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Review Article

Association between depth of anesthesia and postoperative outcome: a systematic review and meta-analysis

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Abstract: Background: The bispectral index (BIS) monitor has increasingly been used to measure anesthetic depth to reduce the incidence of intraoperative awareness with recall (AWR). Studies reported conflicting results on the association between anesthetic depth and risk of clinical outcomes after surgery. Objective: We aimed to examine the association between low BIS or triple low state and risk of postoperative mortality and complications by conducting a meta-analysis of prospective cohort studies. Methods: We comprehensively searched PubMed and all available randomized controlled trials (RCTs) and retrospective comparative studies were retrieved. Results: 2 RCTs and 9 retrospective studies met the selection criteria, among which 9325 patients were studied on low BIS, 54160 patients were studied on triple low state. The synthesis of studies pointed to a statistically significant positive association between prolonged exposure to low BIS and increased intermediate mortality (relative risk [RR], 1.10; 95% confidence interval [CI], 1.05 to 1.15, per hour). On the contrary, significant association was noted neither between triple low state and higher 30-day mortality risk (RR, 1.08; 95% CI, 1.00 to 1.17, per 15 min), nor between low BIS duration and postoperative wound infection or major complications (RR: 1.28; 95% CI, 0.69 to 2.41, and RR: 1.72; 95% CI, 0.43 to 6.87, respectively). Conclusions: Cumulative duration of low BIS was associated with an increased risk of mortality. Given the inherent limitations of the included studies, future cohort studies adjusting for a variety of meaningful confounders and well-designed large scale RCTs are waited before sound conclusions are drawn.

Keywords: Anesthetic depth, bispectral index, triple-low state, mortality, major complications, postoperative outcome, general anesthesia

Introduction

The use of BIS technology for brain monitoring was first described in 1994 [1], and had been introduced as a device measuring the anesthetic depth by Aspect Medical Systems (Natick, MA, USA) [2]. The BIS monitor was then recognized to be able to predict the absence of consciousness undergoing general anesthesia [3, 4]. Furthermore, anesthesia guided by BIS monitor within 40-60 were proved to reduce the incidence of intraoperative awareness and improve postoperative recovery in surgical patients with high risk of awareness [5]. Currently, the BIS index value has been established as the most common measure for the depth of anesthesia.

Although it's generally accepted that the BIS values of patients undergoing general anesthesia should vary from 30 to 60, the optimal anesthetic depth is still controversial in clinical work. Recent researches indicated there was correlation between anesthetic depth and prognosis. It has been reported that relatively deep anesthesia reflected by low BIS values or burst suppression might lead to an increased postoperative delirium incidence [6, 7]. A recent meta-analysis by Siddiqi N et al. suggested that using the Bispectral Index for lighter sedation might reduce the incidence of postoperative delirium [8].

Reports on the association between deep hypnotic status and postoperative mortality have emerged since 2005 [9], and most positive findings indicated that cumulative time of low bispectral index or triple low state were related to poor short-term and long-term outcomes after surgery. This scientific evidence,

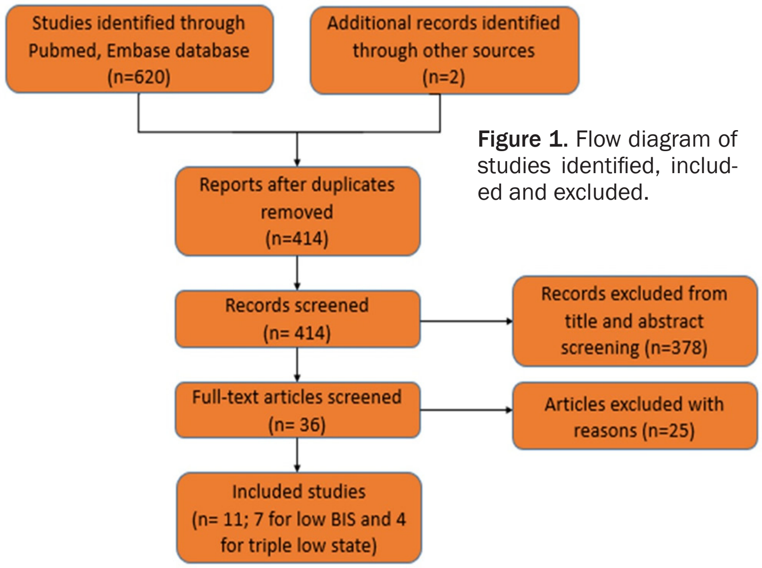

Figure 1. Flow diagram of studies identified, included and excluded.

however, was still weak and controversial, for most of them were observational studies, and few randomized trials of BIS-targeted anesthesia have been reported. Even though several prospective cohort studies have examined prolonged duration of low BIS or triple low state was associated with higher postoperative mortality, some have yielded conflicting results, showing a weak or null association.

The aim of this study is to systematically review and meta-analyze the published studies on the association between low bispectral index or triple low state and the risk of postoperative mortality and morbidities.

Methods

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis [10] and Meta-analysis of Observational Studies in Epidemiology recommendations [11], a prospective protocol of objectives, literature-search strategies, inclusion and exclusion criteria, outcome measurements, and methods of statistical analysis was agreed by all authors [12].

Literature-search strategy

A literature search was performed in December 2016 with no restrictions to language. We combined various synonyms for low bispectral index and major postoperative outcomes to find published manuscripts from PubMed and Embase. The following terms and their combinations were searched in [Title/Abstract]: anesthetic depth/bispectral index, death/mortality. We also reviewed articles by The Related Article Function to supplement the search, and all reference lists of the selected studies, review articles, and conference abstracts were screened for additional articles potentially fulfilling the search criteria. When the same population was included in multiple reports, the most recent or complete report was used. We did not contact authors for original information.

Eligibility criteria

The inclusion criteria of this meta-analysis were: (i) cohort studies or RCTs; (ii) comparing different durations of low BIS or triple low state undergoing general anesthesia, (iii) at least relative to one of the following endpoints: 30-day/in-hospital mortality, intermediate mortality, (iv) the RR and the corresponding 95% CI for longer duration of low BIS or triple low state on mortality or major morbidities. The exclusion criteria were: review articles, case reports, study protocol descriptions, editorials, and letters to the editor, in *vitro* and animal studies.

Data extraction and principle endpoints

Data from each included study were extracted independently, using a standardized data-extraction by two of the authors (Zhao and Shan). Two authors also independently assessed the validity of the studies and any discrepancies was resolved, when necessary, by a third reviewer (Xu).

Low bispectral index was generally defined as: undergoing general anesthesia with the cumulative duration of bispectral index < 45 in observational studies [9, 13-16] or targeted by low BIS value at 35 in randomized controlled trails [17, 18]. Triple low state was defined by mean arterial pressure (MAP) less than 65-75

Table 1. Characteristics of included studies

Author	Publication time	Design	Age	Type of Surgery	Cohort size	Definition	Outcome Measures	Matching	Follow-up (n)*	Quality score	Mortality
Studies on low BIS											
Monk *et al.* [9]	2005	RP	≥ 18 yr	NC	1064	BIS<45	Mortality	1, 3, 4, 5, 6, 7	1 y	★★★★★★	5.50%
Lindholm *et al.* [13]	2009	RP	≥ 16 yr	NC	4087	BIS<45	Mortality	1, 2, 3, 4, 5, 6, 7, 8	1 y/2 y	★★★★★★★	6.51%
Kertai *et al.* [14]	2010	RP	≥ 18 yr	CS	460	BIS<45	Mortality	1, 2, 3, 4, 5, 6, 7, 8	3 y	★★★★★★★	14.30%
Kertai *et al.* [15]	2011	RP	≥ 18 yr	NC	1473	BIS<45	Mortality	1, 2, 3, 4, 5, 6, 7, 8, 9	3.2 y	★★★★★★★	24.30%
Abdelmalak *et al.* [17]	2013	RCT	≥ 40 yr	NC	381	BIS=35	Mortality, major complications	1, 2, 3 ,4, 5, 6, 7, 8	1 y	RCT	11.81%
Short *et al.* [18]	2014	RCT	≥ 60 yr	NC	125	BIS=35	Mortality, major complications	1, 2, 3, 4, 6, 7, 9	1 y	RCT	10.40%
Lindholm *et al.* [16]	2014	RP	≥ 16 yr	NC	766	BIS<45	Mortality	1, 2, 4, 5, 6, 7, 8, 9	5 y	★★★★★★★	38%
Studies on triple low state											
Sessler *et al.* [19]			≥ 16 yr	NC	24210	BIS < 45, MAP < 75, MAC < 0.8	Mortality	1, 2, 4, 5, 6	30 d	★★★★★	0.80%
Kertai *et al.* [20]			≥ 18 yr	NC	16263	BIS < 45, MAP < 75, MAC < 0.7	Mortality	1, 2, 4, 5	30 d/2.6 y	★★★★★	0.80%/9.5%
Willingham *et al.* [21]			≥ 18 yr	ALL	13198	BIS < 45, MAP < 75, MAC < 0.8	Mortality	1, 2, 4, 5, 6, 9	30 d/90 d	★★★★★★	0.80%/1.9%
Xin-qi Cheng *et al.* [22]			≥ 18 yr	CS	489	BIS < 45, MAP < 75, Ce < 0.8	Mortality	2, 4, 5, 6, 7	30 d	★★★★★	3.27%

BIS=bispectral index; MAP = mean arterial pressure; MAC = minimum alveolar concentration; Ce = effect-site concentration, NC = non-cardiac surgery; CS = cardiac surgery; ALL = all surgery; RP = retrospective design, prospective data collection; RCT = randomized controlled trail; R = retrospective study; *mean or median. Matching: 1 = American Society of Anesthesiologists score; 2 = gender; 3 = intraoperative blood pressure; 4 = surgery time; 5 = age; 6 = body mass index; 7 = surgery type; 8 = smoke; 9 = malignant disease.

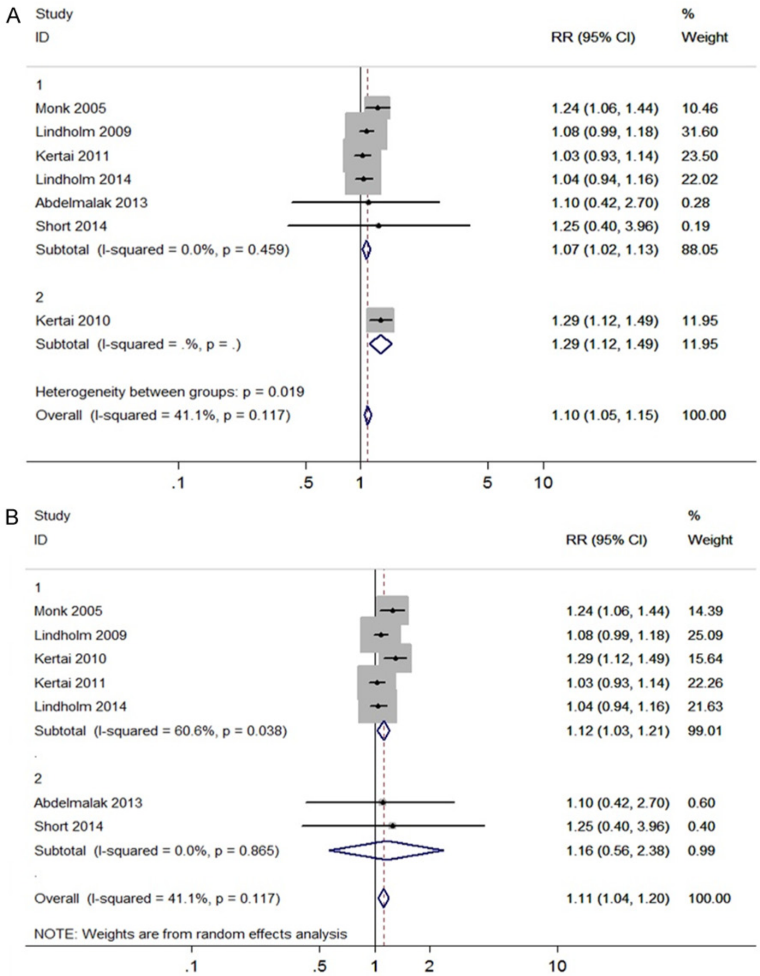

Figure 2. A. Forest plot presenting combined relative risk (RR) of intermediate mortality for cumulative $T_{BIS<45}$ by surgery types. B. Forest plot presenting combined relative risk (RR) of intermediate mortality for cumulative $T_{BIS<45}$ by research designs.

mmHg, BIS (bispectral index) less than 45, minimal alveolar concentration (MAC) less than 0.7-0.8 or low effect-site concentration (Ce) of propofol < 1.5 μg ml^{-1} [19-22].

The primary endpoints were the association between intermediate term (less than 5 years) mortality and low BIS duration as well as the association between 30 day mortality and triple low state. The secondary outcomes were postoperative major complications (pneumonia, stroke, myocardial infraction, heart failure, and pulmonary embolism) and wound infection.

Quality assessment

The quality of randomized studies was assessed according to the Cochrane risk of bias tool [23] (Supplementary Table 1). Criteria that were used for the methodological quality of observational studies were: patient selection, comparability of the study groups, and assessment of outcome (Supplementary Table 2), by the modified Newcastle-Ottawa scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). RCTs or observational studies reaching five or more scores denoted a high-quality study.

Statistical analysis

Meta-analysis were performed with Stata version 12.0 (Stata Corp, College Station, TX). Continuous and dichotomous variables were measured with weighted mean difference (WMD) and odds ratio (OR). Association was measured by risk ratios (RRs), odds ratios (ORs), or the hazard ratios (HRs) and their 95% confidence intervals (CIs) across studies. HR was directly considered as RR, OR were also considered as RR when mortality is rare in all populations or subgroups and the distinctions can be ignored [24]. Maximally adjusted effect estimates (RRs, ORs and HRs) were extracted wherever possible.

We used Q with significance set at $p < 0.1$, and the I^2 statistic to quantify the statistical heterogeneity of the studies included. In general, Random-effects model was intended to be used when the I^2 value > 50%, which indicates the presence of heterogeneity across trials; fixed-effects model were also performed for comparison [25].

Subgroup analysis of the association between low BIS and intermediate mortality were performed to assess the potential effect modification of variables on outcomes, according to different research methods and surgery

Table 2. Results of the meta-analyses examining the association between anesthetic depth and mortality

	Low BIS and intermediate-term mortality					Triple Low and 30-day mortality				
	n[a]	ES (95% CI)	P*	Heterogeneity		n[a]	ES (95% CI)	P*	Heterogeneity	
				I^2	P[b]*				I^2	P[b]*
General analysis										
Fix model	7	1.10 (1.05, 1.15)	0.000	41.1%	0.117	4	1.04 (1.03, 1.05)	0.000	95.9%	< 0.001
Random model	7	1.11 (1.04, 1.20)	0.004	41.1%	0.117	4	1.08 (1.00, 1.17)	0.063	95.9%	< 0.001
Subgroup analysis										
Surgery type										
Non-cardiac surgery	6	1.07 (1.02, 1.03)[f]	0.007	< 0.01%	0.459	3	1.29 (1.04, 1.61)[r]	0.023	95.0%	< 0.001
Cardiac surgery	1	1.29 (1.12, 1.49)[f]	0.000	NC	NC	1	1.02 (1.00, 1.03)[r]	0.029	NC	NC
Study design										
R	5	1.12 (1.03, 1.21)[r]	0.008	60.6%	0.038					
RCT	2	1.16 (0.56, 2.38)[r]	0.692	< 0.01%	0.865					
Sensitivity analysis	6	1.08 (1.03, 1.14)[f]	0.003	31.9%	0.197	3	1.29 (1.04, 1.61)[r]	0.023	95.0%	< 0.001

ES, effect estimate. CI, confidence interval. NC, not calculable. R = retrospective study, RCT = randomized controlled studies. [a]Number of studies. [b]P-value derived from Cochran Q statistic. [f]Effect estimates were derived from fixed-effects analyses. [r]Effect estimates were derived from random-effects analyses. *Statistically significant results are shown in bold.

types. In addition, sensitivity analysis were performed for excluding study with substantial heterogeneity.

Results

Result of literature search

The literature search identified 620 articles, of which 609 were excluded as unfulfilled the predefined inclusion criteria. Another study [26] that reported on relative risk of long-term survival by comparing $T_{BIS < 40}$ > 5 mins (time for BIS < 45) with other-BIS monitored was also excluded, for the rest 10 studies had reported on the relative risk of intermediate mortality for a one hour longer duration of BIS < 45. The study selection process is presented in **Figure 1**.

Characteristics of studies

The characteristics of the included studies were presented in **Table 1**. Among the included studies on association between $T_{BIS < 45}$ and intermediate mortality, there were 2 small sampled RCTs [17, 18] and 5 retrospective observational studies [9, 13-16]. The length of the follow-up period ranged from 1 to 5 y, with a median of 2.3 y. All observational cohort studies reported on the RRs of intermediate mortality for a one hour longer duration of BIS < 45. Data on association between triple-low state and 30-day mortality were available in four retrospective studies [19-22] with RRs of 30-day mortality for per 15 mins of triple-low state longer.

A wide range of potential confounders were adjusted for mortality. Covariates included combinations of: (i) demographic and biophysical characteristics (e.g. age, sex, and body mass index); (ii) baseline co-morbidity (e.g. American Society of Anesthesiologist, Cleveland Clinic Risk Index, and Charlson Comorbidity Index); (iii) surgery-related variables (e.g. surgery duration, surgery type, and preexisting malignance); (iv) dynamic variables (e.g., mean blood pressure); and (v) history of smoking (**Table 1**).

Quality of included studies

The quality of included studies ranged from moderate to high according to the Newcastle-Ottawa score. True randomization was used in only two RCTs. All the follow-up time was mentioned and ranged between 1 and 5 years. Matching criteria between the groups were variable. Nearly all studies adjusted for a wide range of potential confounders for mortality, including age, BMI (body mass index), gender, smoking, baseline co-morbidity, types and duration of surgery, while few matched for preexisting malignance, one of the major cause of death.

Primary outcomes

Association of Low BIS with intermediate mortality: 7 studies reported on the correlations between cumulative time of BIS less than 45 and intermediate mortality (1-5 years). Three

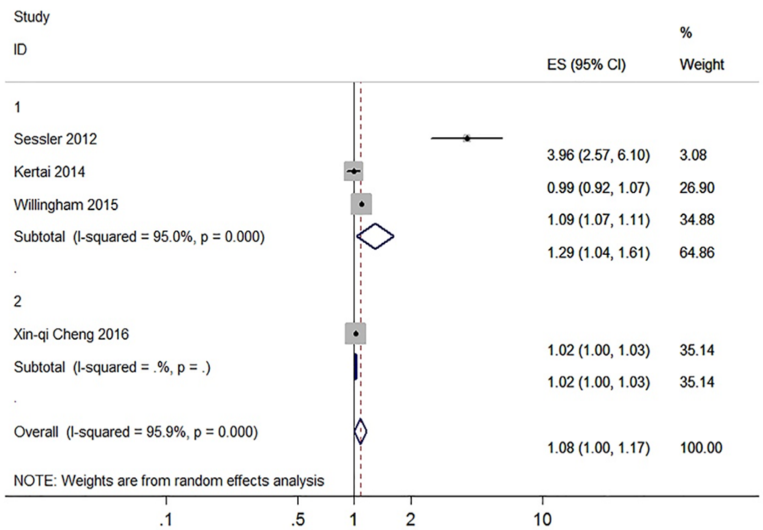

Figure 3. Forest plot presenting combined relative risk (RR) of 30-day mortality for cumulative times of triple low state [low bispectral index (BIS), low mean arterial pressure (MAP), low minimum alveolar concentration (MAC) or target effect-site concentration (Ce)] according by surgery types.

studies showed increased risk of intermediate mortality with longer duration of low BIS, while the other 2 studies found it not statistically significant. Pooling the data from 7 studies [9, 13-18], a fixed-effects model was applied for the synthesis, the combined multivariable-adjusted RR of intermediate mortality for one hour longer duration of low BIS was 1.10 (95% CI, 1.05 to 1.15, $p < 0.001$) (**Figure 2**). The heterogeneity was not statistically significant (I^2: 41.1%, $p = 0.117$). Based on a random-effects model, the corresponding estimate yielded similar result (RR, 1.14; 95% CI, 1.05 to 1.23, $p = 0.004$), which confirmed our finding that increasing cumulative time of low BIS was associated with a higher risk of intermediate mortality.

In further exploration of heterogeneity, subgroup analysis was performed according by surgery types and research methods (**Table 2**). In the subgroup analysis regarding surgery types, heterogeneity became minimal after excluding the only research on cardiac surgery [14] ($I^2 < 0.01\%$, $p = 0.459$). Non-cardiac surgery might be associated with a lower risk of intermediate mortality compared with cardiac surgery [RR, 1.07; 95% CI, 1.02 to 1.13, $p = 0.007$ vs. 1.29; 95% CI, 1.12 to 1.49, $p < 0.001$, respectively] (**Figure 2A**). When studies were further divided into retrospective researches and RCTs, the analysis showed different results between subgroups. Subgroup analysis of retrospective studies with low BIS defined by BIS < 45 revealed result similar to the general analysis (RR, 1.12; 95% CI, 1.03 to 1.21, $p = 0.008$) with higher heterogeneity (I^2: 60.6%, $p = 0.038$). Synthesis of two RCT comparing light BIS group with deep BIS group also indicating that longer duration time of low BIS may be associated with increasing risk of intermediate mortality but was not statistically significant and alternative weighting models had little impact on the results (RR, 1.16; 95% CI, 0.56 to 2.38; $I^2 < 0.01\%$, $p = 0.865$) (**Figure 2B**).

Triple low state and 30-day mortality: 4 studies [19-21, 27] reported on the 30-day mortality of triple low state. Three studies [19-21] defined Triple low state by MAP less than 65-75 mmHg, BIS less than 45, MAC less than 0.7-0.8. One study [27] defined triple low state by MAP less than 65-75 mmHg, BIS less than 45, Propofol Ce < 1.5 undergoing cardiac surgery. There was substantial heterogeneity across the 4 studies (I^2: 95.9%, $p < 0.001$) not explained by available study-level characteristics such as surgery types or definitions of triple low state. Combined RR under random-effects model suggested no significant association between triple low state and 30-day mortality (RR, 1.08; 95% CI, 1.00 to 1.17, $p = 0.063$). However, both subgroup analyses according to surgery types showed positive evidence of triple-low state associated with higher risk of 30-day mortality (RR, 1.02; 95% CI, 1.00 to 1.03, $p = 0.029$ with cardiac surgery vs. RR, 1.29; 95% CI, 1.04 to 1.61, $p = 0.023$ with non-cardiac surgery) (**Figure 3**).

Secondary outcomes

Postoperative complications: Two RCTs [17, 18] with 506 included patients, reported on major complications (pneumonia, stroke, myocardial infraction, heart failure, and pulmonary embolism), with 21 events in the low BIS group and 17 events in the high BIS group (8.5% vs 6.6%).

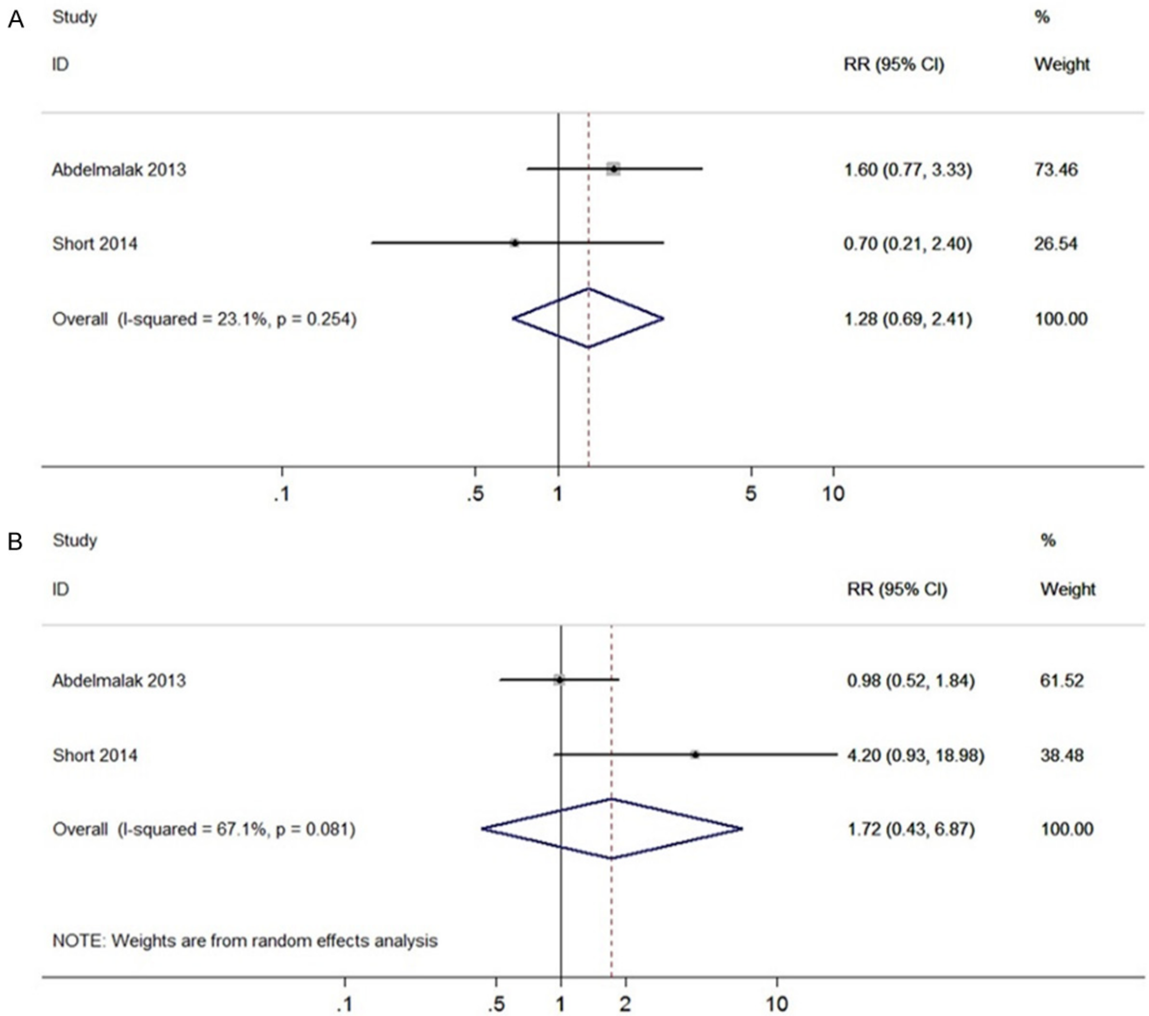

Figure 4. A. Forest plot presenting combined relative risk (RR) of major complications for cumulative $T_{BIS<45}$. B. Forest plot presenting combined relative risk (RR) of wound infection for cumulative $T_{BIS<45}$.

No evidence of statistical heterogeneity was found from the I^2 statistical (I^2: 24%, p = 0.25), the result from fixed-effect analysis showed a higher risk of major complications for patients receiving low BIS but not significantly different (RR, 1.28; 95% CI, 0.69 to 2.41, p = 0.437) (**Figure 4A**). These two RCTs also reported on wound infection. Wound infection was higher in deep BIS group comparing to light BIS group, but the difference was not statistically significant (10.1% and 7.8%; RR, 1.72; 95% CI, 0.43 to 6.87, p = 0.446) (**Figure 4B**).

Sensitivity analysis and publication bias: Sensitivity analysis of primary outcomes were presented in **Table 2**. Both syntheses yielded similar results. The heterogeneities in sensitivity analysis between two RCTs [17, 18] and 4 retrospective studies [9, 13-16] on "low BIS" that scored seven or more stars on the modified Newcastle-Ottawa scale were generally decreased significantly after elimination, whereas between-study heterogeneities on the relation between cumulative time of triple-low state and 30 day mortality still remained substantial after dropping data from largest or smallest sample [19, 27].

The publication bias across studies separately by low BIS and triple low state was intended to be assessed using Egger's formal statistical test [28]. However, the number of included studies was small (7 for low BIS and 4 for triple low state, < 10 respectively), which resulted in low power. Therefore, no testing for publication bias was carried out.

Discussion

This meta-analysis of 2 RCTs and 9 retrospective studies demonstrating the association between "low BIS" and mortality suggested that longer duration of low BIS might be associated with higher intermediate mortality risk, but no sufficient evidence showed the prolonged duration of triple-low state increased 30-day mortality or anesthetic depth was related to risk of wound infection and major complications.

With the increasing application of BIS-guided anesthesia, the safety of specific anesthetic depth is always of paramount importance. The pooled data of mortality after surgery indicated that relatively deep anesthesia might associate with an increased risk of intermediate mortality. The subgroup analyses were conducted on surgery type and generated similar result. In addition, we found that duration of low BIS was associated with higher intermediate mortality risk in cardiac surgery than non-cardiac surgery, but whether it contributed to mortality when combined with other perioperative risk factors such as serum troponin T is uncertain.

Subgroup analysis of observational studies also indicated the association between longer duration of BIS < 45 and increased intermediate mortality. However, the pooled data of two RCTs [17, 18] showed no significant difference in intermediate mortality risk between groups of anesthesia depth. The variation of these results might be due to the small amount of RCTs. Moreover, in a study of Abdelmalak et al., no significant separation was shown in mean BIS value between groups [17]. These characteristics might lead to an error of false negative. This findings, however, indicated that reducing cumulative time of BIS < 45 can result in a better long-term outcome.

It was first reported by Sessler et al. that the potential risk of triple low state was to increase 30 day mortality [19]. However, the viewpoint was overthrown by Kertai et al. after they accounted for other co-variables [20]. Our finding indicated that triple low state was not associated with higher 30-day mortality based on the analysis of current researches. Given all included studies were observational studies with high risks of residual confounding and colinearity, more relevant prospective clinical trials are in great need before the definitive conclusion can be made. Sessler et al. [19] also demonstrated that the increased duration of both low BIS and low MAC was correlated with poorer 30 day mortality. Many researchers wondered if triple low state associated with anesthetic sensitivity was an independent risk predictor or just a marker correlated with other perioperative risk factors indicating poorer postoperative mortality.

In our meta-analysis, no correlation between wound infections, major complications and anesthetic depth was found. A recent research by Lindholm et al. [29] reported that cumulative time of low BIS had no impact on the development of new malignant disease at any thresholds (i.e., < 30, < 40, < 45 and < 50, respectively). A study by Leslie et al. [26] demonstrated presence of BIS 40 for 5 min increased the incidence of myocardial infarction and stroke in patients during their long-term follow-up. Given few researches reported on postoperative outcomes and major complications were rare events, whether these potential impacts can be demonstrated in future well-designed RCTs is unknown.

Related to the limitations of this review, our research mainly included retrospective studies, along with two RCTs with small sample sizes. The number of RCTs was rare that prevented |us from reaching more definitive conclusions based on a meta-analysis of RCTs only. The heterogeneity across overall studies was substantial but decreased after subgroup analyses. We also conducted sensitivity analysis and yielded similar results. Future researches can evaluate RCTs based on clinical outcomes of different BIS target level separately when enough literature is available.

In addition, the follow-up period was generally short and varied from 1 to 5 years, so further studies about long-term outcomes under different durations of "low BIS" are in needed. That's also a limitation should be taken account into our meta-analysis.

Moreover, the heterogeneity between studies on "triple low" was generally significant even when sensitivity analysis were performed. Different surgical types, patient ages, physical status, anesthesiologists, preexisting malignant diseases in our included studies might contribute to the heterogeneity, of which the effect can only be reduced by using the random-effects model but not be avoided. Considering the lack of high-quality randomized controlled trials and the heterogeneity in our results, further work is necessary for definitive recommendation for optimal sedation target level during to be made general anesthesia.

Nevertheless, this meta-analysis was conducted necessarily with available data as possible, and provided further epidemiological support for the potential detrimental effect of low-BIS or triple-low state on the risk of short-term and long-term mortality. An update on anesthetic depth and long-term survival by Leslie et al. [30] has reviewed the relevant studies by 2015, but they just described the available evidence from relative studies and did not make conclusion on the relationship between anesthetic depth and survival. Moreover, we have taken other operative outcomes such as major complication into consideration. Therefore, we provide the most up-to-date information in this area.

In summing up the results of published studies, prolonged exposure to low BIS was associated with a higher intermediate mortality risk. Extended duration of triple-low state increased 30 day mortality. Different durations of low BIS or triple low state appear to have little impact on major complications, wound infection, and length of stay in hospital so far. Concerning that our available data are based on observational studies and hence prevent us from reaching certain conclusions, we are looking forward to large scale, well designed RCTs with adequate follow-up time to confirm and update the findings of this analysis in the future.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Risk of bias in the prospective randomized controlled studies

Study	Adequate random sequence generation	Allocation concealment	Blinding of participants and personnel	Adequate assessment of each outcome	Selective outcome reporting avoided	Handling of missing data
Short *et al.* [17]	Yes	Yes	Double-blinded	Yes	Yes	ITT
Abedelmalak *et al.* [18]	Yes	Yes	Double-blinded	Yes	Yes	ITT

ACA = *available case analysis.*

Supplementary Table 2. Risk of bias in retrospective studies using modified Newcastle-Ottawa scale

Study	Selection			Comparability		Outcome		Quality score
	Assignment for treatment†	Representative treatment group	Representative reference group	Comparable for 1, 2, 3, 4*	Comparable for 5, 6, 7, 8, 9*	Assessme-nt of outcome	Adequate follow-up	
Monk *et al.* 2005 [9]	No	Yes	Yes	1, 3, 4	5, 6, 7	Yes	Unclear	★★★★★★
Lindholm *et al.* 2009 [13]	No	Yes	Yes	1, 2, 3, 4	5, 6, 7, 8	Yes	Unclear	★★★★★★★
Kertai *et al.* 2010 [14]	No	Yes	Yes	1, 2, 3, 4	5, 6, 7, 8	Yes	Unclear	★★★★★★★
Kertai *et al.* 2011 [15]	No	Yes	Yes	1, 2, 3, 4	5, 6, 7, 8, 9	Yes	Unclear	★★★★★★★
Sessler *et al.* 2012 [19]	No	Yes	Yes	1, 2	4, 5, 6	Yes	Unclear	★★★★★
Kertai *et al.* 2014 [20]	No	Yes	Yes	1, 2	4, 5	Yes	Unclear	★★★★★
Lindholm *et al.* 2014 [16]	No	Yes	Yes	1, 2, 4	5, 6, 8, 9	Yes	Yes	★★★★★★★
Willingham *et al.* 2015 [21]	No	Yes	Yes	1, 4	5, 6, 9	Yes	Unclear	★★★★★
Xin-qi Cheng *et al.* 2016 [22]	No	Yes	Yes	2, 4	5, 6, 7	Yes	Unclear	★★★★★

NA = *data not available*. Comparability variables: 1 = *American Society of Anesthesiologists score* ; 2 = *gender* ; 3 = *intraoperative blood pressure* ; 4 = *surgery time*; 5 = *age* ; 6 = *body mass index*; 7 = *surgery type*; 8 = *smoke*; 9 = *malignance*. †*Details of criteria for adequate random assignment of patients to treatments were provided*. **If all characteristics were comparable, two stars; if two or three characteristics were comparable, one star; otherwise, no star.*