Low-level laser therapy in the prevention and treatment of oral mucositis: a systematic review and meta-analysis

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Objective. The aim of this study was to determine whether prophylactic and therapeutic low-level laser therapy (LLLT), compared with placebo or no therapy, reduced the risk of severe oral mucositis (OM) in patients receiving chemotherapy or radiotherapy.
Study Design. We searched for articles published on randomized controlled trials (RCTs) in the databases MEDLINE, EMBASE, Cochrane Library, Cochrane Central Register of Controlled Trials, Web of Science, and Clinical Trials, until December 2018. RCTs were filtered on the basis of eligibility criteria, and data were analyzed by using R software 3.5.2.
Results. Overall, 30 studies were included in the meta-analysis. Prophylactic LLLT reduced the overall risk of severe OM (relative risk [RR] = 0.40; 95% confidence interval [CI]: 0.28−0.57; $P < .01$). Therapeutic LLLT substantially reduced the duration of severe OM ($P < .01$). LLLT also reduced the overall mean grade of OM, overall incidence of severe pain, mean score of pain, and incidence of severe OM, at the most anticipated time.
Conclusions. Prophylactic and therapeutic LLLT can reduce the risk of severe OM in patients receiving chemotherapy or radiotherapy. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:387−397)

Oral mucositis (OM) is one of the most frequent complications arising from the cytotoxic effects of therapies for malignancies, for example, radiotherapy for head and neck squamous cell cancer (HNSCC), chemotherapy for leukemia and HNSCC, and hematopoietic stem cell transplantation (HSCT) for malignant hematologic disorders.[1-3] The incidence of OM is approximately 20% to 40% in patients receiving chemotherapy, 60% to 85% in patients undergoing allogeneic HSCT with myeloablative conditioning, and almost 100% in patients with HNSCC receiving radiotherapy.[4] The clinical manifestations of OM, which include mouth ulceration, pain, infection, and dysphagia, increase the demand for analgesia and result in the deterioration of general nutritional status and lower the quality of life.[5-7] Moreover, severe OM could result in dosage reduction, which may lead to recurrence of the disease.[8] Considering these adverse reactions of chemotherapy or radiotherapy in patients with malignancies, it is highly recommended that appropriate management of OM be taken into account during the course of therapy.

Both prophylactic and therapeutic interventions after radiotherapy-induced or chemotherapy-induced OM are continuously being discussed. Furthermore, available plans have been published by the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology suggesting low-level laser therapy (LLLT) as an optional method to prevent and control OM caused by antitumor irradiation or medication.[9] LLLT, commonly used in physiotherapy, utilizes the effect of light energy on living cells. The light energy applied in LLLT is absorbed by cytochromes and porphyrins in mitochondria. The light triggers several pathways to activate cells, promotes cell proliferation and differentiation, and results in an accelerated regeneration process.[10] In addition, the light also triggers pathways that regulate inflammatory control and cause pain reduction.[11-13] The anti-inflammatory, analgesic, and biomodulatory effects of LLLT are considered to be beneficial in inflammatory disorders (e.g., OM).[10] This laser has a wide range of parameters, including wavelength, power, energy density, irradiation duration, and continuity among others,[14] which are essential for its effectiveness and safety.

A meta-analysis[4] summarizing a positive prophylactic effect of LLLT on OM was published in 2014; however, that analysis was focused only on the prevention of OM. To systematically evaluate both the prophylactic and therapeutic effects of LLLT in patients who might develop or have developed OM during chemotherapy or radiotherapy, we planned to integrate the latest data of clinical trials to conduct a statistical analysis.

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Received for publication Dec 6, 2019; returned for revision May 9, 2020; accepted for publication May 26, 2020.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2020.05.014

Statement of Clinical Relevance

According to the results of this meta-analysis, prophylactic and therapeutic low-level laser therapy appear to be effective in preventing and treating oral mucositis in patients receiving chemotherapy and radiotherapy.

MATERIALS AND METHODS

Search strategies

We searched MEDLINE (from 1946 to December 1, 2018); EMBASE (from 1946 to December 1, 2018); Cochrane Library (to December 1, 2018); Cochrane Central Register of Controlled Trials (to December 1, 2018); Web of Science (to December 1, 2018); Clinicaltrials (to December 1, 2018); CINAHL (1983 to December 1, 2018); SCOPUS (to December 2018); and LILACS (to December 2018), and selected only articles published in English. The search strategy is shown in the supplemental material available online. All relevant citations were selected for further evaluation.

Inclusion and exclusion criteria

Two researchers (Y.S. and J.W.) independently completed the study selection. Any disagreement between the 2 researchers was resolved through discussion with another researcher (F.W.). Articles without full texts or necessary data were excluded. Studies were included if they met the standard of randomized control trials (RCTs), with control, placebo, usual care, or no treatment groups and patients who underwent radiotherapy or chemotherapy, along with use of LLLT for either prevention or treatment. Studies were excluded if they were identified as (1) retrospective studies, case reports, animal experiments, reviews, and commentary articles; (2) nonrandomized studies or studies without a control group; and (3) duplicate publications.

Risk of bias and quality of evidence evaluation

The potential risk of bias in included studies was examined by using the Jadad scale[15] to assess the generation of randomization, application of blinding, and reports of dropouts. Additionally, allocation concealment was separately assessed.

The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system[16] was used to evaluate the overall quality of the evidence. This system can be used to summarize the following aspects of an evidence: risk of bias, imprecision, inconsistency, indirectness, and publication bias.[16]

All the evaluations above were independently completed by the 2 researchers (Y.S. and J.W.). Another researcher (F.W.) re-evaluated the studies if there was a disagreement.

Types of outcomes

The primary prophylactic outcome was the overall incidence of severe OM in the study population; this outcome was also considered as the primary outcome of the effect of LLLT. OM was evaluated by using the World Health Organization (WHO) scale,[17] the Radiation Therapy Oncology Group (RTOG) scale,[18] the National Cancer Institute Common Terminology Criteria (NCICTC),[19] and the Tardieu scale.[20] Severe OM was defined on the basis of the following: a score of 3 to 4 on the WHO and RTOG scales, or 3 to 5 on the NCICTC, or 2 to 3 on the Tardieu scale. For studies using multiple scales, the WHO scale was considered first, if applicable. The secondary prophylactic outcomes included (1) the incidence of OM of any grade; (2) the incidence of severe OM at the most anticipated periods (at approximately 6 weeks of radiotherapy or chemoradiotherapy in patients with HNSCC; and day 10 of HSCT or chemotherapy); and (3) overall mean grade of OM, which could also be measured by using other scales, such as the oral mucositis assessment scale[21] and the oral mucositis index.[22] Other prophylactic outcomes, such as (1) incidence of severe pain defined by the visual analogue scale (VAS)[23] (VAS score $>$ 7); (2) overall mean VAS score; (3) the number of patients requesting analgesia; and (4) the number of unplanned radiotherapy interruption events because of the presence of OM, were also analyzed.

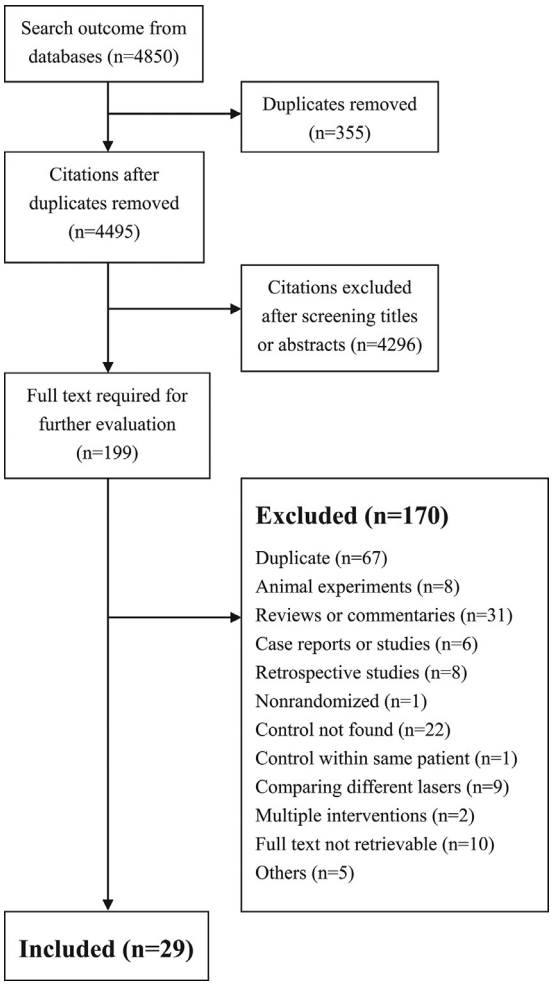

Fig. 1. Flow diagram of the study inclusion.

Table I. Baseline information of the selected studies

Author	*Year*	*Country*	*Treatment*	*Laser usage*	*Underlying condition*	*Age (years)*	*Laser type*	*Wavelength (nm)*	*Power (mW)*	*Time per site (seconds)*	*Energy density (J/cm^2)*	*Laser schedule*	*Evaluation schedule*	*Evaluation Scale*
Gobbo	2018	Italy	Chemotherapy	Treatment	Severe mucositis	3−18	K-laser	660 and 970 combined	3.2	25	36.8	Daily, 4 days	Every 3 days	WHO
Libik	2017	Russia	Radiotherapy	Prevention	Head and neck cancer	34−83	He-Ne	630	30	NA	5.16−16.2	Daily, until OM occurs	Weekly	WHO
Salvador	2017	Brazil	Chemotherapy	Prevention	Hematologic neoplasm	14−17	InGaAlP	660	40	4	4	Daily, 7 days	Daily, until day 20 or discharge	WHO
Vitale	2017	Italy	HSCT or chemotherapy	Treatment	Severe mucositis	3−18	GaAlAs	970	3200	230	NA	Daily, 4 days	Every 4 days	NCI-CTCAE
Amadori	2016	Italy	HSCT or chemotherapy	Treatment	Hematologic and solid tumor	3−18	NA	830	150	30 per cm2	4.5	Daily, 4 days	Every 3 days	WHO
Ahmed	2015	Iraq	Chemotherapy	Prevention	Hematologic and solid tumor	Child	AlGaInAs	940 ± 15	0.3	30	4.2	Daily, 3 weeks	Every 2 days	WHO
Ferreira	2015	Brazil	HSCT	Prevention	Hematologic neoplasm	Adult	InGaAlP	650	100	20	70	Daily, from 5 days before HSCT	Daily	WHO
Gautam	2015	India	Radiotherapy	Prevention	Head and neck cancer	> 60	He-Ne	632.8	24	125	36	Daily, 5 days every week	Weekly	RTOG/EORTC
Oton-Leite	2015	Brazil	Chemoradiotherapy	Prevention	Head and neck cancer	Adult	InGaAlP	660	25	10	NA	Every other day, 7 weeks	Weekly	WHO and NCI-CTC
Silva	2014	Brazil	HSCT	Prevention	Hematologic neoplasm	14−17	InGaAlP	660	40	4	4	Daily, 7 days	Daily, until day 20 or discharge	WHO
Antunes	2013	Brazil	Chemoradiotherapy	Prevention	Head and neck cancer	Adult	InGaAlP	660	100	10	4	Daily, 5 days every week	Daily	WHO and OMAS
Arbabi-Kalati	2013	Iran	Chemotherapy	Prevention	Tumor	17−79	Mustang	630	30	NA	5	Before chemotherapy	Every 2 weeks	WHO
Gautam	2012 (a)	India	Chemoradiotherapy	Prevention and treatment	Head and neck cancer	Adult	He-Ne	632.8	24	125	3	Daily, 5 days every week, 9 weeks	Weekly	RTOG/EORTC
Gautam	2012 (b)	India	Chemoradiotherapy	Prevention and treatment	Oral cancer	Adult	He-Ne	632.8	24	145	3.5	Daily, 5 days every week	Weekly	RTOG/EORTC
Hodgson	2012 (a)	USA	HSCT	Prevention	Hematologic and solid tumor	3−18	infrared LED	670 ± 10	50	80	4	Daily, 14 days	3 days per week	WHO, NCI-CTCAE and OMAS
Hodgson	2012 (b)	USA	HSCT	Prevention	Multiple myeloma	3−18	infrared LED	670 ± 10	50	80	4	Daily, 14 days	3 days per week	WHO, NCI-CTCAE and OMAS
Oton-Leite	2012	Brazil	Chemoradiotherapy	Prevention	Head and neck cancer	30−80	InGaAlP	685	35	25	2	Daily, 5 days every week	Twice (week 3 and 6)	WHO
Silva	2011	Brazil	HSCT	Prevention	Hematologic and solid tumor	4−64	InGaAlP	660	40	4	4	Daily, from Day -4 to day 4	Daily	WHO
Chor	2010	Brazil	HSCT	Prevention	NA	Adult	GaAlAs	660	50	NA	NA	Daily, from Day -7 to day 0	Daily	Tardieu
Lima	2010	Brazil	Chemoradiotherapy	Prevention	Head and neck cancer	18−75	GaAlAs	660	10	10	2.5	Daily, 5 days every week	Every 2 weeks	NCI-CTC
Khouri	2009	Brazil	HSCT	Prevention	Hematologic neoplasm	all	InGaAlP and GaAlAs	660 and 780	25	10	6.3	Daily, until day 15 or day of engraftment	NA	WHO and OMAS

(*continued on next page*)

Table I. Continued

Author	Year	Country	Treatment	Laser usage	Underlying condition	Age (years)	Laser type	Wavelength (nm)	Power (mW)	Time per site (seconds)	Energy density (J/cm^2)	Laser schedule	Evaluation schedule	Evaluation Scale
Kuhn	2009	Brazil	HSCT	Treatment	Hematologic and solid tumor	3–18	GaAlAs	830	100	Depending on area	4	Daily, 5 days	Daily	NCI-CTCAE
Abramoff	2008	Brazil	Chemotherapy	Prevention	Hematologic neoplasm	7–23	GaAlAs	685	35	54	72	Every other day	NA	NCI-CTC
Arora	2008	India	Radiotherapy	Prevention	Oral cancer	Adult	He-Ne	632.8	10	60	1.8	Daily, 33 days	Daily	RTOG/EORTC
Antunes	2007	Brazil	HSCT	Prevention	Hematologic neoplasm	Adult	InGaAlP	660	46.7	16.7	4	Daily, from Day -7 to recovery	Daily	WHO and OMAS
Cruz	2007	Brazil	HSCT or chemotherapy	Prevention	Hematologic and solid tumor	3–18	NA	780	60	NA	4	Daily, 5 days after chemotherapy	day 8 and day 15	NCI-CTC
Schubert	2007	USA	HSCT	Prevention	Hematologic and solid tumor	20–69	GaAlAs	650	40	2	2	Daily, from Day -1 to day 2	Twice a week	OMI
Maiya	2006	India	Radiotherapy	Prevention	Oral cancer	Adult	He-Ne	632.8	60	10	1.5	Daily, 5 days every week	Once (in week 6)	WHO
Bensadoun	1999	France	Radiotherapy	Prevention	Head and neck cancer	36–78	He-Ne	632.8	60	33	2	Daily, 5 days every week	Weekly	WHO
Cowen	1997	France	HSCT	Prevention	Hematologic neoplasm	17–58	He-Ne	632.8	60	10	1.5	Daily, from Day -5 to Day -1	Daily	Tardieu

EORTC, The European Organization for Research and Treatment of Cancer; *HSCT*, hematopoietic stem cell transplantation; *NCI-CTC*, The National Cancer Institute–Common Terminology Criteria; *NCI-CTCAE*, The National Cancer Institute–Common Terminology Criteria for Adverse Events; *OM*, oral mucositis; *OMAS*, oral mucositis assessment scale; *OMI*, oral mucositis index; *RTOG*, Radiation Therapy Oncology Group; *WHO*, World Health Organization.

The therapeutic outcomes were the number of patients with severe OM after 7-day treatment of LLLT, which was the primary outcome, as well as the duration of severe OM, which was the secondary outcome. The definition of severe OM was in line with the definition in the first paragraph of this section. Other therapeutic outcomes, such as the median VAS score and the number of patients who required analgesia, were also analyzed.

Data extraction

Two researchers (J.P. and H.X.) independently extracted the baseline information, demographic features of the participants, settings of the intervention, and outcome data from the selected studies. If the data necessary for analysis were not provided in the full texts, the corresponding authors were contacted and the missing data requested.

Data synthesis and statistical analysis

The pooled effects of these trials were defined by the relative risk (RR) and weighted mean difference (WMD) or standardized mean difference (SMD), depending on the type of data. For dichotomous data, data were synthesized by using the RR with its 95% confidence interval (CI); for continuous data measured with different scales, SMD was used to synthesize the outcomes; for continuous data measured with the same scale, outcomes were synthesized by using WMD. The I^2 value was calculated to estimate heterogeneity. If I^2 was greater than 50%, the random effect model was used; otherwise, the fixed effect model was used.

Analysis of publication bias was conducted by visualization of a funnel plot, along with Egger's test. If the P value was greater than 0.05, publication bias was considered to be absent.

Subgroup analysis of the primary outcome was conducted subsequently, in which the patients were stratified by age (adult, child, all); underlying condition (HSCT, chemotherapy, radiotherapy, chemoradiotherapy); wavelength (red: < 760 nm; infrared: ≥ 760 nm); energy density (low: ≤ 4 J/cm^2; high: > 4 J/cm^2); location of laser irradiation (intraoral, extraoral); evidence quality (high: Jadad score ≥ 3; low: Jadad score < 3); and proper allocation concealment (yes, no, uncertain).

Meta-analysis was conducted by using R software version 3.5.2 and its "meta" package.

RESULTS

General results

Figure 1 shows the process of study inclusion. Of the 4850 articles that were identified under the current search strategy, 29 were selected and included in the analysis.[11-13,24-51] One of the 29 studies[40] reported its outcomes as a stratified analysis and, therefore, was

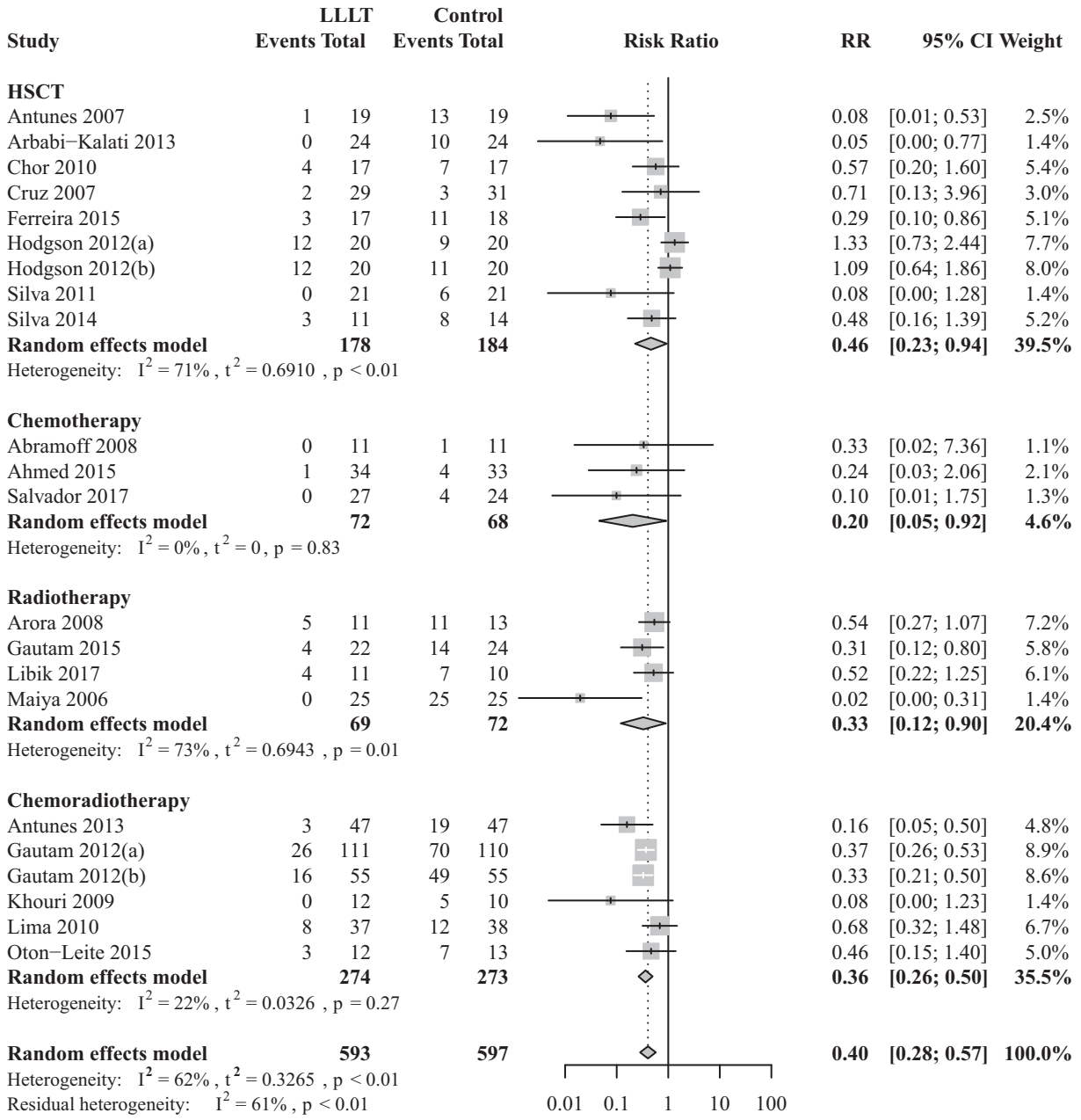

Fig. 2. The forest plot of overall incidence of severe oral mucositis stratified by underlying condition. Each horizontal line with a square in the center stands for the relative risk and the confidence interval of low-level laser therapy; diamonds represent the pooled effects of each subgroup, respectively.

regarded as 2 separate trials. Overall, 1616 patients were randomly assigned within these 30 trials.

Table I shows the baseline information of the 30 included studies. Prophylactic LLLT was used in 26 studies, and 6 studies[13,25,36-38,51] reported therapeutic LLLT intervention. The studies were conducted in 8 countries, with nearly half of them (n = 14) in Brazil. One-third of the studies (n = 10) were published between 2014 and 2018, and the earliest publication was in 1997. Almost two-thirds of the studies (n = 19) included patients who underwent HSCT or chemotherapy, and others, including patients with HNSCC, underwent radiotherapy (n = 5) or chemoradiotherapy (n = 6). Three studies were on both adults and children, 10 only on children, and 17 only on adults. Only 2 studies applied extraoral laser irradiation. The parameters of laser equipment differed, with wavelengths ranging from 630 nm to 970 nm and energy density from 1.5 J/cm^2 to 72 J/cm^2.

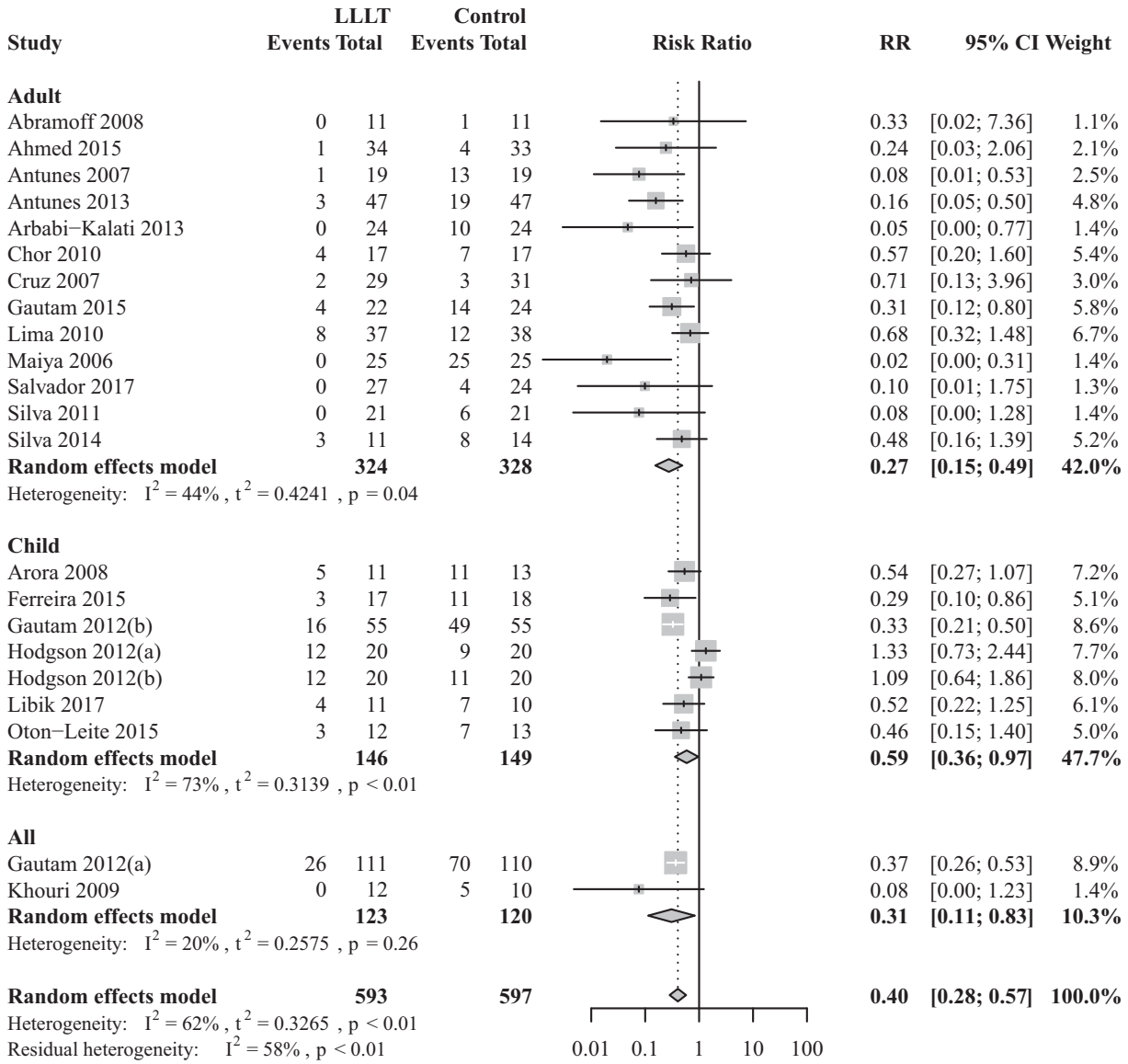

Fig. 3. The forest plot of overall incidence of severe oral mucositis stratified by age. Each horizontal line with a square in the center stands for the relative risk and the confidence interval of low-level laser therapy; diamonds represent the pooled effects of each subgroup, respectively.

Heterogeneity of the included trials was examined (I^2 = 62.1%), and the random effect model was adopted to demonstrate the results.

Risk of bias and quality of evidence

The risk of bias in the studies is summarized in Supplemental Table SI. On the Jadad scale, 19 studies scored no less than 3 points out of 5 and were considered to be of high quality; the remaining 11 were considered to be of low quality. Only 10 studies correctly reported allocation concealment, resulting in 8 of the 30 trials generally being considered to be low-risk-of-bias trials.

The quality of evidence was assessed by using the GRADE system, and the results showed that the overall quality levels of most outcomes ranged from moderate to high, although low levels of quality were found in 2 outcomes with substantial inconsistencies and high risk of bias. A "summary of findings" is shown in Supplemental Table SII.

Prophylactic outcomes

Incidence of severe OM (the primary outcome). Twenty-two studies with 1190 patients reported the incidence of severe OM during the treatment of hematologic disorders or HNSCC in their experimental (593 patients) and

Table II. Subgroup analysis of the primary outcome, namely the overall incidence of severe oral mucositis

Subgroup	*No. of studies*	*No. of patients*	*RR*	*95% CI*	I^2	*P value*
Underlying condition						**.79**
HSCT	9	362	0.46	[0.23−0.94]	71%	.03
Chemotherapy	3	140	0.20	[0.05−0.92]	0%	.04
Radiotherapy	4	141	0.33	[0.12−0.90]	73%	.03
Chemoradiotherapy	6	547	0.36	[0.27−0.50]	21%	< .01
Age groups						**.13**
Adult	13	652	0.27	[0.15−0.49]	44%	< .01
Child	7	295	0.59	[0.36−0.97]	73%	.04
All	2	243	0.31	[0.12−0.82]	19%	.02
Wavelength						**.16**
Red	17	1023	0.36	[0.23−0.56]	70%	< .01
Infrared	4	145	0.56	[0.37−0.84]	0%	< .01
Combined	1	22	0.08	[0.00−1.23]	NA	.07
Energy density						**.56**
High	15	868	0.41	[0.27−0.63]	71%	< .01
Low	6	288	0.33	[0.18−0.60]	0%	< .01
Location of laser irradiation						< **.01**
Intraoral	20	1088	0.37	[0.28−0.48]	22%	< .01
Extraoral	2	80	1.19	[0.80−1.78]	0%	.39
Evidence quality						**.20**
High	12	762	0.47	[0.31−0.73]	65%	< .01
Low	10	428	0.28	[0.14−0.56]	63%	< .01
Proper allocation concealment						**.44**
Yes	5	460	0.34	[0.26−0.44]	0%	< .01
No or uncertain	17	730	0.42	[0.26−0.69]	66%	< .01
Laser schedule						**.89**
Daily	19	1095	0.41	[0.29−0.60]	65%	< .01
Every other day	2	47	0.45	[0.16−1.26]	0%	.13
Timing of laser						**.66**
Before treatment	10	619	0.36	[0.28−0.47]	8%	< .01
During treatment	12	571	0.43	[0.22−0.82]	71%	.01
Evaluation schedule						**.24**
Daily	8	343	0.31	[0.18−0.55]	35%	< .01
Over daily	12	803	0.48	[0.31−0.76]	72%	< .01

CI, confidence interval; *HSCT,* hematopoietic stem cell transplantation; *NA,* not available; *RR,* relative risk.

control (597 patients) groups. The analysis indicated that LLLT significantly reduced the risk of severe OM (RR = 0.40; 95% CI 0.28−0.57; $P < .01$). Outcomes stratified by different underlying conditions (HSCT: RR = 0.46, 95% CI: 0.23−0.94, $P = .03$; chemotherapy: RR = 0.20, 95% CI 0.05−0.92, $P = .04$; radiotherapy: RR = 0.33, 95% CI 0.12−0.90, $P = .03$; chemoradiotherapy: RR = 0.36, 95% CI 0.27−0.50, $P < .01$) or by age groups (adult: RR = 0.27, 95% CI 0.15−0.49, $P < .01$; child: RR = 0.59, 95% CI: 0.36 to 0.97 $P = .04$; all: RR = 0.31, 95% CI 0.12−0.82, $P = .02$) revealed the same effect of incidence risk reduction in corresponding groups (Figures 2 and 3). We also found that intervention groups that received red laser; infrared laser; laser of high energy density (> 4 J/cm^2) or low energy density (≤ 4 J/cm^2); and intraoral laser irradiation had a lower risk of severe OM compared with the control groups (all P values < .01) (Table II and Supplemental Figures S1−S5). Furthermore, patients receiving LLLT daily were also at low risk of severe OM ($P < .01$); however, in those receiving LLLT every 2 days, the risk of severe OM was not at significantly lower ($P = .13$) compared with that in the control group. Substantial reductions in the incidence of severe OM were found in the study groups, whether the patients received LLLT before ($P < .01$) or during ($P = .01$) treatments for malignancies and whether they received OM evaluation daily ($P < .01$) or less frequently ($P < .01$) (see Table II and Supplemental Figures S6−S8).

Incidence of OM of any grade. Of the included studies, 15 reported the incidence of any OM. Of the 900 patients in these studies, 449 were assigned to the LLLT group and the others (451 patients) to the control group. The results showed that LLLT can reduce the incidence of OM of any grade to 90% (95% CI 0.81−1.00; $P = .06$) (Table III). Patients who underwent chemotherapy, radiotherapy, or chemoradiotherapy were included in a subgroup analysis. In the chemotherapy group, the results (RR 0.73; 95% CI

Table III. Prophylactic and therapeutic outcomes

Types of outcomes	*Outcomes*	*Number of studies*	*Effect*	*95% CI*	I^2	*P value*
Prophylactic	1. Overall incidence of severe oral mucositis	22	RR = 0.40	[0.28−0.57]	62%	< .01
	2. Incidence of oral mucositis of any grade	15	RR = 0.90	[0.81−1.00]	95%	.06
	3. Incidence of severe oral mucositis at the most anticipated time	9	RR = 0.35	[0.18−0.70]	78%	< .01
	4. Overall mean grade of oral mucositis	9	SMD = −1.23	[−1.69to −-0.77]	82%	< .01
	5. Overall incidence of severe pain	6	RR = 0.38	[0.13−1.06]	86%	.06
	6. Number of patients requesting analgesia	6	RR = 0.61	[0.45−0.81]	17%	< .01
	7. Number of unplanned radiotherapy interruption events because of mucositis	5	RR = 0.22	[0.12−0.42]	0%	< .01
Therapeutic	8. Number of patients with severe oral mucositis after 7-day treatment with LLLT	3	RR = 0.37	[0.10−1.36]	72%	.14
	9. Duration of severe oral mucositis*	3	WMD = −5.81	[−9.34 to −2.28]	90%	< .01

*The unit of "Duration of severe oral mucositis" is "day."*CI,* confidence interval; *RR,* relative risk; *SMD,* standardized mean difference; *WMD,* weighted mean difference.

0.55−0.96; P = .03) were considered significant, whereas in the radiotherapy and chemoradiotherapy groups, the results were not significant (RR = 1.00, 95% CI 0.92−1.09; and RR = 1.00, 95% CI 0.98−1.01, respectively).

Incidence of severe OM at the most anticipated periods. At the most anticipated periods, a reduction (RR = 0.35; 95% CI 0.18−0.70; P < .01) was found in the incidence of severe OM that was estimated by combining the data from 9 studies with 737 patients (367 underwent LLLT intervention and 370 received placebo or no therapy) (see Table III).

Overall mean grade of OM. In 9 studies, 602 patients were allocated to the experimental (n = 300) or control (n = 302 patients) groups. The mean grades of OM in the 9 LLLT groups ranged from 0.36 to 2.18, whereas in the 9 control groups, they ranged from 0.58 to 3.33. The pooled SMD estimate was −1.23 (95% CI −1.67 to −0.77; P < .01) (see Table III).

Other prophylactic outcomes. The effect of prophylactic LLLT on pain control was also analyzed. There was a reduced incidence (RR = 0.38; 95% CI 0.13−1.06; P = 0.06) of severe pain (VAS score > 7) in 6 studies. The mean VAS score was also lower (SMD = −3.97; 95% CI −6.42 to −1.52; P < .01) in the LLLT group. Fewer patients requested analgesia after LLLT intervention (RR = 0.61; 95% CI 0.45−0.81; P < .01) compared with those in the control group. Unplanned radiotherapy interruption events (RR = 0.22; 95% CI 0.12−0.42; P < .01) were also fewer (see Table III). Furthermore, Cowen et al.[32] reported a statistically significant reduction (P = .01) in the duration of severe OM in the LLLT group (0.69 ± 1.40 days) compared with the control group (2.41 ± 2.30 days). No studies reported adverse reactions after prophylactic LLLT.

Therapeutic outcomes

Remission of severe OM (the primary outcome). Three studies (71 patients underwent LLLT and 72 were controls) reported the severity of OM after LLLT treatment on different days; and only the data on the seventh day after treatment could be pooled. The number of patients with severe OM decreased after 7-day treatment with LLLT (RR = 0.36; 95% CI 0.10−1.36; P = .14) compared with the number in the control group (see Table III and Supplemental Figure S9).

Duration of severe OM. There was a significant reduction in the duration (WMD = −5.81 days; 95% CI −9.34 to −2.28; P < .01) of severe OM in the LLLT-treated group (175 patients) compared with that in the control group (177 patients) from 3 studies (see Table III and Supplemental Figure S10).

Other therapeutic outcomes. Additionally, Gobbo et al.[38] reported that after 7-day treatment, the median VAS score in the LLLT group (median = 1) was significantly lower than that in the control group (median = 2.5) (P = .006); a reduction (49% in the LLLT group vs 62% in the control group, P = .60) of analgesic use was also observed. No studies reported adverse reactions to therapeutic LLLT.

Analysis of publication bias

The funnel plot of RR was drawn (see Supplemental Figure S11) to examine whether publication bias existed in the selected studies, and the result indicated that there was no significant publication bias. The Egger's test results also proved that there was no publication bias (P > .05).

Sensitivity analysis

We also analyzed the impact of each study on the primary outcome and found that the results were still robust,

indicating that there were no studies that could have altered the result (see Supplemental Figure S12). Subgroup analysis (see Table II) also suggested that the pooled estimates of all but 3 subgroups (specifically, "extraoral" in "location of laser irradiation," the RR of which was over 1; "combined" in "wavelength"; and "every other day" in "laser schedule," the RR values of which were less than 1 but *P* values were greater than .05) were in accordance with the primary outcome.

DISCUSSION

The results presented in this study suggest that application of prophylactic LLLT could reduce the overall risk of severe OM induced by treatments of malignancies. Subgroup analysis showed similar results when stratifying studies on the basis of underlying conditions, age groups, laser parameters, and LLLT schedules, with the exception of extraoral laser irradiation, which had no effect on reducing the risk of OM. Incidences of severe OM at the most anticipated time, overall mean grade of OM, overall mean VAS score, the number of patients requesting analgesia, and the number of unplanned radiotherapy interruption events because of OM were found to be reduced substantially after prophylactic LLLT. As for therapeutic LLLT, it seemed to have no substantial effect on the remission of severe OM, although it substantially reduced the duration of severe OM. Additionally, sensitivity analysis proved the robustness of our findings.

Our findings integrated the prophylactic and therapeutic effects of LLLT in patients receiving treatments for a wide range of malignancies, including various hematologic disorders, head and neck cancers, and other solid tumors, supplementing the findings of a previous 2014 meta-analysis,[4] which only provided conclusions regarding the prophylactic effect of LLLT. In addition, our meta-analysis included a total number of 30 studies from 8 countries, with both prophylactic and therapeutic effects analyzed.

Heterogeneity was detected in the included studies because the 30 studies were carried out by different institutions using different methods. Of the studies included, only 19 (63%) showed a relatively low risk of bias, according to our evaluation based on the Jadad scale, indicating that the quality of these studies differed and might have affected their results. Additionally, only 10 (34%) of the 30 included studies provided an appropriate statement of allocation concealment. Furthermore, the complexity of the laser parameters and LLLT schedules prevented a more specific allocation of subgroups, and this might have resulted in high heterogeneity among included RCTs.

In our report, we have presented evidence that extraoral laser irradiation did not have a protective effect against OM (see Table II). As reported by Hodgson et al.[40], their preliminary studies had identified a low ability of low-level lasers for tissue penetration, which could explain why the fluence of light at the interior mucosal surface had been only slightly higher than one-half of the minimum fluence that can have a positive effect on OM. No included RCTs reported any adverse reaction to LLLT. Therefore, the safety of LLLT is guaranteed.

Although the effects of LLLT have been systematically evaluated and discussed above, the optimal use of LLLT in patients requires additional evidence. Laser parameters and LLLT schedules in current clinical practice differ greatly among institutions, implying lack of evidence regarding laser intervention. This may require more sophisticated RCTs focusing on laser parameters and LLLT schedules.

CONCLUSIONS

Our findings indicate that prophylactic LLLT is effective in preventing OM in patients receiving chemotherapy or radiotherapy and that therapeutic LLLT is effective in reducing severe OM duration. On the basis of the results of our risk of bias assessment and heterogeneity analysis, we believe that more well-designed multicenter RCTs on this subject are needed. The uncertain influence of different laser parameters and LLLT schedules indicate the need to determine the optimal setting for LLLT, which ought to be the focus in future studies.

ACKNOWLEDGMENTS

We are grateful to Sichuan University for allowing access to their library and their online contents.

FUNDING

This work was supported by the Sichuan University Post-doctoral Research and Development Fund (grant No. 19 XJ0008).

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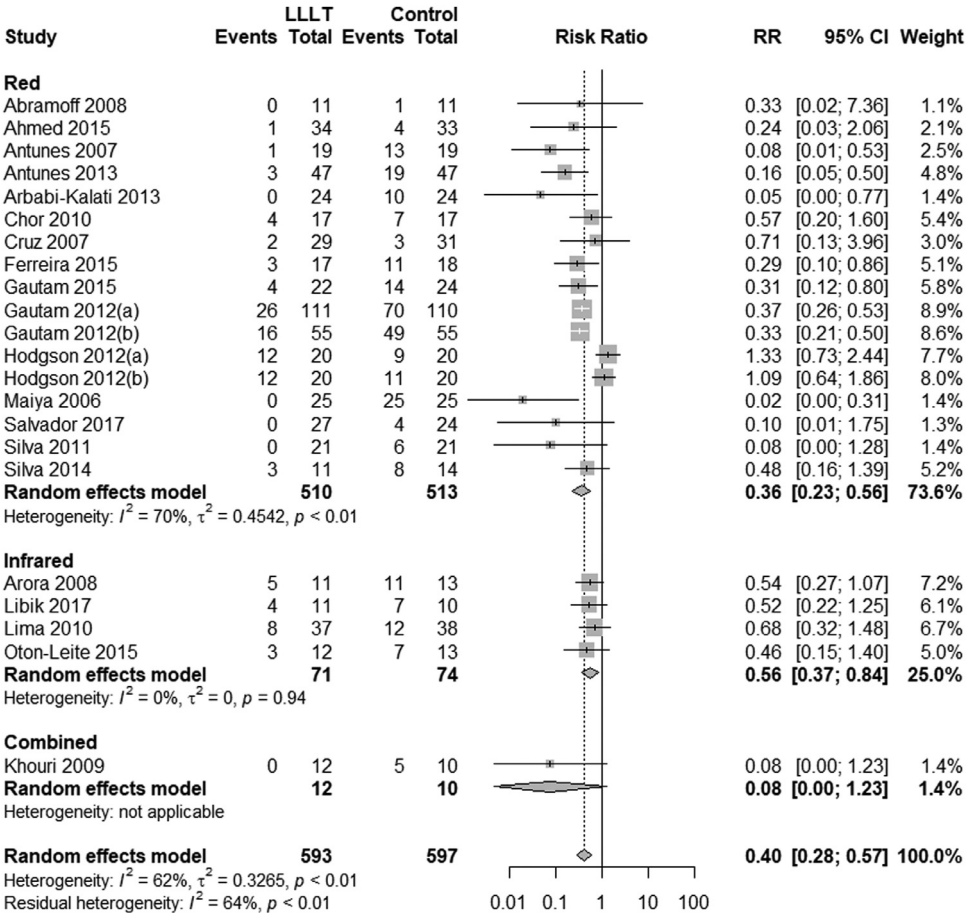

Fig. S1. The forest plot of overall incidence of severe oral mucositis stratified by wavelength. Each horizontal line with a square in the center stands for the relative risk and its confidence interval of low-level laser therapy; diamonds represent the pooled effects of each subgroup respectively.

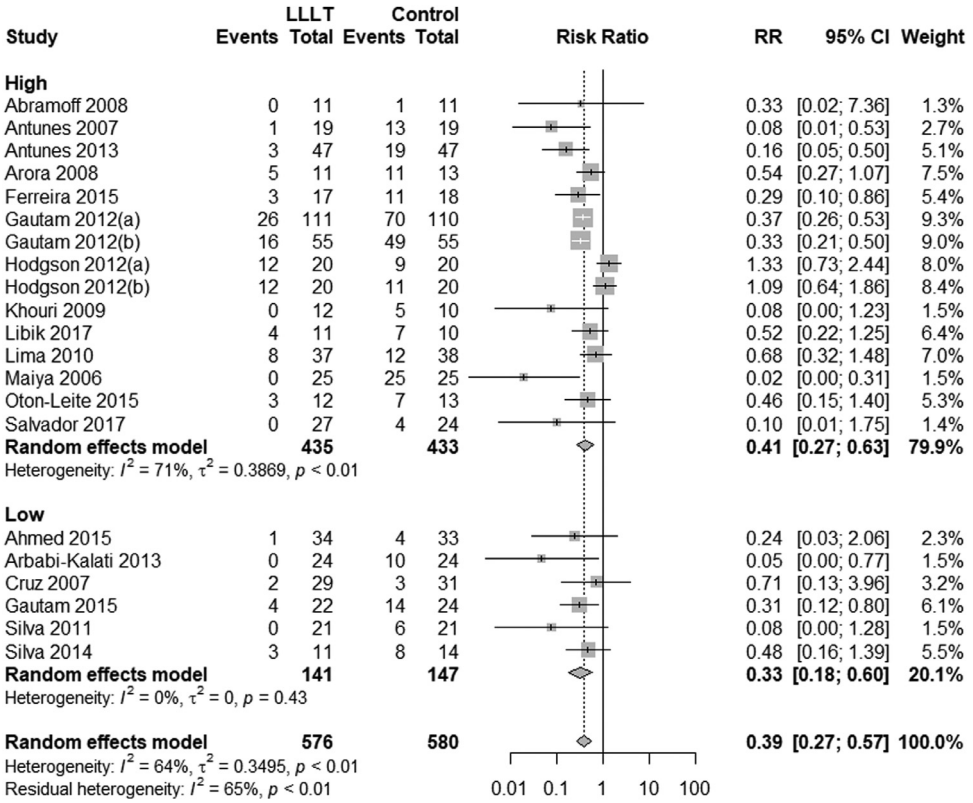

Fig. S2. The forest plot of overall incidence of severe oral mucositis stratified by energy density. Each horizontal line with a square in the center stands for the relative risk and its confidence interval of low-level laser therapy; diamonds represent the pooled effects of each subgroup respectively.

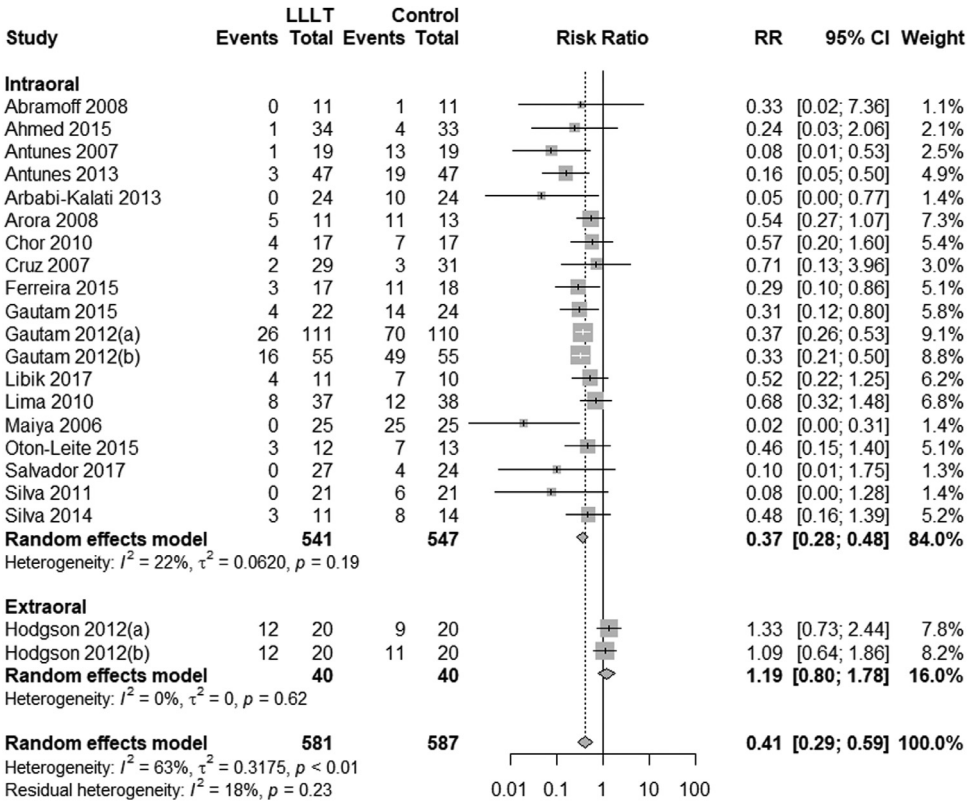

Fig. S3. The forest plot of overall incidence of severe oral mucositis stratified by the location of irradiation. Each horizontal line with a square in the center stands for the relative risk and its confidence interval of low-level laser therapy; diamonds represent the pooled effects of each subgroup respectively.

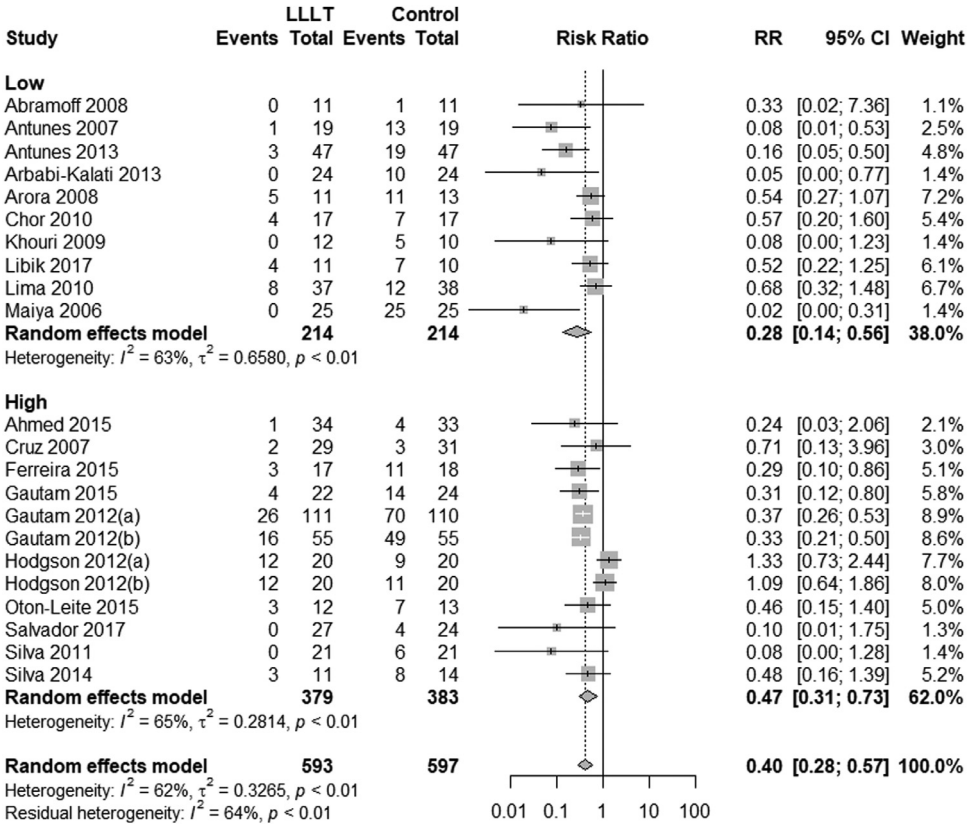

Fig. S4. The forest plot of overall incidence of severe oral mucositis stratified by the quality of evidence. Each horizontal line with a square in the center stands for the relative risk and its confidence interval of low-level laser therapy; diamonds represent the pooled effects of each subgroup respectively.

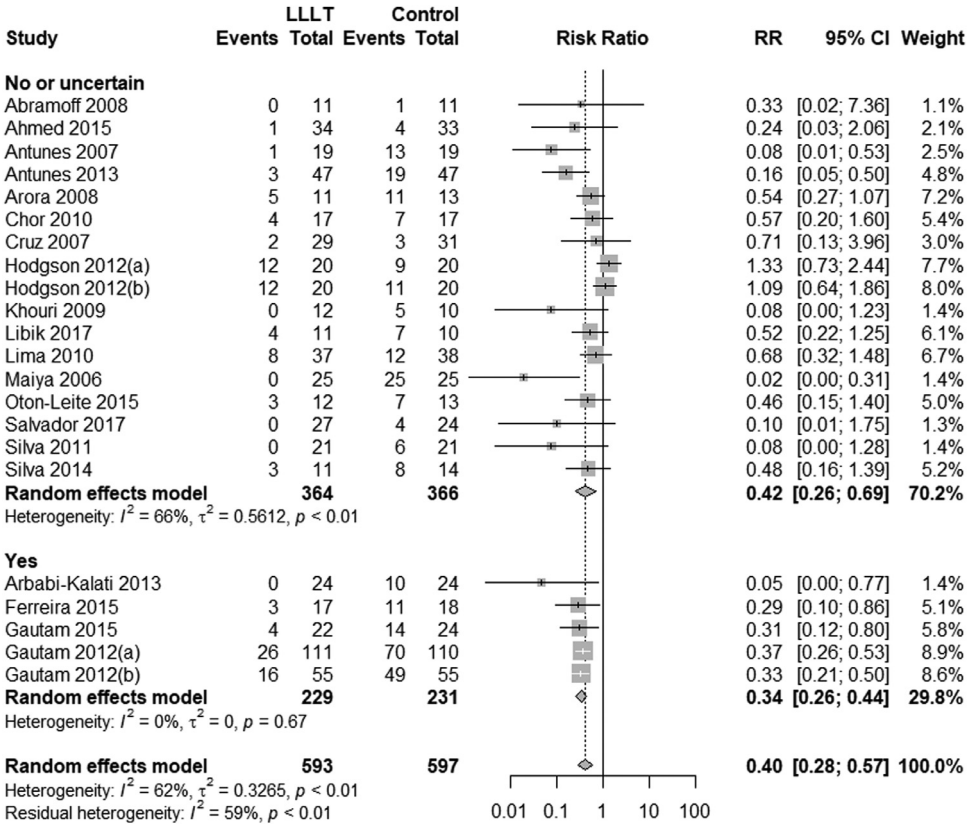

Fig. S5. The forest plot of overall incidence of severe oral mucositis stratified by the existence of proper allocation concealment. Each horizontal line with a square in the center stands for the relative risk and its confidence interval of low-level laser therapy; diamonds represent the pooled effects of each subgroup respectively.

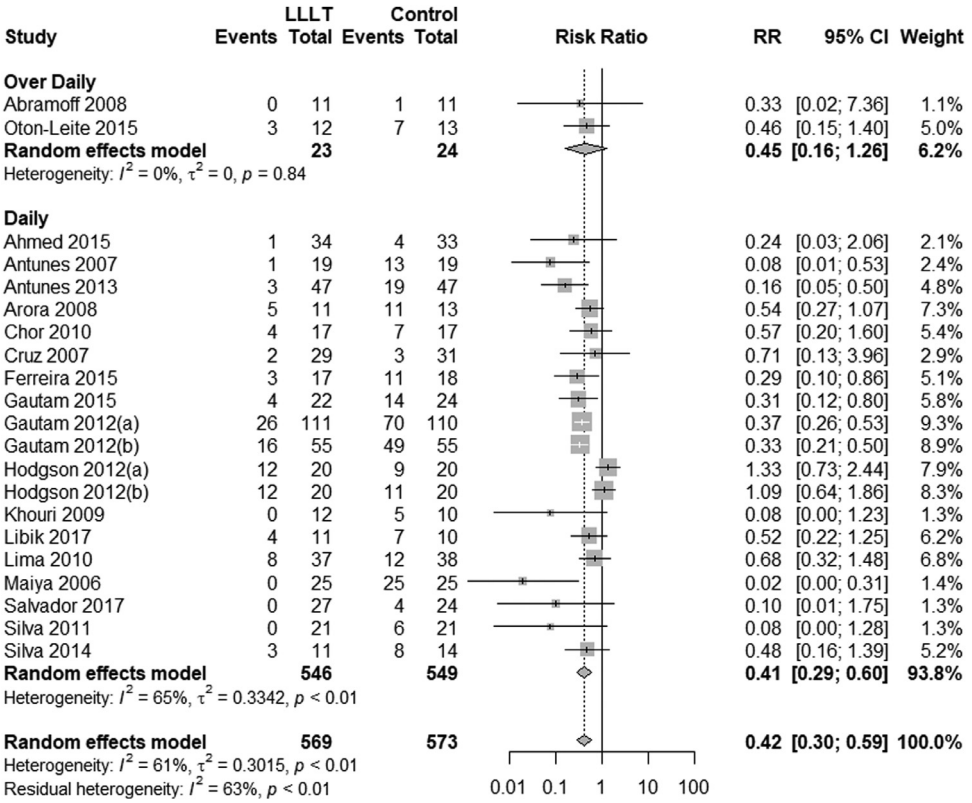

Fig. S6. The forest plot of overall incidence of severe oral mucositis stratified by laser schedule. Each horizontal line with a square in the center stands for the relative risk and its confidence interval of low-level laser therapy; diamonds represent the pooled effects of each subgroup respectively.

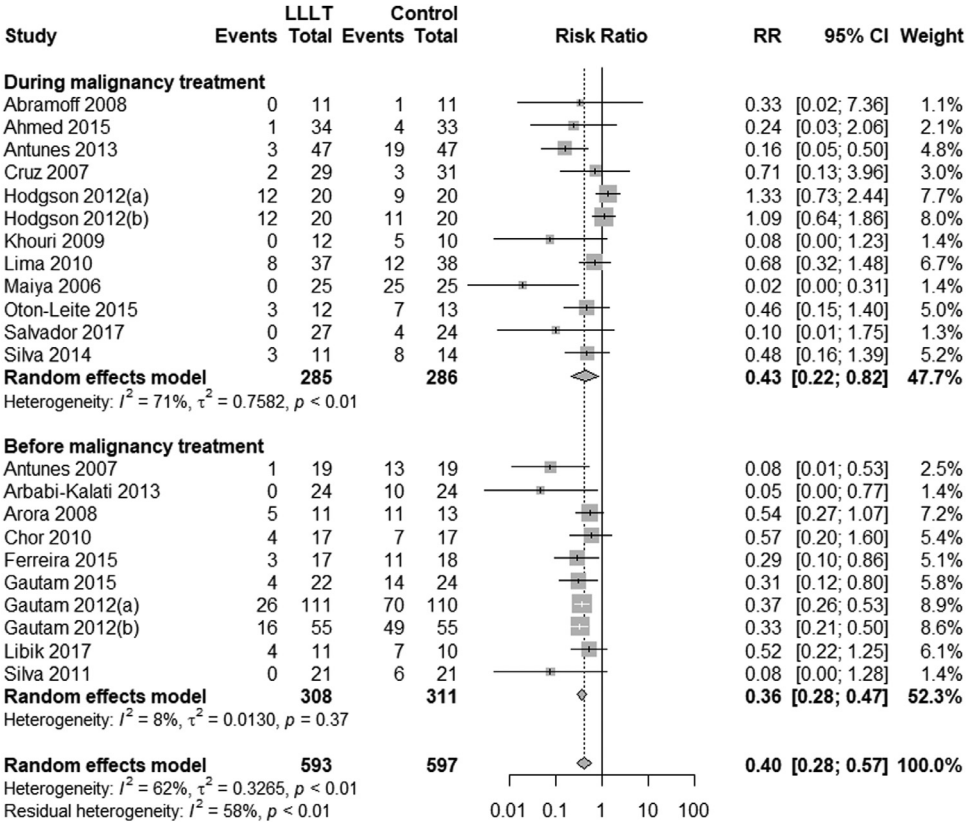

Fig. S7. The forest plot of overall incidence of severe oral mucositis stratified by timing of laser. Each horizontal line with a square in the center stands for the relative risk and its confidence interval of low-level laser therapy; diamonds represent the pooled effects of each subgroup respectively.

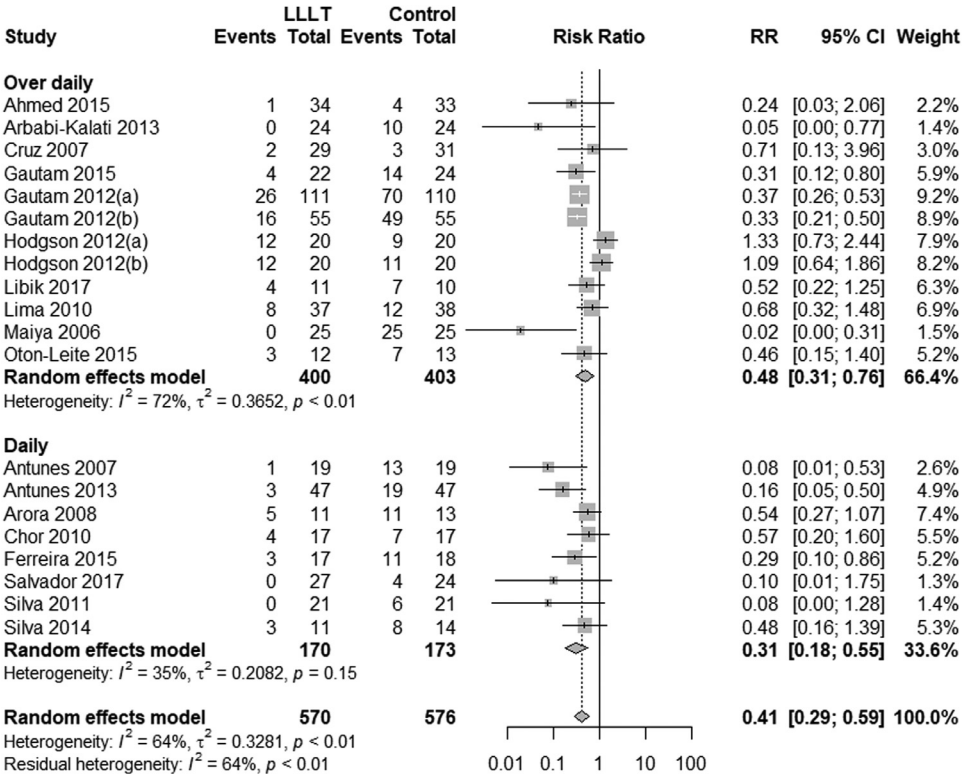

Fig. S8. The forest plot of overall incidence of severe oral mucositis stratified by evaluation schedule. Each horizontal line with a square in the center stands for the relative risk and its confidence interval of low-level laser therapy; diamonds represent the pooled effects of each subgroup respectively.

Table SI. Evaluation of risk of bias of selected trials using the Jadad scale and additional allocation concealment assessment. Jadad score is the sum of three parts: method of randomization, double-blind and drop-outs. Method of randomization and double-blind have a maximum of 2 scores (0 for inappropriate, 1 for uncertain, 2 for appropriate), and drop-outs can be 0 (inappropriate) or 1 (appropriate).

Author	*Year*	*Allocation concealment*	*Jadad score*	*Method of randomization (2)*	*Double-blind (2)*	*Drop-outs (1)*
Gobbo	2018	Yes	5	2	2	1
Libik	2017	No or uncertain	1	1	0	0
Salvador	2017	No or uncertain	4	2	1	1
Vitale	2017	No or uncertain	4	2	2	0
Amadori	2016	Yes	4	2	2	0
Ahmed	2015	No or uncertain	4	1	2	1
Ferreira	2015	Yes	5	2	2	1
Gautam	2015	Yes	5	2	2	1
Oton-Leite	2015	No or uncertain	5	2	2	1
Silva	2014	No or uncertain	4	2	1	1
Antunes	2013	No or uncertain	2	1	1	0
Arbabi-Kalati	2013	Yes	2	1	1	0
Gautam	2012(a)	Yes	5	2	2	1
Gautam	2012(b)	Yes	5	2	2	1
Hodgson	2012(a)	No or uncertain	4	1	2	1
Hodgson	2012(b)	No or uncertain	4	1	2	1
Oton-Leite	2012	No or uncertain	5	2	2	1
Silva	2011	No or uncertain	4	2	1	1
Chor	2010	No or uncertain	1	1	0	0
Lima	2010	No or uncertain	2	2	0	0
Khouri	2009	No or uncertain	0	0	0	0
Kuhn	2009	Yes	5	2	2	1
Abramoff	2008	No or uncertain	2	1	0	1
Arora	2008	No or uncertain	1	0	0	1
Antunes	2007	No or uncertain	2	1	1	0
Cruz	2007	No or uncertain	3	1	1	1
Schubert	2007	No or uncertain	4	1	2	1
Maiya	2006	No or uncertain	2	2	0	0
Bensadoun	1999	Yes	2	1	1	0
Cowen	1997	Yes	3	0	2	1

Search strategy in databases: ("Low-level laser therapy" OR LLLT OR "low power laser therapy" OR "low-energy laser therapy" OR "low power laser irradiation" OR LPLT OR "soft laser therapy" OR "low-intensity laser therapy" OR "cold laser therapy" OR "bio-stimulation laser therapy" OR photobiomodulation OR photo-biotherapy OR "therapeutic laser" OR "monochromatic infrared light energy therapy" OR MIRE OR "light-emitting diodes" OR LED) AND ("oral mucositis" OR oromucositis OR stomatitis OR stomatititises OR stomatititides)

Table SII. Summary of findings table.

LLLT compared to no therapy for OM induced by chemotherapy or HSCT or radiotherapy

Patient or population: OM induced by chemotherapy or HSCT or radiotherapy
Setting: /
Intervention: LLLT
Comparison: no therapy

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
				Difference		
incidence of severe OM № of participants: 1190 (22 RCTs)	**RR 0.40** (0.28 to 0.57)	51.4%	**20.6%** (14.4 to 29.3)	**30.9% fewer** (37 fewer to 22.1 fewer)	⊕⊕⊕⊕ HIGH	
incidence of OM of any grade № of participants: 900 (15 RCTs)	**RR 0.90** (0.81 to 1.00)	89.1%	**80.2%** (72.2 to 89.1)	**8.9% fewer** (16.9 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	
incidence of OM at anticipated time № of participants: 737 (9 RCTs)	**RR 0.35** (0.18 to 0.70)	50.5%	**17.7%** (9.1 to 35.4)	**32.9% fewer** (41.4 fewer to 15.2 fewer)	⊕⊕⊕⊕ HIGH	
mean grade № of participants: 602 (9 RCTs)	-	-	-	SMD **1.23 SD lower** (1.69 lower to 0.77 lower)	⊕⊕◯◯ LOW	
incidence of severe pain № of participants: 319 (6 RCTs)	**RR 0.38** (0.13 to 1.06)	57.1%	**21.7%** (7.4 to 60.6)	**35.4% fewer** (49.7 fewer to 3.4 more)	⊕⊕⊕◯ MODERATE	
mean VAS score № of participants: 143 (4 RCTs)	-	-	-	SMD **3.97 SD lower** (6.42 lower to 1.52 lower)	⊕⊕◯◯ LOW	
number of patients requesting analgesia № of participants: 503 (6 RCTs)	**RR 0.61** (0.45 to 0.81)	56.7%	**34.6%** (25.5 to 46)	**22.1% fewer** (31.2 fewer to 10.8 fewer)	⊕⊕⊕⊕ HIGH	
number of unplanned radiotherapy interruption events due to OM № of participants: 512 (5 RCTs)	**RR 0.22** (0.12 to 0.42)	17.9%	**3.9%** (2.1 to 7.5)	**14.0% fewer** (15.8 fewer to 10.4 fewer)	⊕⊕⊕⊕ HIGH	
number of patients with severe OM after a 7-day treatment of LLLT № of participants: 243 (3 RCTs)	**RR 0.30** (0.10 to 1.36)	28.5%	**8.5%** (2.8 to 38.7)	**19.9% fewer** (25.6 fewer to 10.2 more)	⊕⊕◯◯ LOW	
duration of severe OM № of participants: 352 (3 RCTs)	-		-	MD **5.81 days fewer** (9.34 fewer to 2.28 fewer)	⊕⊕⊕◯ MODERATE	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **SMD:**Standardised mean difference; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

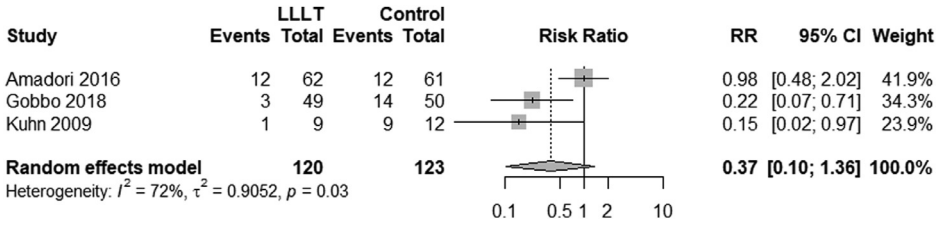

Fig. S9. The forest plot of the number of patients with severe oral mucositis after 7-day treatment of low-level laser therapy. Each horizontal line with a square in the center stands for the relative risk and its confidence interval of low-level laser therapy; the diamond represents the pooled effect of these studies.

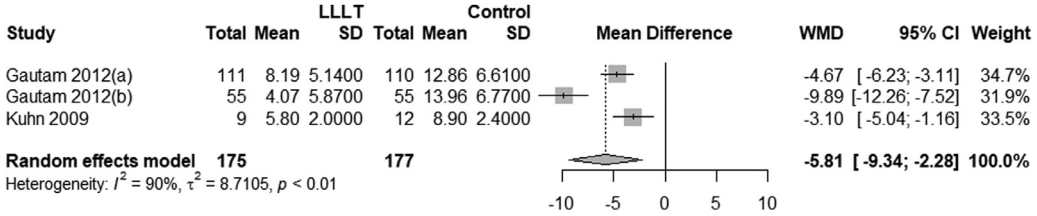

Fig. S10. The forest plot of the duration of severe oral mucositis. Each horizontal line with a square in the center stands for the weighted mean difference and its confidence interval of low-level laser therapy; the diamond represents the pooled effect of these studies.

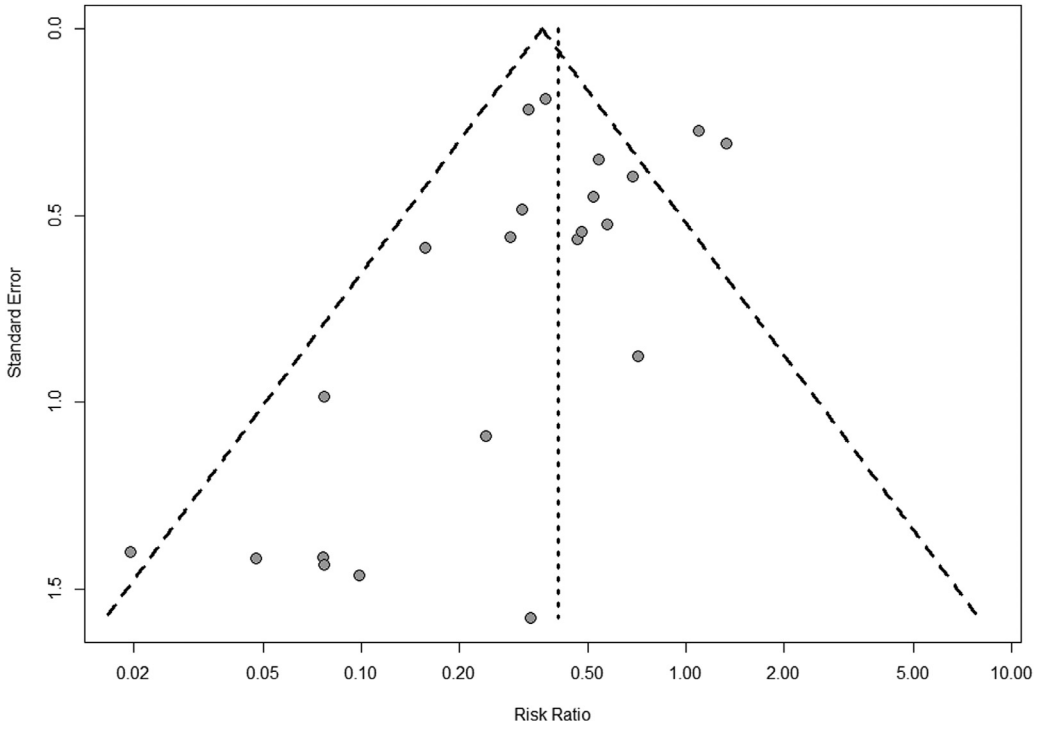

Fig. S11. The funnel plot indicating no bias of publication.

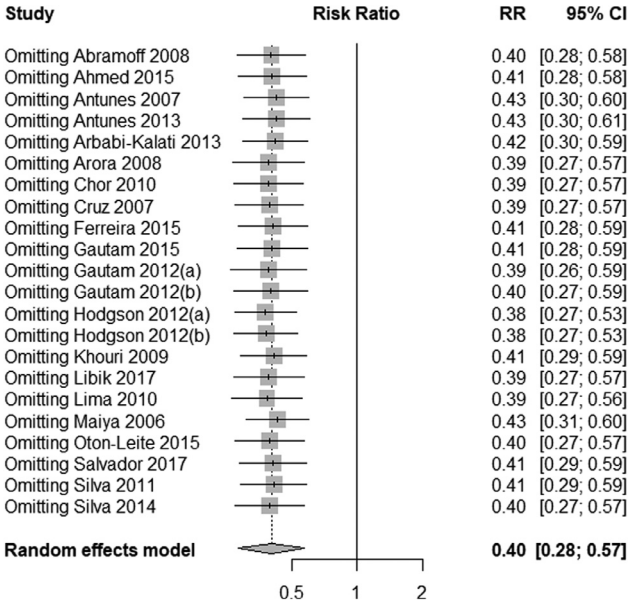

Fig. S12. The result of the sensitivity analysis. This forest plot shows the pooled effects and their 95% confidence intervals after the removal of each study.