Cumulative Duration of "Triple Low" State of Low Blood Pressure, Low Bispectral Index, and Low Minimum Alveolar Concentration of Volatile Anesthesia Is Not Associated with Increased Mortality

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ABSTRACT

Background: Mortality after noncardiac surgery has been associated with the "triple low state," a combination of low mean arterial blood pressure (<75 mmHg), low bispectral index (<45), and low minimum alveolar concentration of volatile anesthesia (<0.70). The authors set out to determine whether duration of a triple low state and aggregate risk associated with individual diagnostic and procedure codes are independently associated with perioperative and intermediate-term mortality.

Methods: The authors studied 16,263 patients (53 ± 16 yr) who underwent noncardiac surgery at Duke University Medical Center between January 2006 and December 2009. Multivariable logistic and Cox regression analyses were used to determine whether perioperative factors were independently associated with perioperative and intermediate-term all-cause mortality.

Results: The 30-day mortality rate was 0.8%. There were statistically significant associations between 30-day mortality and various perioperative risk factors including age, American Society of Anesthesiologists Physical Status, emergency surgery, higher Cleveland Clinic Risk Index score, and year of surgery. Cumulative duration of triple low state was not associated with 30-day mortality (multivariable odds ratio, 0.99; 95% CI, 0.92 to 1.07). The clinical risk factors for 30-day mortality remained predictors of intermediate-term mortality, whereas cumulative duration of triple low was not associated with intermediate-term mortality (multivariable hazard ratio, 0.98; 95% CI, 0.97 to 1.01). The multivariable logistic regression (c-index = 0.932) and Cox regression (c-index = 0.860) models showed excellent discriminative abilities.

Conclusion: The authors found no association between cumulative duration of triple low state and perioperative or intermediate-term mortality in noncardiac surgery patients. **(ANESTHESIOLOGY 2014; 121:18-28)**

PATIENTS undergoing noncardiac surgery can be at substantial risk for perioperative and intermediate-term mortality.[1] Patient- and surgery-related factors have been linked to perioperative and late survival. However, the association between anesthesia-related factors and perioperative and intermediate-term survival after noncardiac surgery remains unclear.[2,3] Recent studies have found that when a processed electroencephalographic index is used during general anesthesia, patients generally receive lower doses of hypnotic drugs emerge faster from anesthesia with less postoperative nausea and vomiting.[4,5] It has also been proposed that intraoperative hypotension and organ toxicity may be avoided if lower doses of anesthetics are administered, which would potentially translate into a reduction in serious morbidity or mortality.[3,6]

The bispectral index (BIS) monitor (BIS® monitor; Covidien, Boulder, CO) is one of several candidate depth-of-anesthesia monitors that are based on processed electroencephalography. Studies have shown that cumulative duration of BIS below certain arbitrary thresholds is associated with an increased morbidity and intermediate-term postoperative mortality.[7–10] These findings may suggest a mortality–hypnosis association, which could be reflective of a relative overdose of anesthetic agents in patients who have anesthetic hypersensitivity.[3] In support of this mortality–hypnosis association, it was recently observed that the occurrence of intraoperative hypotension, expressed as low mean arterial

What We Already Know about This Topic

- The so-called triple low state of low mean arterial pressure, low bispectral index, and low minimum alveolar concentration of anesthesia has been associated with perioperative mortality
- Whether duration of time in the triple low state imparts risk of mortality is not known

What This Article Tells Us That Is New

- In a review of over 16,000 patients, there was no association between duration of triple low state intraoperatively and either perioperative or intermediate-term mortality

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pressure (MAP) during low minimum alveolar concentration (MAC) fraction of volatile anesthetics, combined with low BIS was a significant predictor of perioperative mortality, indicating anesthetic hypersensitivity.[11]

Thus, the results of this study indicate that the combination of low MAP, low MAC, and low BIS—a triple low state—could be a predictor of poor outcome. This association is especially concerning because the threshold and average low values for each state are well within the range that is routinely tolerated.[11] However, a recent mortality substudy of the B-Unaware Trial[12] found no evidence that cumulative BIS values below a threshold of 45, or cumulative inhalational anesthetic dose, or low intraoperative MAP was associated with increased risk for intermediate-term mortality. Therefore, using comprehensive, multivariable models of a large dataset of patients who underwent noncardiac surgery, we sought to determine whether a combination of cumulative duration of low MAP, BIS, and MAC (a triple low state), comorbidities, and type of surgery are independently associated with increased perioperative and intermediate-term mortality.

Materials and Methods

Study Population

A dataset of patients who underwent noncardiac surgery at Duke University Medical Center (Durham, North Carolina) between January 1, 2006 and December 31, 2009 was constructed from the Duke Perioperative Electronic Database (Innovian® Anesthesia; Draeger Medical Inc., Telford, PA). The Institutional Review Board for Clinical Investigations at Duke University Medical Center approved the study and waived the requirement for informed consent.

On the basis of Duke Perioperative Electronic Database, we identified a set of 72,236 records of cases with intraoperative BIS monitoring. We included only the first surgery for any patient, excluding 15,882 cases in which the same patient had additional surgeries. We further excluded 12,592 cases with no record of intraoperative monitoring of MAP and end-tidal MAC; 21,727 cases that met any of the following criteria: less than 18 yr old, cardiac surgical procedure, primary anesthetic was not a single volatile agent, or intraoperative BIS monitoring was not available for at least 55% of the case time; 4,679 that lacked essential clinical information needed for the estimation of the Cleveland Clinic Risk Index score[13]; and 1,093 in which duration of MAP, BIS, and end-tidal MAC monitoring was less than 10 min, or all three parameters were simultaneously monitored for less than 75% of the case time. Consequently, 16,263 cases were included in the current analyses.

At Duke University Medical Center, general anesthesia for adult noncardiac surgery is usually induced with a small amount of propofol (1 to 1.5 mg/kg) and fentanyl (100 to 150 μg). One of the potent volatile anesthetic agents—desflurane, sevoflurane, or isoflurane—in an oxygen–nitrous oxide or oxygen–air mixture, with an inspiratory oxygen concentration of at least 50%, is used to maintain general anesthesia. In addition, as part of routine anesthesia care, patients undergo tracheal intubation; the lungs are ventilated volume or pressure controlled, with a positive end-expiratory pressure of 5 cm H_2O; and end-tidal anesthetic gas concentration is monitored throughout the case. After adult noncardiac surgery, patients are routinely admitted to the postoperative anesthesia recovery unit or intensive care unit as indicated.

Data Extraction and Analysis

We extracted data on BIS, MAP, and end-tidal volatile anesthetic concentration. Data were also extracted on age at surgery, sex, race, American Society of Anesthesiologists (ASA) Physical Status Classification System scores, duration of operating room time, and International Classification of Diseases and Procedures, version 9, billing codes,* which are determinants of the Cleveland Clinic Risk Stratification Index.[13] The Cleveland Clinic Risk Stratification Index is a method of predicting 30-day and late mortality in patients undergoing noncardiac surgery. The Risk Stratification Index value† was calculated for each patient according to published methodology validated with published example standards.

Bispectral index values and end-tidal anesthesia gas concentration values were recorded at 1-min intervals. As part of routine intraoperative care, a BIS Quatro Sensor® (Covidien) was applied to the forehead of each patient. Age-adjusted MAC values were calculated according to the charts published by Nickalls and Mapleson,[14] which include adjustment for nitrous oxide. In the final sample of 16,263 patients, all but 21 patients had some nonzero expired concentration of nitrous oxide recorded.

Mean arterial pressure values were also recorded at 1-min intervals when an arterial catheter was used or at 2- to 5-min intervals when blood pressure was measured oscillometrically. Similar to the definition used by Sessler *et al.*,[11] MAP values were considered to be artifactual and were excluded when the recorded value was less than 30 mmHg or greater than 250 mmHg. The BIS, the end-tidal anesthesia gas concentration, and MAP values assigned to a given minute, if missing, were interpolated linearly between the preceding and following values. No case was included with more than 15 consecutive minutes missing.

Classification of Outcomes

The outcomes chosen for the current study were all-cause mortality occurring within 30 days after surgery and intermediate-term all-cause mortality for patients who survived

* International Classification of Diseases and Procedures version 9. Available at: http://www.cdc.gov/nchs/icd/icd9cm.htm. Accessed August 12, 2013.

† Cleveland Clinic Risk Stratification Index. Available at: http://my.clevelandclinic.org/anesthesiology/outcomes-research/risk-stratification-index.aspx. Accessed August 12, 2013.

beyond 30 days. Survival information was obtained from return hospital encounters, the National Cancer Registry,‡ the National Death Index,§ and the Social Security Death Index,‖ all accessed to verify vital status as of March 22, 2011.

Statistical Analysis

Continuous variables are presented as means (±SD) or medians (interquartile range), and categorical variables are presented as group frequencies and percentages. Descriptive comparisons were made by using Kruskal–Wallis test, or chi-square test, as appropriate.

A recent study reported that patients with the triple low state—a combination of MAP less than 75 mmHg, BIS values less than 45, and MAC less than 0.70 of volatile anesthesia—had an increased risk for 30-day all-cause mortality.[11] Therefore, in the current study, this definition was specified *a priori* and calculated for each patient as cumulative, but not necessarily consecutive, minutes in a triple low state to study the association between cumulative duration of triple low state and 30-day and intermediate-term all-cause mortality.

Univariable and multivariable logistic regression models were applied to evaluate the association between all-cause mortality at 30 days and cumulative duration of triple low state and baseline and clinical characteristics. In addition to the Risk Stratification Index, age, sex, race, ASA Physical Status Classification System, emergency status, duration of surgery, and year of surgery were prespecified for inclusion as covariates in the multivariable models. Logistic regression diagnostic tests and plots for goodness-of-fit and influence were inspected.

To study the association between the cumulative duration of triple low state and intermediate-term mortality, we first applied the Kaplan–Meier method to evaluate the prognostic importance of the cumulative duration of triple low state with respect to survival. Differences among survival curves for quartiles of cumulative duration of triple low state were compared using the log-rank test. Subsequently, univariable and multivariable Cox proportional hazard regression models were applied to assess the association of cumulative duration of triple low state and intermediate-term all-cause mortality, adjusting for the same set of baseline and clinical variables used in the 30-day analysis.

Furthermore, we quantified the discriminatory power of the final multivariable models for logistic and Cox regression analyses by the c-index, which corresponds to the area under the receiver operating characteristics curve, ranging from 0.5 (performance at chance) to 1.0 (optimal performance).[15] To further evaluate the performance of the final multivariable models for logistic and Cox regression analyses, the bootstrap method was used to assess the degree of overoptimism. Overoptimism occurs when statistical models fitted on one set of data inaccurately predict the outcomes on subsequent datasets.[12]

A bootstrapping procedure is one method that can be used to try to correct for this "overoptimism."[16] First, the covariates in the final regression models were fitted for each bootstrap sample. The original dataset was then fitted using the coefficients of the bootstrap sample model, and thus, a c-index statistic was generated from this fit on the original dataset. The degree of overoptimism was then estimated as the difference in the c-index statistic from the bootstrap sample and that from the bootstrap model fit on the original sample. These differences were averaged across 1,000 bootstrapped samples, and the difference in the original model c-index statistic and the average optimism provided the model c-index corrected for overoptimism.

The model fit of the final multivariable logistic regression model was further assessed using the Hosmer–Lemeshow goodness-of-fit test,[17] and for the Cox regression by comparing the average model prediction to the observed mortality rate across deciles of predicted risk.[18,19] Odds ratios or hazard ratios and the corresponding 95% confidence limits are reported. The analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC).

Results

Patient Characteristics

The mean age (±SD) of the 16,263 patients was 53 ± 16 yr, and 7,595 patients (46.7%) were men. Seventy percent of the study population were whites; 6.6% of the cohort were classified as category P1 using the ASA Physical Status Classification System; 46%, P2; 43.4%, P3; 3.7%, P4; and 0.03%, P5. Ten percent of the patients underwent emergency surgery.

The median Cleveland Clinic Risk Index score was −0.42 (interquartile range, −1.37 to 0.08); the median cumulative duration of MAP of less than 75 mmHg was 34 min (interquartile range, 14 to 70); the median cumulative duration of BIS value of less than 45 was 70 min (interquartile range, 31 to 122); the median cumulative duration of MAC value of less than 0.70 was 65 min (interquartile range, 27 to 127); and the median cumulative duration of triple low state was 3 min (interquartile range, 0 to 13).

The most common International Classification of Diseases and Procedures, version 9, diagnosis category was cancer (44.2% of patients); 20.3% had genitourinary diseases, and 17.5% had diseases in the digestive system. The most frequently performed procedures in the International Classification of Diseases and Procedures, version 9, procedure category involved the digestive system (23.2%), the musculoskeletal system (20.4%), and the female genital organs (15%). Demographic and clinical characteristics of the patients stratified according to the quartiles of the cumulative duration of triple low state are presented in table 1.

‡ National Cancer Registry. Available at: http://www.cdc.gov/cancer/npcr/. Accessed March 22, 2011.

§ National Death Index. Available at: www.cdc.gov/nchs/ndi.htm. Accessed March 22, 2011.

‖ Social Security Death Index. Available at: http://www.ntis.gov/products/ssa-dmf.aspx. Accessed March 22, 2011.

Table 1. Baseline Clinical Characteristics (n = 16,263)

Characteristics	Cumulative Duration of Triple Low								P Value*
	None (n = 6,240; 38.4%)		1 to 5 min (n = 3,513; 21.6%)		6 to 17 min (n = 3,232; 19.9%)		>18 min (n = 3,278; 20.1%)		
Age, yr	6,240	49 ± 16	3,513	54 ± 16	3,232	56 ± 15	3,278	58 ± 14	<0.0001
Male sex	6,240	2,911 (46.7)	3,513	1,611 (45.9)	3,232	1,491 (46.1)	3,278	1,582 (48.3)	0.20
Race	6,237		3,513		3,230		3,275		<0.0001
White		3,917 (62.8)		2,485 (70.7)		2,375 (73.5)		2,595 (79.2)	
Black		1,878 (30.1)		847 (24.1)		670 (20.7)		514 (15.7)	
Asian		75 (1.2)		35 (1.0)		43 (1.3)		28 (0.9)	
Native American		79 (1.3)		30 (0.9)		33 (1)		35 (1.1)	
All Other		288 (4.6)		116 (3.3)		109 (3.4)		103 (3.1)	
ASA category	6,031		3,390		3,122		3,165		<0.0001
P1		515 (8.5)		241 (7.1)		175 (5.6)		120 (3.8)	
P2		3,121 (51.7)		1,553 (45.8)		1,378 (44.1)		1,177 (37.2)	
P3		2,254 (37.4)		1,491 (44.0)		1,434 (45.9)		1,651 (52.2)	
P4		141 (2.3)		103 (3.0)		135 (4.3)		213 (6.7)	
P5		0		2 (0.1)		0		4 (0.1)	
Emergency surgery	6,031	616 (10.2)	3,390	292 (8.6)	3,122	309 (9.9)	3,165	370 (11.7)	0.0006
Cleveland Clinic Risk Index	6,240	−0.48 [−1.35; −0.10]	3,513	−0.47 [−1.44; 0.04]	3,232	−0.47 [−1.41; 0.14]	3,278	−0.26 [−1.34; 0.64]	<0.0001
Surgery date, mm/dd/yy median (min, max)		2/8/08 (1/9/06, 12/31/09)		5/7/08 (1/8/06, 12/30/09)		5/22/08 (3/21/06, 12/31/09)		5/30/08 (1/13/06, 12/31/09)	<0.0001
Minutes MAP <75 mmHg	6,240	17 [3; 44]	3,513	28 [13; 56]	3,232	34 [20; 62]	3,278	78 [50; 124]	<0.0001
Minutes BIS <45	6,240	49 [16; 96]	3,513	56 [23; 103]	3,232	75 [39; 123]	3,278	117 [73; 177]	<0.0001
Minutes MAC <0.70	6,240	30 [13; 70]	3,513	59 [28; 110]	3,232	84 [46; 136]	3,278	142 [92; 214]	<0.0001
									P Value†
ICD-9 diagnosis category†	9,454		5,367		4,991		5,290		
Infectious and parasitic		34 (0.4)		26 (0.5)		28 (0.6)		46 (0.9)	
Neoplasm		2,570 (27.2)		1,625 (30.3)		1,504 (30.1)		1,497 (28.3)	
Endocrine, nutritional, metabolic, and immunity disorders		253 (2.7)		173 (3.2)		183 (3.7)		262 (5.0)	
Blood and blood-forming organs		50 (0.5)		38 (0.7)		33 (0.7)		53 (1.0)	
Mental		12 (0.1)		11 (0.2)		12 (0.2)		18 (0.3)	
Nervous systems and sense organs		100 (1.1)		70 (1.3)		49 (1.0)		83 (1.6)	
Circulatory system		259 (2.7)		161 (3.0)		191 (3.8)		322 (6.1)	
Respiratory system		128 (1.4)		112 (2.1)		119 (2.4)		143 (2.7)	
Digestive system		1,439 (15.2)		754 (14.0)		656 (13.1)		475 (9.0)	
Genitourinary system		1,344 (14.2)		751 (14.0)		642 (12.9)		564 (10.7)	
Pregnancy, childbirth, puerperium		167 (1.8)		77 (1.4)		48 (1.0)		17 (0.3)	

(*Continued*)

Table 1. (*Continued*)

Characteristics	Cumulative Duration of Triple Low				
	None (n = 6,240; 38.4%)	1 to 5 min (n = 3,513; 21.6%)	6 to 17 min (n = 3,232; 19.9%)	>18 min (n = 3,278; 20.1%)	*P* Value*
Skin and subcutaneous tissue	93 (1.0)	39 (0.7)	33 (0.7)	32 (0.6)	
Musculoskeletal system	1,030 (10.9)	542 (10.1)	573 (11.5)	717 (13.6)	
Congenital anomalies	92 (1.0)	45 (0.8)	40 (0.8)	54 (1.0)	
Conditions originating in the perinatal period	0	1 (0)	1 (0)	0	
Symptoms, signs, ill-defined	364 (3.9)	217 (4.0)	182 (3.6)	156 (2.9)	
Injury and poisoning	1,245 (13.2)	583 (10.9)	534 (10.7)	675 (12.8)	
External causes	33 (0.3)	8 (0.1)	6 (0.1)	5 (0.1)	
Supplementary factors	241 (2.5)	134 (2.5)	157 (3.1)	171 (3.2)	
					P Value*
ICD-9 primary procedure category	6,240	3,513	3,232	3,276	<0.0001
Miscellaneous diagnostic and therapeutic	36 (0.6)	20 (0.6)	12 (0.4)	12 (0.4)	
Obstetrical	17 (0.3)	3 (0.1)	0	1 (0)	
Cardiovascular system	157 (2.5)	103 (2.9)	97 (3.0)	165 (5.0)	
Digestive system	1,518 (24.3)	834 (23.7)	763 (23.6)	664 (20.3)	
Ear	54 (0.9)	34 (1)	38 (1.2)	28 (0.9)	
Endocrine	172 (2.8)	104 (3)	116 (3.6)	153 (4.7)	
Eye	2 (0)	2 (0.1)	3 (0.1)	2 (0.1)	
Female genital organs	1,078 (17.3)	576 (16.4)	469 (14.5)	319 (9.7)	
Hemic and lymphatic system	149 (2.4)	98 (2.8)	79 (2.4)	73 (2.2)	
Integumentary system	332 (5.3)	182 (5.2)	161 (5)	223 (6.8)	
Male genital organs	471 (7.5)	308 (8.8)	234 (7.2)	207 (6.3)	
Musculoskeletal system	1,280 (20.5)	630 (17.9)	631 (19.5)	787 (24)	
Nervous system	149 (2.4)	76 (2.2)	84 (2.6)	118 (3.6)	
Nose, mouth, and pharynx	51 (0.8)	27 (0.8)	34 (1.1)	28 (0.9)	
Respiratory system	154 (2.5)	173 (4.9)	148 (4.6)	169 (5.2)	
Urinary system	593 (9.5)	330 (9.4)	348 (10.8)	301 (9.2)	
Other procedures and interventions	27 (0.4)	13 (0.4)	15 (0.5)	26 (0.8)	

Values are mean ± SD, median [25th percentile; 75th percentile], or numbers (percentages).

* Descriptive comparisons were made using Kruskal–Wallis test or chi-square tests, as appropriate. *P* values presented in the table are for overall comparisons among all groups and do not reflect comparisons between specific groups. † All diagnoses per patient were counted, resulting in a higher number of diagnoses than patients. Hence, no *P* value was calculated for diagnoses.

ASA = American Society of Anesthesiologists; BIS = bispectral index; ICD-9 = International Classification of Diseases and Procedures, version 9; MAC = minimum alveolar concentration; MAP = mean arterial pressure; P = Physical Status Classification.

Perioperative Mortality

The 30-day mortality rate was 0.8% (130 of 16,263). Univariable predictors of 30-day mortality are shown in table 2. Many of the baseline and clinical characteristics were associated with an increased risk for 30-day mortality. However, female sex was associated with a significant reduction in the risk for 30-day mortality. In addition, cumulative duration of the triple low state showed a strong association with 30-day mortality before accounting for other covariates. The result of the univariable analysis showed that year of surgery was not associated with a decreased risk of 30-day mortality. Finally, there was no significant association between the duration of operating room time and 30-day mortality.

Of the 16,263 patients, 555 case records were missing information on the ASA Physical Status Classification System category and 8 were missing information on the race designation; thus, these patients were excluded from multivariable analysis. Based on mortality, Cleveland Clinic Risk Index score, and cumulative duration of triple low, we compared cases dropped from the final analyses to those included. Although the 30-day mortality appeared higher in patients with missing data (1.6 *vs.* 0.8%; P = 0.0302), there was no difference in the Cleveland Clinic Risk Index score (mean of −0.474 *vs.* −0.564; P = 0.3854) and cumulative duration of triple low (mean of 13.2 *vs.* 12.3 min; P = 0.5635) between cases dropped from the final analyses compared with those included.

In the multivariable analysis, higher mean age at surgery, higher ASA Physical Status Classification System category, emergency surgery, and higher Cleveland Clinic Risk Index score remained significant predictors of 30-day mortality (table 2). A more recent year of surgery was associated with decreased 30-day mortality. After adjusting for differences in baseline and clinical characteristics, the association between the cumulative duration of triple low state and the risk for 30-day mortality was not significant (P = 0.85).

Because it has been recently suggested that frail patients may be prone to entering a triple low state, and the low blood pressure component of the triple low state may lead to poor outcome, we repeated our multivariable analysis by adding, in a stepwise manner, the cumulative duration of low MAP followed by the cumulative duration of low BIS. We found that cumulative duration of low MAP alone did not add significantly to the predictive value of the logistic regression model of 30-day mortality, which included the Cleveland Clinic Risk Index score and age (P = 0.0929). However, when cumulative duration of low MAP and cumulative duration of low BIS were both added into the logistic regression model after Cleveland Clinic Risk Index score and age, low MAP showed a significant association with risk for 30-day mortality (odds ratio, 1.04 per 15 min; 95% Cl, 1.006 to 1.076; P = 0.0197), whereas low BIS did not (odds ratio, 0.967 per 15 min; 95% Cl, 0.933 to 1.003; P = 0.0683).

The final multivariable model for 30-day mortality showed good discriminative ability and good fit (c-index = 0.926; overall goodness-of-fit Hosmer–Lemeshow test, chi-square test = 5.71; P = 0.6795). The degree of overoptimism was minimal (0.0071), which resulted in an adjusted c-index of 0.919.

Intermediate-term Mortality

The 16,133 patients who survived surgery for at least 30 days were followed until March 22, 2011. The follow-up duration was 2.6 ± 1.2 yr, and the overall mortality rate was 9.5% (1,535 of 16,133).

Table 3 shows univariable predictors of intermediate-term mortality. Again, many baseline and clinical characteristics were associated with intermediate-term mortality. There was a significant association between the quartiles of cumulative duration of triple low state and event-free survival, reflected by the event-free survival curves (fig. 1).

Table 2. Univariable and Multivariable Predictors of 30-day Mortality

	Univariable		Multivariable*	
Predictors	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Age at surgery, per year increase	1.05 (1.04–1.06)	<0.0001	1.03 (1.02–1.04)	<0.0001
Female sex	0.70 (0.50–0.96)	0.047	0.98 (0.66–1.45)	0.91
Race		0.09		0.09
White	1.0		1.0	
African-American	0.88 (0.58–1.31)		0.71 (0.44–1.15)	
All other	0.12 (0.01–0.53)		0.16 (0.01–0.79)	
ASA Physical Status, per category increase	9.02 (6.74–12.15)	<0.0001	2.96 (2.09–4.22)	<0.0001
Emergency surgery	2.97 (1.93–4.45)	<0.0001	1.65 (1.02–2.62)	0.03
Year of surgery, per year increase	0.88 (0.76–1.02)	0.08	0.82 (0.69–0.98)	0.03
Duration of operating room time, per 30 min	1. 0 (0.96–1.01)	0.97	0.99 (0.93–1.01)	0.61
Cleveland Clinic Risk Index, per 1 point increase	1.99 (1.87–2.14)	<0.0001	1.71 (1.57–1.86)	<0.0001
Cumulative duration of triple low, per 15 min	1.15 (1.09–1.20)	<0.0001	0.99 (0.92–1.07)	0.85

* The final multivariable logistic regression analysis was based on n = 15,700 due to missing ASA class (n = 555) and race (n = 8).
ASA = American Society of Anesthesiologists.

Table 3. Univariable and Multivariable Predictors of Intermediate-term Mortality

	Univariable		Multivariable*	
Predictors	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Age at surgery, per year increase	1.046 (1.043–1.05)	<0.0001	1.036 (1.032–1.04)	<0.0001
Female sex	0.82 (0.74–0.67)	<0.0001	0.90 (0.81–0.99)	0.03
Race		<0.0001		0.16
White	1.0		1.0	
African-American	0.99 (0.89–1.12)		0.94 (0.83–1.06)	
All other	0.51 (0.39–0.68)		0.77 (0.58–1.04)	
ASA Physical Status, per category increase	3.65 (3.37–3.96)	<0.0001	1.55 (1.42–1.70)	<0.0001
Emergency surgery	1.02 (0.86–1.21)	0.82	0.78 (0.66–0.93)	0.005
Year of surgery, per year increase	0.86 (0.83–0.90)	<0.0001	0.82 (0.78–0.86)	<0.0001
Duration of operating room time, per 30 min	0.99 (0.98–1.01)	0.68	0.98 (0.96–0.99)	0.0009
Cleveland Clinic Risk Index, per 1 point increase	1.73 (1.70–1.76)	<0.0001	1.66 (1.62–1.70)	<0.0001
Cumulative duration of triple low, per 15 min	1.09 (1.07–1.11)	<0.0001	0.98 (0.97–1.01)	0.37

* The final multivariable Cox proportional hazard regression analysis was based on n = 15,579 due to missing ASA class (n = 546) and race (n = 8).
ASA = American Society of Anesthesiologists.

Of the 16,133 patients, 546 case records were missing information on the ASA Physical Status Classification System category and 8 were missing information on the race designation; thus, these patients were excluded from multivariable analysis. When patients with missing information were compared with those included in the multivariable model, the intermediate-term mortality rate (9.57 *vs.* 9.51%; $P = 0.966$), Cleveland Clinic Risk Index score (mean of −0.524 *vs.* −0.591; $P = 0.564$), and cumulative duration of triple low (mean = 12.7 *vs.* 12.2 min; $P = 0.741$) were not statistically different.

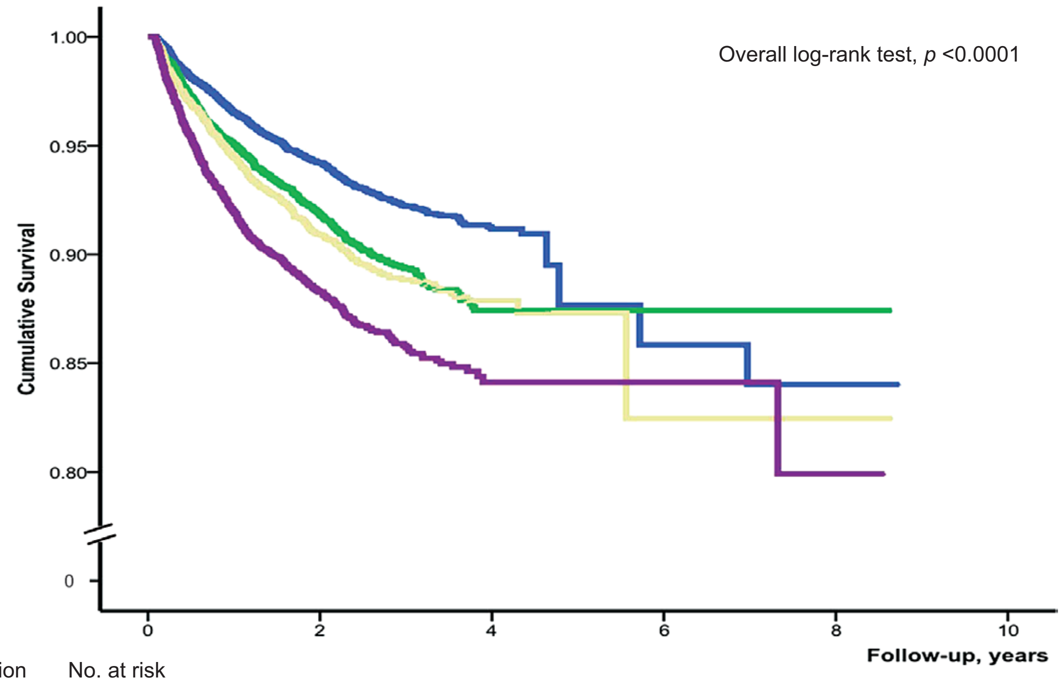
In multivariable analysis, age at surgery, ASA Physical Status Classification System category, and a higher Cleveland Clinic Risk Index score were significant predictors of intermediate-term mortality (table 3). Female sex, emergency surgery, year of surgery, and duration of operating room time were associated with decreased intermediate-term mortality. After adjusting for differences in baseline and clinical characteristics, there was no significant association between the cumulative duration of triple low state and the risk for intermediate-term mortality ($P = 0.37$). Similar to the analysis of 30-day mortality, we repeated our multivariable analysis by adding, in a stepwise manner, the cumulative duration of low MAP followed by the cumulative duration of low BIS. With the Cleveland Clinic Risk Index score and age in the model, we found no significant association with intermediate-term mortality of either cumulative duration of low MAP (multivariable hazard ratio, 0.991 per 15 min; 95% CI, 0.980 to 1.003; $P = 0.1394$) or of low BIS (multivariable hazard ratio, 0.997 per 15 min; 95% CI, 0.988 to 1.007; $P = 0.5803$).

The final multivariable Cox regression model for intermediate-term mortality showed good discriminative ability (c-index = 0.860). The degree of overoptimism was minimal (0.00032), and the adjusted c-index remained 0.860. The calibration of the final model (observed *vs.* predicted) showed agreement between the predicted and observed intermediate-term mortality rates across deciles of predicted risk (fig. 2). The model-estimated effect of cumulative duration of triple low state on intermediate-term mortality is shown in figure 3. With covariates held constant, the four lines representing the quartile values of duration virtually overlap.

Discussion

This study of patients undergoing noncardiac surgery demonstrates that the combination of intraoperative hypotension, low MAC fraction of volatile anesthetics, and low BIS is not associated with worse 30-day and intermediate-term mortality after adjusting for specific patient- and procedure-related characteristics. In contrast, our results reinforce previous findings that specific patient- and procedure-related characteristics are strongly associated with 30-day and intermediate-term mortality after noncardiac surgery.

Several studies have shown that cumulative duration of BIS less than 45 alone is a predictor of mortality after noncardiac[7–9] and cardiac surgery.[10] Other studies in noncardiac surgery patients have either failed to adjust for preexisting malignant disease status[7] or, when preexisting malignancy status was taken into consideration, have found that the association between cumulative duration of BIS less than 45 and mortality no longer persists.[8] A more recent study suggests that BIS monitoring and the absence of BIS values less than 40 for more than 5 min are associated with improved survival, but again, this study failed to adjust for diagnosis and procedure categories as well as other clinical risk factors.[9] In a subset of cardiac patients, the association between cumulative duration of BIS less than 45 and an increased risk for mortality was explained by an observed association among clinical variables, intraoperative factors, and BIS values less than 45.[10] The results of that study indicated that BIS values less than 45 are likely markers of systemic illness, poor



Cumulative duration of triple low	No. at risk				
None	6,211	4,408	1,013	47	16
1 to 5 min	3,491	2,269	395	25	13
6 to 17 min	3,211	2,053	328	17	12
≥ 18 min	3,220	2,008	239	20	13

Fig. 1. Kaplan–Meier estimates of intermediate-term mortality according to the quartiles of duration of cumulative triple low state. *P* value (log-rank test) indicates the differences in survival.

cardiac function, or complicated intraoperative course.[10] These observations were also supported by a substudy of the B-Unaware Trial,[12] which found no evidence that cumulative BIS values below a threshold of 40 or 45 were associated with an increased risk for intermediate-term mortality. However, there was strong association between perioperative risk factors, diagnosis and procedure categories, and mortality.

Recently, Sessler *et al.*[11] reported that mortality after noncardiac surgery is increased in patients who have low blood pressure and low BIS during a low MAC fraction, indicating that triple low state may represent anesthetic sensitivity. This study was a retrospective, single-center study in 24,120 patients who underwent noncardiac surgery. The investigators defined low blood pressure, low BIS, and low MAC fraction values as 1SD from the single-center population means, rather than clinical thresholds. Therefore, center-specific patterns of care likely influenced the authors' observations and limit the generalizability of the study findings.[2]

In the current study, therefore, we sought to validate these findings and study the potential role of triple low monitoring in relation to 30-day and intermediate-term mortality in patients who underwent noncardiac surgery. In contrast to the Sessler *et al.'s* study,[11] we found no relation between cumulative duration of triple low state and 30-day or intermediate-term mortality. This discrepancy suggests that the association between cumulative duration of triple low state and mortality is likely epiphenomenal and, when present, is reflective of specific patient- or procedure-related characteristics rather than anesthetic management.[2,12] For instance, advanced age, higher ASA Physical Status Classification System category, emergency surgery, and higher Cleveland Clinic Risk Index score were significantly associated with longer cumulative duration of triple low state. Indeed, in an exploratory stepwise analysis, we found that the strongest risk factor associated with 30-day mortality and intermediate-term mortality was the Cleveland Clinic Risk Index score. When only the Cleveland Clinic Risk Index score was added to either statistical model with the cumulative duration of triple low state, the association between the cumulative duration of triple low state and mortality was no longer significant.

The role of optimal perioperative management strategies in preventing perioperative and intermediate-term mortality in high-risk patients undergoing noncardiac surgery has been controversial. In our study, we confirmed the value of many previously described risk factors for predicting perioperative

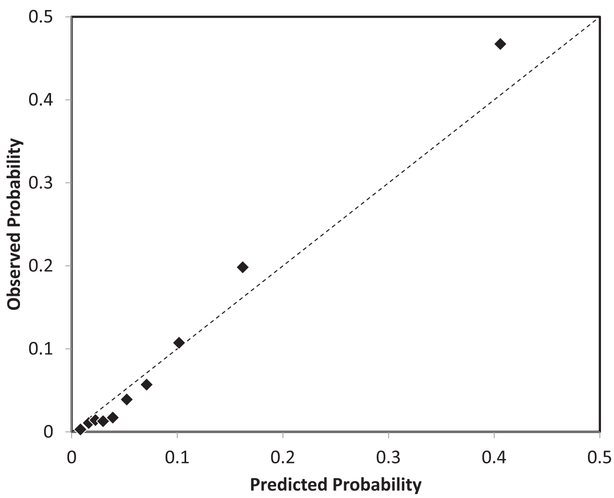


Fig. 2. Observed *versus* predicted probability of intermediate-term mortality at 2.5 yr. The figure represents the calibration of the final multivariable Cox proportional hazard model presented in table 3. Perfect fit is represented by the *dotted line*. The *diamonds* indicate the mean model–predicted event risks per decile plotted against Kaplan–Meier-observed event risks.

and intermediate-term mortality after noncardiac surgery. In particular, higher age,[20] higher categories within the ASA Physical Status Classification System,[21] and higher Cleveland Clinic Risk Index scores,[11] an aggregate of diagnosis and surgical procedure categories, were consistently significant predictors of perioperative and intermediate-term mortality. We also found, however, that these strong risk factors were associated with cumulative duration of triple low state.

In a secondary analysis, we determined whether there was an association between cumulative duration of low BIS as an individual component of triple low state, and 30-day and intermediate-term mortality, adjusting for cumulative duration of low MAP and clinical risk factors. The cumulative duration of low BIS was not significantly associated with 30-day or intermediate-term mortality indicating, as described in the editorial by Kheterpal and Avidan,[2] "that the interaction between cumulative duration of low MAP, clinical risk factors, and postoperative outcomes is more complex than the concept that exposure to an increased duration of 'deeper hypnotic time' can be potentially dangerous."

Our study also showed that emergency surgery was significantly associated with increased risk for perioperative mortality but carried a significantly lower risk for intermediate-term mortality. This may seem contradictory; however, it is likely that this discrepancy arises from the fact that patients who survive their emergency surgical procedure beyond 30 days gain survival benefit and are at significantly lower risk for intermediate-term mortality.

Many of these patient- and surgery-related factors have previously been identified as modifiable predictors of perioperative[20,22] and intermediate-term[12] and long-term[12,23–25] outcomes after noncardiac surgery. Identifying patients at risk for perioperative complications has improved considerably in recent years. We observed that a more recent year of surgery was associated with a significantly decreased risk for perioperative and intermediate-term mortality, which indeed could reflect recent improvements in perioperative management of patients undergoing noncardiac surgery.[1,20,22] Our

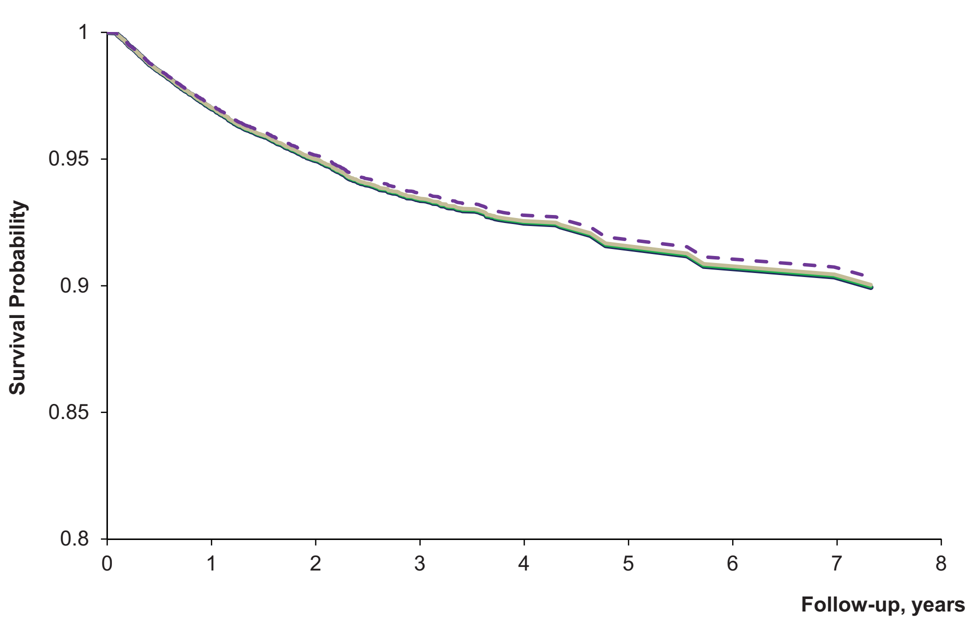


Fig. 3. Covariate-adjusted estimates of intermediate-term mortality for cumulative duration of triple low states of 0 (*blue solid line*), 5 (*green solid line*), 15 (*grey solid line*), and 60 (*purple dotted line*) min (to match quartiles observed; fig. 1). Covariates for the estimates are held constant at their median or most frequent category: age = 55 yr, female sex, white race, American Society of Anesthesiologists Physical Status Classification System = P2, Cleveland Clinic Risk Index score = 0, date of surgery = April 17, 2008, and duration of surgery = 180 min.

findings reinforce the need to identify and address modifiable risk factors so that both perioperative and intermediate-term postoperative outcomes can be improved.

Study Limitations

Our study has some limitations. First, data were derived from the Duke Perioperative Electronic Database, which was designed for documentation and administrative purposes, and not for scientific research. Thus, data on specific patient, diagnosis, and procedure-related characteristics may not have been entered properly or may have been overlooked. Consequently, the relative contribution of these factors to perioperative and intermediate-term mortality may have been over- or underestimated.[26]

Second, data on other important clinical risk factors including previous or current medical history and pharmacotherapy are not recorded into the Duke Perioperative Electronic Database, and thus, were not available for our analyses. Furthermore, we could adjust the association between cumulative duration of triple low state and mortality only for clinical diagnoses that were coded according to the International Classification of Diseases and Procedures, version 9, system. As a result of these limitations, residual confounding may still exist.

Third, we did not characterize hospital length of stay but chose perioperative and intermediate-term mortality as our principal outcomes. The length of stay is influenced by many patient- and procedure-related characteristics, but most importantly, by the number of complications after surgery.[27] Because the information on postoperative complications was not available for electronic retrieval, we did not consider hospital length of stay as an outcome measure in the current study.

Finally, as part of modern multimodal anesthesia, patients receive a combination of intravenous and inhalational anesthetic agents and potent opioids in varying concentrations. Therefore, assessing the potential impact of anesthetic dose on mortality can be challenging. Given the retrospective nature of our study and its sample size, we were not able to retrieve information on total intravenous hypnotic and potent opioid doses, and thus, could not study their potential effect on perioperative and intermediate-term mortality.

Conclusions

In this study, we observed a univariable association between cumulative duration of triple low state—a combination of low MAP, low MAC, and low BIS—and 30-day and intermediate-term mortality. However, after adjusting for differences in baseline and clinical characteristics, this association no longer persisted. In contrast, mortality was strongly associated with perioperative risk factors, disease, and procedure categories. This study does not support the hypothesis that a triple low state may identify patients who are unusually sensitive to anesthesia and at risk for perioperative and intermediate-term mortality after noncardiac surgery. However, only an appropriately designed, randomized, prospective trial# clarifies further the presence and strength, or absence, of an association between triple low state and perioperative and intermediate-term mortality.

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Competing Interests

The authors declare no competing interests.

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