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The Characteristics and Level of Evidence of Clinical Studies Published in Five Leading Orthodontic Journals

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Abstract

Objectives: To assess the characteristics and level of evidence (LOE) of clinical studies recently published in leading orthodontic journals, and explore the association between LOE and potentially related factors.

Methods: The official online archives of five leading orthodontic journals were hand-searched to identify clinical research articles published during 2015 to 2017. The LOE of all included studies was assessed using a modified LOE classification system developed based on the Oxford LOE and GRADE (Grading of Recommendations Assessment, Development and Evaluation). Univariable and multivariable logistic regression analyses were performed to identify the association between the LOE of each article (high LOE vs. low LOE) and 7 factors.

Results: A total of 637 studies were included and assessed. Of these, 8 (1.3%) were *level-1* studies, 160 (25.1%) were *level-2*, 326 (51.2%) were *level-3*, and 143 (22.4%) were *level-4*. According to multivariable logistic regression analyses, journal of publication ($P<0.001$), funding status ($P=0.003$), and the geographic origin of the first author ($P=0.006$) were significantly associated with LOE.

Conclusions: The number of high LOE studies in leading orthodontic journals was limited. There is still need for further improvement in the overall LOE of clinical studies in orthodontics.

Key words: *orthodontics, clinical studies, evidence-based orthodontics, level of evidence*

Introduction

Evidence-Based Medicine (EBM) has been regarded as a major landmark during the progression of medicine.¹ As a combination of research evidence, clinical expertise and patient preferences,^{2,3} EBM aims to enable the safe, reliable and cost-efficient delivery of healthcare to patients.^{4,5} However, the practice of EBM has been associated with challenges in all domains of healthcare because of the explosive growth of articles published.⁶ Lack of time and heavy workload are also widely accepted barriers to evidence-based practice (EBP) for clinicians.⁷ Due to the above-mentioned factors and a lack of awareness and understanding of EBP,⁸ many orthodontists still prefer to rely on the opinion of experts and colleagues when faced with clinical uncertainties.⁹

The advent of Levels of Evidence (LOE) allows readers to complete a quick overview of a study's methodological quality.⁵ In general, studies with higher LOE have better reproducibility and more reliable outcomes.^{10,11} Oxford LOE, developed by Oxford Centre for Evidence-Based Medicine, is one of the most widely used LOE classification tools.^{5,12} Different from other LOE assessment tools, the latest version Oxford LOE (2011) takes into account not only the design of studies, but also their results.^{5,13} Similar to the methods used in GRADE, for an observational study, when the magnitude of effect is regarded as dramatic, its LOE should be rated up.^{13,14} However, the Oxford 2011 LOE did not provide an explicit standard for the judgement of 'dramatic effect', making it difficult for readers / clinicians to determine whether or not to rate up an observational study during making clinical decision.

The year of 2017 marks the 20th year after the concept of evidence-based orthodontics (EBO) was proposed by Sheldon Peck in *Angle Orthodontist*.¹⁵ However, to our knowledge, the current LOE status of the orthodontic literature has not been assessed. In addition, despite the aforementioned advantages of Oxford 2011 LOE, most previous LOE related studies either used an obsolete version¹⁶⁻¹⁸ or did not consider the effect sizes when assessing observational studies.^{11,12,19} Therefore, the primary objective of this study was to assess the characteristics and LOE of recently published clinical research articles in leading orthodontic journals, using the Oxford 2011 LOE accompanied with the rating up standards of GRADE. A secondary objective was to investigate and explore the association between LOE and potentially related factors, such as funding status, geographic origin and type of institution.

Methods and Materials

Journal selection

We used the Thomson Reuters 2016 Journal Citation Report (JCR) ²⁰ to select the top-5 SCIE-indexed orthodontic journals that have the highest impact factors (IF), i.e. *European Journal of Orthodontics* (EJO, IF=1.622), *American Journal of Orthodontics and Dentofacial Orthopedics* (AJO-DO, 1.472), *Angle Orthodontist* (AO, 1.366), *Korean Journal of Orthodontics* (KJO, 1.182) and *Orthodontics & Craniofacial Research* (OCR, 1.115).

Article selection

The official online archives of all five selected journals were hand-searched to identify clinical research articles published in these journals from January 2015 to December 2017. Pre-determined inclusion criteria were original studies with patients receiving orthodontic care in the clinical setting. When the eligibility of a study cannot be determined based on its title and abstract, the full-text was retrieved and screened. Two authors (Y.C and Y.M) carried out all the hand search and screening procedures independently and in duplicate, with any uncertainty resolved by consulting two experts (F.H and H.H) until consensus was reached.

Data extraction

For each included article, we extracted the following information: title of article, title of journal, IF, publication year, study design, funding status, number of institutions (single vs. multiple), name of institutions, and geographical origin (first author). If the first author had more than one affiliation, only the first one was extracted. In addition, we classified all institutions into 4 types: 1) university, 2) public health service, 3) private practice and 4) others.²¹ Funding status was categorized into: 1) funded by industry, 2) funded by other sources and 3) unfunded/unreported.

Initially, one author (Y.C) carried out the data extraction process. Thereafter, a 10% random sample of the extracted data was examined by another author (Y.M). This process could reveal items for which a discrepancy exists between two reviewers on at least one occasion. One author (Y.C) then verified the data for these items from all articles.²²

Assessment of LOE

All articles were classified into four levels of evidence (Table 1) using a modified LOE classification system developed based on Oxford 2011 LOE, Oxford 2009 LOE, and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) guidelines.^{13,14,23-26} For ease of description, we defined *level-1* & *-2* as high level, *level-3* & *-4* as low level.

An internal pilot study was performed to calibrate examiners in the assessment of LOE and to indicate necessary refinement of the assessment protocol. During this process, two authors (Y.C and F.H.) carried out independent assessments in rounds of 15 randomly selected articles, until significant agreement was reached (weighted kappa statistics, $k > 0.61$).²⁷ Then, one author (Y.C) assessed the LOE of all remaining articles. All uncertainties were resolved by discussing with two experts (F.H and H.H).

Statistical analyses

We used descriptive statistics to summarize characteristics of included articles. Univariable and multivariable logistic regression analyses were performed to investigate the association between LOE (dependent variable; high LOE vs. low LOE) and 7 potential related factors (independent variables). Previous literature has suggested significant associations between LOE and the following factors: journal of publication, funding status, geographical origin (first author), and number of authors.^{16,28,29} We decided *a priori* to study three more factors, i.e. type of institution, number of affiliations, and the international ranking of the first affiliation (according to 2018 QS ranking of the top-50 dental schools).³⁰ All explanatory variables with $P < 0.1$ in univariable analyses were entered into multivariable modelling. For all statistical analyses, a two-sided $P < 0.05$ was set as the criterion for statistical significance.

Sensitivity analysis

According to GRADE, the quality of evidence should be rated up if the risk ratio (RR) of a study was greater than 2 (or less than 0.5) or greater than 5 (or less than 0.2), which was recognized as strong (+1 grade) or very strong (+2 grades) association, respectively.^{14,29} In the main analysis, we decided to define $RR > 5$ (or < 0.2) as dramatic effect. To evaluate the influence of this definition, a *post hoc* sensitivity analysis was

carried out by repeating our analyses with dramatic effect being defined as $RR > 2$ (or < 0.5).

Results

Characteristics of the included articles

A total of 2100 articles were identified during the hand search, of which 637 remained after applying the eligibility criteria (Figure 1). Data regarding the characteristics of these articles were listed in Table 2.

The majority of authors of included studies worked in universities (86.7%). Most articles were collaborative work by multiple affiliations (67.5%), some of which were international collaboration (27.9%), while only one-third obtained financial support (32.2%).

In terms of geographic origin, most of the included articles were published in *AJO-DO* (40.3%) or *AO* (30.9%), with a geographical origin in Europe (41.1%) or Asia (30.1%). Journals based in Europe (*EJO* and *OCR*) and Asia (*KJO*) published more studies from the corresponding continent, with the percentage being 71.6%, 55.6% and 69.2%, respectively. Whereas journals originated from America (*AJO-DO* and *AO*) presented a relatively even distribution of studies from different continents. Compared with three non-European journals,

Cohort study was most widely used study design among the included studies (50.1%), followed by RCT (18.1%) and case series/case report (17.9%). The *EJO* and *OCR* had a relatively higher proportion of SRs and RCTs, while the *AJO-DO* and *AO* published more case-series and case reports.

Results of LOE assessment

During the internal pilot study, almost perfect agreement between 2 reviewers was reached in the first round ($k=0.864$, 95% confidence interval (CI): 0.72 to 1.00). Of 637 studies, 3 studies met the rating up criteria. Finally, there were 8 *level-1* (1.26%), 160 *level-2* (25.12%), 326 *level-3* (51.18%), and 143 *level-4* (22.45%) studies. *EJO* had the largest proportion of high LOE studies (48.4%), followed by *AO* (28.4%), *AJO-DO* (20.7%), *OCR* (19.5%) and *KJO* (11.5%) (Figure 2).

Results of sensitivity analysis. When we changed the definition of dramatic effect to $RR > 2$ (or < 0.5), the studies that met our rating up criteria remained the same ($n=3$). The results of the above-mentioned main analyses were therefore robust.

Factors associated with LOE

Table 3 shows the results of logistic regression analyses. Univariable analyses showed that journal ($P < 0.001$), geographical origin ($P < 0.001$) and funding status ($P = 0.005$) were significantly associated with LOE. No significant association was found between LOE and international collaboration ($P = 0.681$), QS top-50 dental school ($P = 0.180$), multiple affiliations ($P = 0.206$), and type of institution ($P = 0.703$).

In multivariable analysis, journal ($P < 0.001$), funding status ($P = 0.003$) and geographic origin ($P = 0.006$) remained significantly associated with LOE. The odds of having high LOE were significantly higher in studies published in EJO than those published in other journals. Compared with studies funded by industry, the odds of having high LOE were 77.7% and 64.8% lower in studies that were unfunded/unreported and those funded by other sources, respectively. Compared with studies from Europe, the odds of having high LOE were significantly lower in studies from Asia and North America, and significantly higher in those from Africa.

Discussion

This study, based on a cross-sectional analysis of clinical research in 5 leading orthodontic journals during 3-year period, provides insight into the current pattern of LOE and identifies potential predictors.

The RCT, due to its ability to minimize bias, is regarded the optimal primary study design to determine the effectiveness of an intervention and therefore a *level-2* study.³¹ Our results indicate that 18.1% of the included studies were RCTs, and the proportion of RCTs in clinical studies has dramatically increased (10.8% to 18.05%) when compared to data of a former analysis of orthodontic literature (1998-2008)³². Such a trend has been reported in other areas.³³⁻³⁵ The remarkable improvement in evidence among orthodontic research during the past two decades is probably associated with researchers' increasing recognition of EBO.^{36,37} Another possible reason is researchers' preference to conduct and publish high quality studies to enhance their profile in a competitive academic environment.³⁸

Compared with the 3 top-tier medical journals (*New England Journal of Medicine*, *Lancet* and *Journal of American Medical Association*), in which a significant increase (22% to 80%) in the proportion of RCTs from 1974 to 2004 was found,³⁹ the quality of orthodontic research still needs considerable improvement. However, the complexity of etiology, the variety of treatment modalities and prolonged treatment time in orthodontics can lead to difficulties in study design, ethics, practicality and maintaining quality.^{7,40} Furthermore, funding and recruitment can be challenging for trials in this field.⁴¹ As a result, it can be difficult to carry out RCTs to answer certain orthodontic questions. Perhaps, this could be the reason that among the 64 SRs included, only 8 (12.5%) were based exclusively on RCTs. Additionally, only four of the five included journals published *level-1* studies during the past 3 years. The samples of our study only include clinical studies published in five leading specialist orthodontic journals. There are orthodontic SRs of RCTs published in medical journals and general dental journals but not captured by this study.⁴² Therefore, our findings could not represent the situation of all clinical studies in orthodontics.

It can be suggested that nonrandomized studies should only be conducted when RCTs are not feasible.⁴³ In some cases, observational studies, though with higher risk of bias, might be the only source of data available for clinicians, and their importance to clinical practice is also associated with the magnitude of their effect sizes.⁴⁴ Some quality evaluation systems have attempted to increase the weight of *level-3* and *level-4* studies that have met certain criteria. For instance, in GRADE, if observational studies have a large magnitude of effect, their quality of evidence will be rated up.¹⁴ The Oxford 2011 LOE also added similar criteria to its previous version,¹³ however, a specific definition of ‘dramatic effect’ was not provided. Considering these, we tried to combine Oxford LOE with the adjustment criteria of GRADE (Table 1). Three observational studies were therefore rated up during the assessment.

During the past 20 years, the proportion of orthodontic case reports has decreased from 31.4% to 17.58%,³² indicating the awareness of clinicians and researchers on the quality of evidence hierarchy. In the present study, the number of *level-4* studies varied among the 5 journals, while more than 70% were published in the *AJO-DO*. Gibson and Harrison presumed that this could be a result of *AJO-DO*’s focus on publishing American Board of Orthodontists examinations’ prize-winning cases.³² In addition, due to their important role in advancing knowledge on adverse effects and rare disorders,⁴⁵

as well as the potential to facilitate precision and personalized orthodontics,⁴⁶ case reports have particular merits among the designs of clinical studies in orthodontics.

In dentistry, to our knowledge, similar studies regarding LOE only exist in the fields of endodontics and oral & maxillofacial surgery (OMFS).^{16,29,47,48} A comparison between these studies and the current one is presented in Table 4. However, readers should be cautious about these comparisons since different studies have used different eligibility criteria and different assessment tools for LOE.

In this study, we analyzed the association between LOE and the following factors: journals, funding status, geographical origin (first author), international collaboration, type of institution, multiple affiliations, and the international ranking of the first institution (according to 2018 QS top-50 dental schools), some of which had not been discussed in similar studies.^{16,29,47,48} The majority of included studies were conducted in universities (86.7%), similar to the results of previous analyses of orthodontic research.^{49,50}

Funding status was found to correlate with LOE, and studies funded by industry had significantly higher LOE. This is not surprising, as funding sources usually need to demonstrate that their funding is used for high quality research. This means, it is unlikely that a non-randomized clinical trial will be funded if there is scope for carrying out a randomized clinical trial in the same clinical area. However, our results are not in accordance with the findings of previous studies about LOE and financial support.^{28,51} This could be because some clinical areas may not be suitable to be tested using a randomized clinical trial methodology.

The geographic origin was also significantly associated with LOE. Studies from Europe performed significantly better in LOE and could account for larger proportion of clinical research than those from most of continents. This discrepancy might be explained by the differences among institutions and countries regarding the availability of research support.³⁸ Because of the current emphasis on basic science research and stringent ethics policies, clinical trials may not be financially and ethically feasible, and the conduct of long-term cohort studies may not be valued.

Strengths and limitations

In this study, we have developed a novel LOE assessment tool combining the strengths of Oxford LOE and GRADE, which recognizes the possibility of observational studies

to provide reliable evidence, and is applicable for the situation where clinicians need to quickly assess the evidence underlying a single study. In addition, we included a large sample of clinical studies in dentistry (Table 4). We also investigated 3 potential factors which have not been explored in previous similar studies.

Like any other literature assessment tools, LOE has its limitations. For example, although classified into different levels, studies with higher LOE do not always have higher clinical importance.⁵¹ First, the methodological and reporting quality can vary greatly among studies of the same design. Second, many important details of the study design, such as the selection of patient-centered research questions and outcome measures, are not considered by LOE.⁵²⁻⁵⁴ Hence, if time allows, we still advise readers to focus on not only study design but also specific methodological details,⁵⁵⁻⁵⁷ and to use multiple assessment tools when evaluating the quality of research articles.

Conclusions

- The number of high LOE studies in leading orthodontic journals was limited. There is still need for further improvement in the overall LOE of clinical studies in orthodontics.
- Financial support and geographic origin of the first author were significantly associated with LOE.

Conflict of Interest

None to declare.

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Tables

Table 1. The modified LOE assessment tool used in this study.

LOE	Description	Summary
Level 1	Systematic reviews of randomized trials or n-of-1 trials	High
Level 2	Randomized controlled trials Observational studies with dramatic effect ^a Systematic reviews of cohort studies with or without randomized trials	
Level 3	Non-randomized and/or uncontrolled trials Cohort studies. Systematic reviews of case-control studies with or without cohort studies	
Level 4	Case-control studies Case-series and Case reports Historically controlled studies Cross-sectional studies	Low

^a When the primary outcome of a study was categorical and the risk ratio (RR) was greater than 5 (or less than 0.2), we considered the effect dramatic. If the sample size and odds ratio (OR) were provided, we calculated the corresponding RR, then decided whether or not to rate up (6).

Table 2. Characteristics of included articles from 5 leading orthodontic journals during the 3-year period

Characteristic	Category	n (%)					
		EJO	AJO-DO	AO	KJO	OCR	Total
Publication year	2015	33 (34.7%)	71 (27.6%)	72 (36.5%)	19 (36.5%)	15 (41.7%)	210 (33.0%)
	2016	29 (30.6%)	98 (38.2%)	70 (35.5%)	13 (25.0%)	6 (16.7%)	216 (33.9%)
	2017	33 (34.7%)	88 (34.2%)	55 (28.0%)	20 (38.5%)	15 (41.7%)	211 (33.1%)
Financial support	Unfunded/unreported	62 (65.3%)	192 (74.7%)	134 (68.0%)	29 (55.8%)	15 (41.7%)	432 (67.8%)
	Funded by other sources	29 (30.5%)	58 (22.6%)	56 (28.4%)	23 (44.2%)	20 (55.6%)	186 (29.2%)
	Funded by industry	4 (4.2%)	7 (2.7%)	7 (3.6%)	0 (0.0%)	1 (2.7%)	19 (3.0%)
International collaboration		34 (35.8%)	66 (25.7%)	55 (27.9%)	9 (17.3%)	14 (38.9%)	178 (27.9%)
QS top-50 dental school		27 (28.4%)	59 (23.0%)	31 (15.7%)	13 (25.0%)	3 (8.3%)	133 (20.9%)
Multiple affiliations		70 (73.7%)	170 (66.1%)	132 (67.0%)	31 (59.6%)	27 (75.0%)	430 (67.5%)
Geographic origin	Europe	68 (71.6%)	77 (30.0%)	84 (42.6%)	13 (25.0%)	20 (55.6%)	262 (41.1%)
	Asia	14 (14.7%)	84 (32.7%)	52 (26.4%)	36 (69.2%)	6 (16.7%)	192 (30.1%)
	North America	5 (5.3%)	42 (16.3%)	37 (18.8%)	2 (3.8%)	8 (22.2%)	94 (14.8%)
	South America	5 (5.3%)	41 (16.0%)	21 (10.7%)	1 (1.9%)	2 (5.6%)	70 (11.0%)
	Africa	1 (1.1%)	9 (3.5%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	13 (2.1%)
	Oceania	2 (2.1%)	4 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (0.9%)

Table 2. Characteristics of included articles from 5 leading orthodontic journals during the 3-year period (Continued)

Characteristic	Category	n (%)					
		EJO	AJO-DO	AO	KJO	OCR	Total
Type of institution	University	87 (91.6%)	215 (83.7%)	171 (86.8%)	48 (92.3%)	31 (86.1%)	552 (86.7%)
	Public health service	1 (1.1%)	1 (0.4%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	3 (0.5%)
	Private practice	3 (3.2%)	31 (12.1%)	21 (10.7%)	4 (7.7%)	2 (5.6%)	61 (9.6%)
	Others	4 (4.2%)	10 (3.9%)	4 (2.0%)	0 (0.0%)	3 (8.3%)	21 (3.3%)
Study design	SRs	25 (26.3%)	17 (6.6%)	15 (7.6%)	3 (5.8%)	4 (11.1%)	64 (10.0%)
	RCTs	24 (25.3%)	39 (15.2%)	44 (22.3%)	4 (7.7%)	4 (11.1%)	115 (18.1%)
	Cohort studies	43 (45.3%)	109 (42.4%)	120 (60.9%)	29 (55.7%)	18 (50.0%)	319 (50.1%)
	Cross-sectional studies	3 (3.1%)	5 (1.9%)	4 (2.0%)	0 (0.0%)	9 (25.0%)	21 (3.3%)
	Case-control studies	0 (0.0%)	2 (0.8%)	1 (0.6%)	0 (0.0%)	1 (2.8%)	4 (0.6%)
	Case-series and Case reports	0 (0.0%)	85 (33.1%)	13 (6.6%)	16 (30.8%)	0 (0.0%)	114 (17.9%)
Total		95 (14.9%)	257 (40.3%)	197 (30.9%)	52 (8.2%)	36 (5.7%)	637 (100%)

Table 3. Univariable and multivariable logistic regression derived odd ratios (OR) and 95% confidence intervals (CI), with LOE ($1 \leq \text{LOE} \leq 2$ vs. $3 \leq \text{LOE} \leq 4$) as the dependent variable.

Independent variable	Category	Univariable			Multivariable ^a		
		OR	95% CI	P value	OR	95% CI	P value
International collaboration	No	Reference		0.681			
	Yes	1.085	(0.74, 1.60)				
QS Top-50 dental school	No	Reference		0.180			
	Yes	0.732	(0.46, 1.16)				
Multiple affiliations	No	Reference		0.206			
	Yes	1.282	(0.87, 1.89)				
Funding status	Funded by industry	Reference		0.005	Reference		0.003
	Funded by other sources	0.298	(0.11, 0.78)		0.352	(0.13, 0.99)	
	Unfunded/unreported	0.228	(0.09, 0.58)		0.223	(0.08, 0.60)	
Type of institution	University	Reference		0.703			
	Public health service	1.378	(0.12, 15.31)				
	Private Practice	0.746	(0.39, 1.42)				
	Others	1.378	(0.55, 3.48)				
Journal of publication	EJO	Reference		<0.001	Reference		<0.001
	AJO-DO	0.277	(0.17, 0.46)		0.322	(0.19, 0.55)	
	AO	0.423	(0.26, 0.70)		0.482	(0.28, 0.82)	
	KJO	0.139	(0.05, 0.36)		0.178	(0.07, 0.47)	
	OCR	0.257	(0.10, 0.64)		0.249	(0.10, 0.64)	

Table 3. Univariable and multivariable logistic regression derived odd ratios (OR) and 95% confidence intervals (CI), with LOE ($1 \leq \text{LOE} \leq 2$ vs. $3 \leq \text{LOE} \leq 4$) as the dependent variable. (Continued)

Independent variable	Category	Univariable			Multivariable ^a		
		OR	95% CI	P value	OR	95% CI	P value
Geographic origin	Europe	Reference		<0.001	Reference		0.006
	Asia	0.472	(0.30, 0.73)		0.591	(0.36, 0.96)	
	North America	0.468	(0.26, 0.83)		0.540	(0.30, 0.99)	
	South America	0.539	(0.29, 1.01)		0.684	(0.36, 1.32)	
	Africa	3.164	(1.01, 9.96)		4.850	(1.49, 15.80)	
	Oceania	0.989	(0.18, 5.50)		0.791	(0.13, 4.89)	

^a Model summary: dependent variable coding: [0] $3 \leq \text{LOE} \leq 4$, [1] $1 \leq \text{LOE} \leq 2$; No. (less common event) = 169; P (Hosmer & Lemeshow) = 0.228; R^2 (Nagelkerke) = 0.132

Table 4. Comparison of assessment results between this study and previous similar research regarding LOE in other fields of dentistry

Study ID	Current study	Lau (2007) (48)	Sandhu (2010) (29)	Shafiei (2013) (16)	Kontakiois (2014) (47)
Area	Orthodontics	OMFS ^a	OMFS ^a	Endodontics	Endodontics
Sample size (included)	2100 (637)	932 (467)	3294 (1986)	1357 (222)	326 (51)
Period	2015-2017	2002-2003	1999-2009	2000,2006 and 2010	1993-2013
LOE Classification Tool	Oxford LOE 2011	NHMRC ^b	AHCPR ^c	RDC ^d	Oxford LOE 2009
Proportion of <i>Level 1</i> studies	1.26%	0%	3.47%	26.13%	0%
Proportion of <i>Level 2</i> studies	25.12%	4%	28.90%	5.41%	39.21%
Proportion of <i>Level 3</i> studies	51.18%	16%	3.27%	44.59%	0%
Proportion of <i>Level 4</i> studies	22.45%	80%	64.36%	2.70%	15.69%
Proportion of <i>Level 5</i> studies	-	-	-	21.17%	80.39%

^a OMFS = Oral and maxillofacial surgery

^b NHMRC = Australian National Health and Medical Research Council guidelines

^c AHCPR = US Agency for Health Care Policy and Research

^d RDC = The National Health Service Research and Development Centre for Evidence-based Medicine

Figure Legends

Figure 1. Flow diagram of the included articles.

Figure 2. A pyramid plot showing the proportion of studies of different LOE by journals.