurrent goiter, and avoidance of the

need for completion surgery in case of occult malignancy, but it is associated with higher morbidity (postoperative thyroidectomy complications: RLN palsy and hypoparathyroidism) and the need for lifelong replacement therapy (L-thyroxin supplementation).

Abbreviations

TT	Total thyroidectomy
ST	Subtotal thyroidectomy
RLN	Recurrent laryngeal nerve
MNG	Multinodular goiter

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Not applicable.

Authors' contributions
Dr. Ahmed Kamel had the idea of this study, supervised the statistical analysis, and contributed to the writing of the paper (corresponding author). Dr. Mohamed Kamel put together the research plan and statistical analysis and contributed to the writing of the paper.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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