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ORIGINAL RESEARCH

Associations Between Preoperative Glucose and Hemoglobin A1c Level and Myocardial Injury After Noncardiac Surgery

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BACKGROUND: Perioperative blood glucose level has shown an association with postoperative outcomes. We compared the incidences of myocardial injury after noncardiac surgery (MINS) and 30-day mortality, according to preoperative blood glucose and hemoglobin A1c (HbA1c) levels.

METHODS AND RESULTS: The patients were divided according to blood glucose level within 1 day before surgery. The hyperglycemia group was defined with fasting glucose >140 mg/dL or random glucose >180 mg/dL. In addition, we compared the outcomes according to HbA1c >6.5% among patients with available HbA1c within 3 months before surgery. The primary outcome was MINS, and 30-day mortality was also compared. A total of 12 304 patients were enrolled and divided into 2 groups: 8324 (67.7%) in the normal group and 3980 (32.3%) in the hyperglycemia group. After adjustment with inverse probability of weighting, the hyperglycemia group exhibited significantly higher incidences of MINS and 30-day mortality (18.7% versus 27.6%; odds ratio, 1.29; 95% CI, 1.18–1.42; $P<0.001$; and 2.0% versus 5.1%; hazard ratio, 2.00; 95% CI, 1.61–2.49; $P<0.001$, respectively). In contrast to blood glucose, HbA1c was not associated with MINS or 30-day mortality.

CONCLUSIONS: Preoperative hyperglycemia was associated with MINS and 30-day mortality, whereas HbA1c was not. Immediate glucose control may be more crucial than long-term glucose control in patients undergoing noncardiac surgery.

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Key Words: blood glucose level ■ hemoglobin A1c ■ myocardial injury ■ noncardiac surgery

Perioperative hyperglycemia is common, reported in 20% to 40% of patients undergoing noncardiac surgery and associated with poor postoperative outcomes.[1] Previous evidence has suggested that preoperative acute hyperglycemia is associated with poor postoperative outcomes[2–4] as well as chronic hyperglycemia accessed via hemoglobin A1c (HbA1c).[5] Several guidelines recommend preoperative blood glucose control in patients with diabetes mellitus,[6–8] but 12% to 30% of patients with perioperative hyperglycemia do not have a history of diabetes mellitus.[4] Therefore, there remains a paucity of data for the best preoperative glucose management in the general population.

Cardiac complication is the leading cause of death after surgery, and hyperglycemia is a well-known major risk factor of ischemic heart disease.[9] Myocardial injury after noncardiac surgery (MINS) is the most common cardiac complication and is defined as any cardiac troponin (cTn) elevation above the 99th percentile upper reference limit within 30 days after

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CLINICAL PERSPECTIVE

What Is New?

- Preoperative hyperglycemia was associated with the development of myocardial injury after noncardiac surgery and 30-day mortality, but the association was not significant for hemoglobin A1c level.

What Are the Clinical Implications?

- Immediate glucose control may be more crucial than long-term glucose control in patients undergoing noncardiac surgery.

Nonstandard Abbreviations and Acronyms

cTn	cardiac troponin
MINS	myocardial injury after noncardiac surgery

surgery as a result of myocardial ischemia without requirement of ischemic symptoms.[10–12] In this regard, the occurrence of MINS may play a certain role in the association between preoperative hyperglycemia and postoperative outcomes, although the relationship between MINS and acute or chronic hyperglycemia has not been fully evaluated. Therefore, in this study, we aimed to evaluate whether preoperative blood glucose level is associated with MINS and mortality and conducted analysis according to HbA1c level to evaluate the association with chronic hyperglycemia. Our findings may provide valuable information for preoperative glucose management in surgical patients.

METHODS

Our study adheres to the American Heart Association Journals' implementation of the Transparency and Openness Promotion Guidelines. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to Samsung Medical Center at jong-hwan.park@samsung.com. The Institutional Review Board at Samsung Medical Center waived approval for this study and the requirement for written informed consent for access to the registry because the data set was initially extracted in deidentified form (Samsung Medical Center [SMC] 2019-08-048). This study is an observational cohort study using data from the SMC-TINCO (Samsung Medical Center Troponin in Noncardiac Operation; KCT0004244) registry, a large single-center cohort containing deidentified data of 43 019 consecutive patients who had cTn I level measured before or within 30 days after noncardiac surgery between January 2010 and June 2019 at Samsung Medical Center, Seoul, Republic of Korea. The SMC-TINCO registry was generated using the "Clinical Data Warehouse Darwin-C," which was built for investigators to search and retrieve deidentified medical records from this electronic archive system. After extracting the raw data of the preoperative evaluation sheets, the baseline characteristics of the patients were organized into a standardized form by independent investigators who were blinded to mortalities and cTn I level. For mortalities that occur elsewhere and not at our institution, this system is consistently updated and confirmed with the National Population Registry of the Korea National Statistical Office using a unique personal identification number when available.

For this study, we excluded the following patients from the registry: (1) patients aged <18 years at the time of surgery, (2) patients without postoperative cTn I level measurement, (3) patients who received cardiac massage before diagnosis of MINS, and (4) patients without available preoperative blood glucose measurement within 1 day before surgery. A total of 12 304 patients were enrolled in the final analysis.

Definitions and Study Outcomes

We divided the patients according to blood glucose level: the hyperglycemia group was defined as fasting glucose >140 mg/dL or random glucose >180 mg/dL, whereas the normal group comprised the rest of the patients according to American Diabetes Association and American Association of Clinical Endocrinology guidelines.[6] Glucose concentration was measured by the central laboratory at the time of the preoperative evaluation in patients who had a remarkable medical history, diabetes mellitus, or a history of surgery greater than low risk. Among the study patients, those with available HbA1c measurement within 3 months before surgery were further divided into 2 groups according to HbA1c level of 6.5%.[13] Active cancer was defined as histologic diagnosis of cancer within the previous 6 months.[14] High-risk surgery was defined according to the 2014 European Society of Cardiology/Anesthesiology guidelines.[15]

The primary outcome was MINS, defined as peak cTn I level above the 99th percentile upper reference limit within 30 days after surgery as a result of myocardial ischemia without requirement of ischemic symptoms. Therefore, an elevation with evidence of nonischemic cause, such as sepsis, pulmonary embolus, atrial fibrillation, cardioversion, or chronic elevation, was excluded.[10–12] The secondary outcome was 30-day mortality, which was classified into cardiovascular and noncardiovascular mortalities. Cardiovascular mortality was death related to myocardial infarction, cardiac arrhythmia, heart failure, stroke, or vascular causes, whereas noncardiovascular mortality was defined as death from a cause other than cardiovascular conditions. All deaths without an undisputed noncardiovascular cause were considered as cardiovascular death.[16]

Perioperative cTn I Measurements and Management

According to the institutional protocol, perioperative cTn was measured for moderate- or high-risk surgeries or in patients with at least one of the major cardiovascular risk factors, such as a history of ischemic heart disease, heart failure, stroke, including transient ischemic attack, diabetes mellitus on insulin therapy, or chronic kidney disease based on current guidelines.[15] In patients with minor risk factors, perioperative cTn was measured at the discretion of the attending clinician with considerations for old age or recently suspected symptoms of ischemic disease. An automated analyzer (Advia Centaur XP; Siemens Healthcare Diagnostics, Erlangen, Germany) was used for cTn measurement. The lowest limit of detection was 6 ng/L, and the 99th percentile upper reference limit was 40 ng/L, as provided by the manufacturer. Patients with elevated cTn level were referred to cardiologists for further evaluation and proper management. Other perioperative management followed the institutional protocol based on current guidelines.

Statistical Analysis

For continuous data, the differences were compared by the *t*-test or the Mann-Whitney test, as applicable, and presented as mean±SD or median with interquartile range. Categorical data were presented as number (percentage) and compared using the χ^2 or Fisher exact test. Kaplan-Meier estimates were used to construct survival curves and compared with the log-rank test. MINS was compared using a logistic regression model and reported as odds ratio (OR) with 95% CI. The mortality outcomes were compared using the Cox regression model and were reported as hazard ratio (HR). Variables with a standardized mean difference >0.1 were retained in the multivariable model. To further reduce selection bias while maintaining balanced confounding variables between the 2 groups, we used weighted regression models with inverse probability weighting and conducted rigorous adjustment for differences in all baseline characteristics of the patients.[17] According to this technique, the inverse probability weights were defined as the reciprocal of propensity scores, and the standardized mean difference under 10% was deemed as an achievement of balance between the groups. To estimate an optimal cutoff point of fasting blood glucose associated with MINS, Pearson correlation coefficient and receiver-operating characteristic (ROC) plots were constructed to estimate the threshold and compute the specificity and sensitivity. For the sample size of this study, the power was estimated to be 0.99 when the OR of MINS occurrence was >1.2 and the HR of 30-day mortality was >1.6. To minimize the effects of the potential confounders and to investigate the robustness of our study, we conducted a sensitivity analysis separately for patients stratified by fasting and random blood glucose levels, for patients with and without diabetes mellitus, and for patients with and without preoperative intensive care unit treatment. We also estimated the potential impact of unmeasured confounders.[18] Statistical analyses were performed with R 3.6.2 (Vienna, Austria; http://www.R-project.org/). All tests were 2 tailed, and *P*<0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

We excluded 1154 patients who were aged <18 years, 6596 patients without postoperative cTn measurement, and 46 patients who underwent cardiac massage before diagnosis of MINS. Among the 35 223 patients, preoperative blood glucose level was available in 12 304 patients. The patient flow of the study is shown in Figure 1. The baseline characteristics of the entire population are summarized in Table 1. Patients in the hyperglycemia group were likely to be older and exhibited higher incidences of diabetes mellitus, hypertension, previous stroke, and preoperative intensive care unit and ventilator treatments. For operative variables, the hyperglycemia group showed higher incidences of high-risk procedures, emergency operations, and use of intraoperative inotropic agents. After an adjustment with inverse probability weighting, the change of standardized mean difference to <10% suggested well-balanced covariates between the 2 groups. The types of surgery in each group are summarized in Table S1.

Short-Term Glucose Control and Clinical Outcomes

Postoperative cTn was elevated in 2755 patients, and 103 of them had nonischemic causes. So, the overall incidence of MINS was 21.6% (2652/12 304). In multivariable analysis, the occurrence of MINS was significantly higher in the hyperglycemia group (18.7% versus 27.6%; OR, 1.31; 95% CI, 1.19–1.44; *P*<0.001) (Table 2). The 30-day mortality was also higher in the hyperglycemia group (2.0% versus 5.1%; HR, 1.77; 95% CI, 1.43–2.19; *P*<0.001) (Table 2 and Figure 2). After an inverse

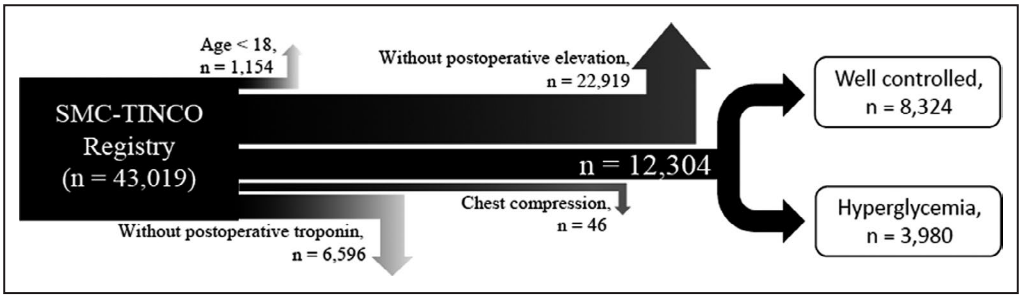

Figure 1. Patient flowchart.
SMC-TINCO indicates Samsung Medical Center Troponin in Noncardiac Operation.

probability weighting adjustment, MINS (OR, 1.29; 95% CI, 1.18–1.42; *P*<0.001) and 30-mortality (HR, 2.0; 95% CI, 1.61–2.49; *P*<0.001) were consistently increased.

In the sensitivity analysis, the observed association was significant in patients stratified by fasting or random blood glucose levels, in patients with and without diabetes mellitus, and in patients with and without preoperative intensive care unit treatment (Table S2). The significance of observed association according to the type of surgery is presented in Figure S1. Sensitivity of the effect of an unmeasured confounder on the observed association was evaluated assuming a 40% prevalence of the measured confounder, and that the association was significant under any circumstances (Table S3). In ROC analysis, the optimal cutoff point of fasting blood glucose for MINS was 141 mg/dL, with an area under the ROC curve of 0.561; and the value was 174 mg/dL, with an area under the ROC curve of 0.521, for random blood glucose. The sensitivity and specificity were 45.6% and 67.2%, respectively, for fasting blood glucose and 23.6% and 84.0%, respectively, for random blood glucose (Figure 3).

Long-Term Glucose Control and Clinical Outcomes

In a total of 12 304 patients, 4373 had HbA1c test findings available within 3 months before surgery. The baseline characteristics of the patients with and without available HbA1c are summarized in Table S4. In patients with HbA1c level, those with chronic hyperglycemia tended to be older and exhibited higher incidences of diabetes mellitus, chronic kidney disease, coronary artery disease, European Society of Cardiology/European Society of Anaesthesiology high-risk operation, emergency operation, active cancer, preoperative insulin and intensive care unit treatments, and use of intraoperative inotropic agents (Table 3). The incidence of MINS did not significantly differ according to HbA1c level in the multivariable and inverse probability weighting adjusted analyses (25.4% versus 21.3%; OR, 1.01; 95% CI, 0.86–1.20; *P*=0.89; and OR, 0.98; 95% CI, 0.85–1.14; *P*=0.80; respectively) (Table 4). The 30-day mortality also did not differ between the 2 groups (Figure 4 and Table 4). The optimal cutoff point of HbA1c for MINS was 6.4%, and the area under the ROC curve was 0.519. Using this value, the sensitivity and specificity were 37.3% and 67.2%, respectively (Figure 3).

DISCUSSION

The main findings of this study are as follows: (1) the incidence of MINS was significantly higher in the patients with high preoperative blood glucose level, and (2) 30-day mortality was also higher in these patients regardless of cause of death, but (3) higher preoperative HbA1c was not associated with occurrence of MINS or 30-day mortality. Together, these findings suggest that control of acute hyperglycemia in the preoperative period may be helpful in preventing MINS occurrence and 30-day mortality regardless of the presence of chronic hyperglycemia.

Glucose control is one of the cornerstones in perioperative management, and preoperative hyperglycemia has shown association with in-hospital mortality and postoperative complications.[3] Several guidelines recommend preoperative glucose control for patients with diabetes mellitus[6–8]; however, because of the lack of large randomized trials, the ideal treatment agent and glucose target level are widely debated.[1] Surgical patients often encounter a state described as “stress hyperglycemia,” comprising hyperglycemia without a history of diabetes mellitus,[19] and perioperative blood glucose control appeared to be important in patients either with or without diabetes mellitus.[2] In this study, we enrolled noncardiac surgical patients regardless of diabetes mellitus and evaluated the association between blood glucose level within 1 day before surgery and MINS, a major cause of postoperative mortality. The incidence of MINS with increased 30-day mortality was significantly higher in patients with hyperglycemia.

Several explanations could be considered for the observed association between patients with

Table 1. Baseline Characteristics, According to Preoperative Blood Glucose Level

Characteristic	Normal (N=8324)	Hyperglycemia (N=3980)	Before IPW *P* Value	Before IPW SMD	After IPW *P* Value	After IPW SMD
Preoperative HbA1c, %*	6.7±1.3	7.5±1.7	<0.001	52.2		
Time to peak cardiac troponin, d	0.50 (0.08–1.73)	0.54 (0.08–1.81)	0.06	2.8	0.49	1.4
Men	4710 (56.6)	1562 (62.2)	0.03	5.8	0.87	0.3
Age, y	62.9±13.8	64.7±12.4	<0.001	14.3	0.55	1.2
Diabetes mellitus	6116 (73.5)	3324 (83.5)	<0.001	24.6	0.76	0.7
Hypertension	5524 (66.4)	2756 (69.2)	0.002	6.2	0.96	0.1
Chronic kidney disease	869 (10.4)	409 (10.3)	0.81	0.5	0.96	0.1
Current smoking	915 (11.0)	461 (11.6)	0.35	1.9	0.95	0.1
Current alcohol	1531 (18.4)	797 (20.0)	0.03	4.1	0.95	0.1
Previous disease						
Coronary artery disease	1516 (18.2)	781 (19.6)	0.06	3.6	0.87	0.3
Heart failure	203 (2.4)	80 (2.0)	0.16	2.9	0.94	0.2
Stroke	685 (8.2)	442 (11.1)	<0.001	9.7	0.84	0.4
Arrhythmia	603 (7.2)	287 (7.2)	0.98	0.1	0.98	0.1
Heart valve disease	108 (1.3)	44 (1.1)	0.42	1.8	0.95	0.1
Active cancer	3124 (37.5)	1506 (37.8)	0.76	0.6	0.96	0.1
Preoperative in-hospital care						
Insulin use	1734 (20.8)	825 (20.7)	0.91	0.3	0.76	0.6
Intensive care unit	516 (6.2)	446 (11.2)	<0.001	17.8	0.89	0.3
ECMO	0	0				
Continuous renal replacement therapy	42 (0.5)	25 (0.6)	0.46	1.6	0.89	0.3
Ventilator	96 (1.2)	93 (2.3)	<0.001	9	0.9	0.2
Operative variables						
ESC/ESA surgical high risk	1519 (18.2)	859 (21.6)	<0.001	8.4	0.93	0.2
Emergency operation	1917 (23.0)	1456 (36.6)	<0.001	30	0.87	0.3
General anesthesia	7220 (86.7)	3482 (87.5)	0.26	2.2	0.87	0.3
Operation duration, h	3.06±2.19	3.03±2.14	0.5	1.3	0.89	0.3
Packed red blood cell transfusion	812 (9.8)	396 (9.9)	0.76	0.7	0.96	0.1
Continuous infusion of inotropic agents	2483 (29.8)	1388 (34.9)	<0.001	10.8	0.87	0.3

Data are presented as number (percentage), mean±SD, or median (interquartile range). ECMO indicates extracorporeal membranous oxygenation; ESA, European Society of Anaesthesiology; ESC, European Society of Cardiology; HbA1c, hemoglobin A1c; IPW, inverse probability weighting; and SMD, standardized mean difference.

*Preoperative HbA1c was not retained in multivariable or IPW adjustments.

hyperglycemia and MINS. First, hyperglycemia induces coronary microvascular dysfunction.[20] Given that type 2 myocardial infarction plays a role as the main mechanism in MINS, we can assume that coronary microvascular dysfunction may have had an influence in the higher incidence of MINS in surgical

Table 2. Incidence of MINS and Mortalities, According to Preoperative Blood Glucose Level

Variable	Normal (N=8324)	Hyperglycemia (N=3980)	Unadjusted OR/HR (95% CI)	*P* Value	Adjusted OR/HR (95% CI)	*P* Value	IPW OR/HR (95% CI)	IPW *P* Value
MINS	1553 (18.7)	1099 (27.6)	1.66 (1.52–1.82)	<0.001	1.31 (1.19–1.44)	<0.001	1.29 (1.18–1.42)	<0.001
30-d Mortality	166 (2.0)	204 (5.1)	2.63 (2.14–3.23)	<0.001	1.77 (1.43–2.19)	<0.001	2.00 (1.61–2.49)	<0.001
Cardiovascular death	40 (0.5)	55 (1.4)	2.93 (1.95–4.40)	<0.001	1.81 (1.19–2.76)	0.01	2.15 (1.39–3.33)	<0.001
Noncardiovascular death	126 (18.7)	149 (3.7)	2.53 (2.00–3.21)	<0.001	1.76 (1.37–2.25)	<0.001	1.95 (1.51–2.51)	<0.001

Data are presented as number (percentage). Multivariable analysis included age, diabetes mellitus, emergency operation, preoperative intensive care unit treatment, and intraoperative inotropic agent use. MINS was presented with OR, and mortalities were presented as HR. HR indicates hazard ratio; IPW, inverse probability weighting; MINS, myocardial injury after noncardiac surgery; and OR, odds ratio.

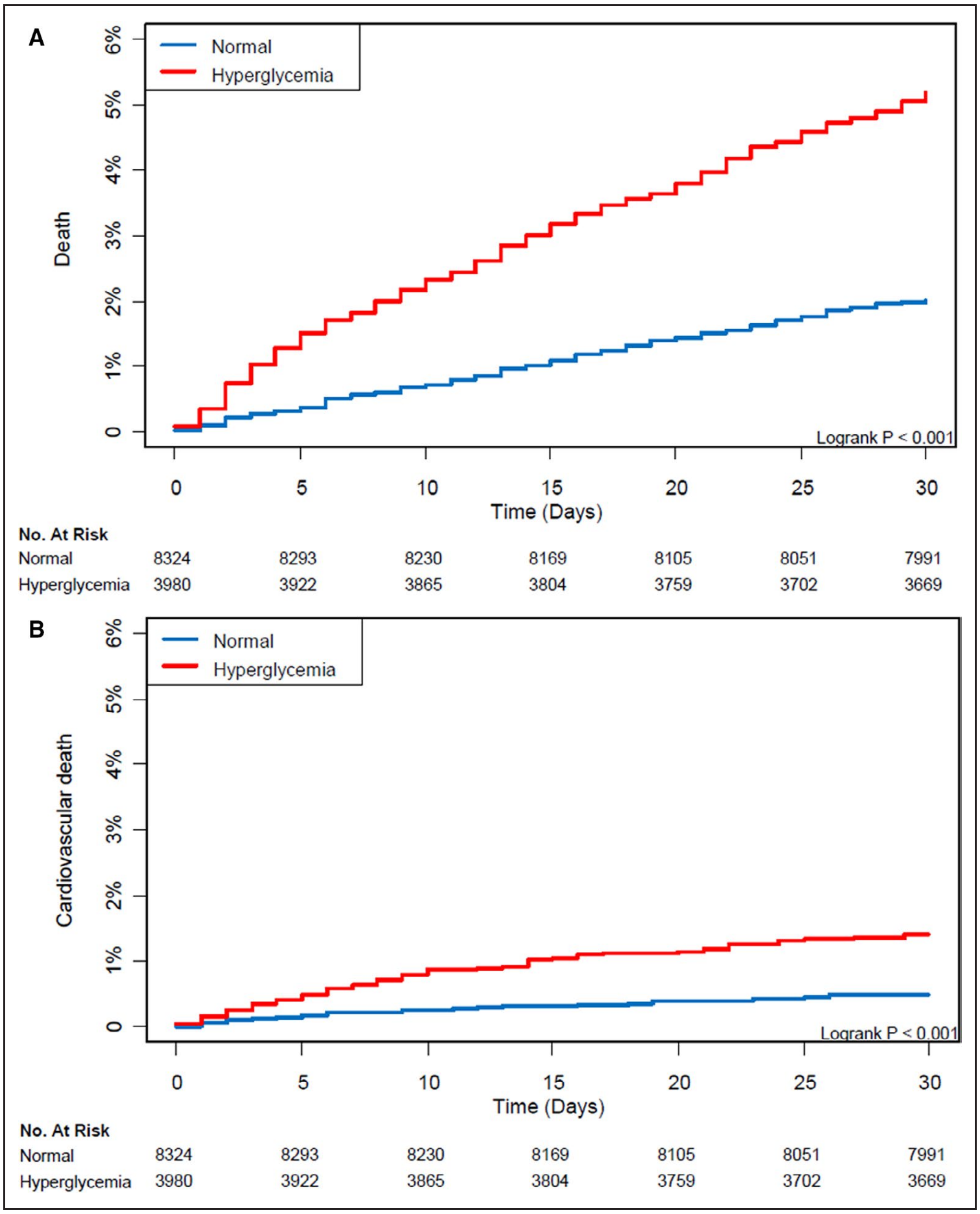

Figure 2. Kaplan-Meier curves of cumulative all-cause mortality (A) and cardiovascular mortality (B) during 30 days after surgery, according to preoperative glucose level.

patients with hyperglycemia.[10] Second, oxidative stress arises directly or indirectly from hyperglycemia. This imbalance between free radical generation and elimination or detoxification is a principle mediator of myocardial injury during ischemia-reperfusion, which frequently occurs during the perioperative period.[21] Finally, endothelial dysfunction in patients with diabetes mellitus may explain the results. The aforementioned oxidative stress also contributes to endothelial dysfunction, one of the causes of type 2 myocardial infarction.[12] In addition to these biologic mechanisms, the increased incidences of MINS and mortality could also be related to higher possibility of underlying disease in patients with hyperglycemia. In our study patients, the hyperglycemia group showed higher incidences of diabetes mellitus, hypertension, and previous history of stroke.

For chronic hyperglycemia, conflicting results have been reported in previous studies.[5,22] Therefore, we also assessed the effect of long-term high glucose level by evaluating only patients with available HbA1c level, and demonstrated that higher

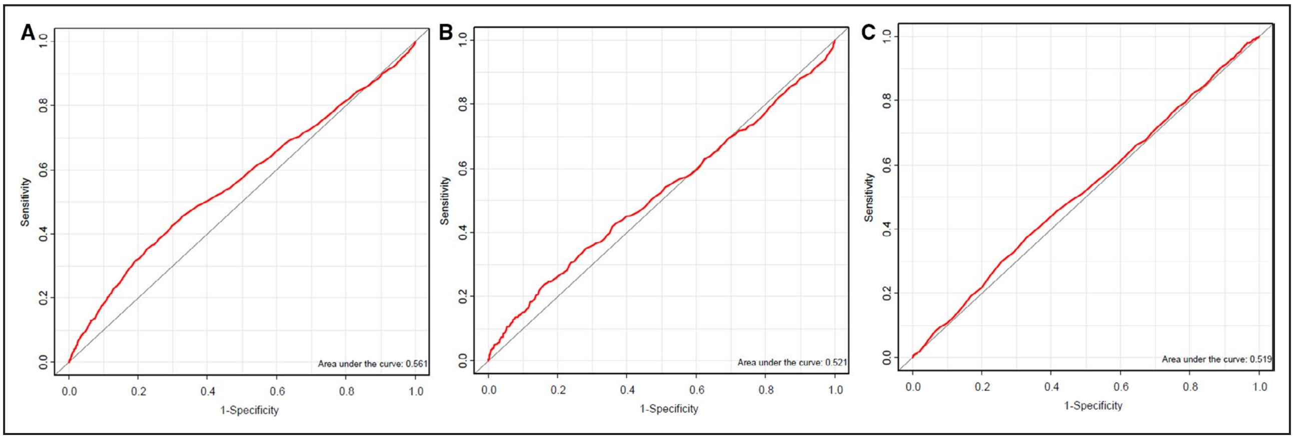

Figure 3. Receiver-operating characteristic curves for preoperative fasting blood glucose level (A), random blood glucose level (B), and hemoglobin A1c level associated with myocardial injury after noncardiac surgery (C).

preoperative HbA1c was not significantly associated with MINS or 30-day mortality. The association between preoperative HbA1c and postoperative outcome is not concluded, and some of previous reports correspond to our result.[22,23] One study from a database of 38 989 patients showed that the risk of surgical complications was increased in patients with diabetes mellitus, but no significant correlation was found for HbA1c level.[22] Another study showed that chronic hyperglycemia was associated with a longer length of hospital stay but not 30-day mortality.[6] For myocardial injury, one study showed an inverse relationship with HbA1c in patients undergoing percutaneous coronary intervention.[24] According to our results, the cutoff point of HbA1c for MINS showed low sensitivity and specificity as well as an insignificant association with MINS or 30-day mortality, suggesting that HbA1c may not be suitable for predicting MINS. However, this result may be related to a selective measurement of HbA1c and the difference between the patients with and without HbA1c level. In our study patients, the patients with HbA1c measurement showed higher incidences of underlying disease, and the insignificant result for HbA1c may also be related to the fact that patients with poorly controlled hyperglycemia are likely to require more frequent medical checkups and closer perioperative monitoring. Also for outcomes, our study was focused on the first 30 days after surgery, because glycemic control and diabetic managements after the discharge were not controlled in this study. HbA1c level is known to correlate well with prognosis of patients with diabetes mellitus,[25,26] so the long-term outcomes might have shown different results. Taken all together, a future study in a prospective setting seems to be needed to reveal an association between HbA1c level and postoperative outcomes.

According to our results, short-term glycemic control in the preoperative period appeared to be more effective in preventing MINS than long-term control, also leading to a difference in 30-day mortality. These findings suggest that the occurrence of MINS may be involved in the increased mortality of patients with hyperglycemia and the importance of short-term preoperative blood glucose control regardless of the presence chronic hyperglycemia. Furthermore, we estimated the optimal cutoff values for fasting blood glucose and random blood glucose using ROC curve analysis. Despite the low area under the curve, the estimated values were relatively well matched with American Diabetes Association/American Association of Clinical Endocrinology guidelines.[6]

Our study has several limitations. First, with the nature of a single-center, observational study, the results may have been affected by selection bias or unmeasured confounding factors. Because our institutional patients were mostly Asian, ethnic differences could not be considered. In addition, the result might be different according to the types of surgery. Second, perioperative cTn I measurement was not included as a routine clinical practice at our institution. Given that patients with a certain cardiovascular risk usually underwent the test, our results may have been exaggerated, and there may be a difference between the patients with and without cTn I measurement. Preoperative blood sugar and HbA1c tests were also not performed in all patients, and some of our patients had either one of fasting or random glucose level. Indeed, patients with HbA1c level showed higher incidences of underlying disease and MINS compared with those without HbA1, and there is a possibility of selection bias. Third, a detailed preoperative cardiac evaluation, such as left ventricular ejection fraction or coronary artery angiogram, was not available for all patients. Despite

Table 3. Baseline Characteristics, According to Preoperative HbA1c Level

Characteristic	HbA1c ≤6.5% (N=1849)	HbA1c >6.5% (N=2524)	Before IPW		After IPW	
			P Value	SMD	*P* Value	SMD
Preoperative HbA1c, %*	5.8±0.5	7.8±1.4	<0.001	>99		
Time to peak cardiac troponin, d	0.66 (0.10–2.19)	0.66 (0.10–1.85)	0.4	3.6	0.28	3.4
Men	1113 (60.2)	1484 (58.8)	0.37	2.9	0.95	0.2
Age, y	64.3±13.4	67.0±10.5	<0.001	22.3	0.38	2.8
Diabetes mellitus	1535 (83.0)	2524 (100.0)	<0.001	64	<0.001	39.2
Hypertension	1472 (79.6)	2043 (80.9)	0.29	3.3	0.52	2
Chronic kidney disease	428 (23.1)	366 (14.5)	<0.001	22.3	0.97	0.1
Current smoking	168 (9.1)	248 (9.8)	0.44	2.5	0.82	0.7
Current alcohol	304 (16.4)	404 (16.0)	0.73	1.2	0.6	1.7
Previous disease						
Coronary artery disease	430 (23.3)	718 (28.4)	<0.001	11.9	0.68	1.3
Heart failure	69 (3.7)	88 (3.5)	0.73	1.3	>0.99	<0.1
Stroke	222 (12.0)	231 (9.2)	0.003	9.3	0.64	1.5
Arrhythmia	176 (9.5)	228 (9.0)	0.62	1.7	0.96	0.25
Heart valve disease	31 (1.7)	30 (1.2)	0.22	4.1	0.7	1.2
Active cancer	478 (25.9)	932 (36.9)	<0.001	24	0.38	2.9
Preoperative in-hospital care						
Insulin use	370 (20.0)	513 (20.3)	0.83	0.8	0.89	0.5
Intensive care unit	175 (9.5)	131 (5.2)	<0.001	16.5	0.65	1.4
ECMO	0	0				
Continuous renal replacement therapy	17 (0.9)	5 (0.2)	0.002	9.7	>0.99	<0.1
Ventilator	38 (2.1)	29 (1.1)	0.02	7.2	0.95	0.2
Operative variables						
ESC/ESA surgical high risk	309 (16.7)	564 (22.3)	<0.001	14.2	0.58	1.9
Emergency operation	513 (27.7)	413 (16.4)	<0.001	27.7	0.07	5.7
General anesthesia	1510 (81.7)	2054 (81.4)	0.84	0.7	0.93	0.3
Operation duration, h	2.99±2.22	2.92±2.10	0.24	3.6	0.62	1.6
Packed red blood cell transfusion	276 (14.9)	220 (8.7)	<0.001	19.3	0.97	0.1
Continuous infusion of inotropic agents	603 (32.6)	638 (25.3)	<0.001	16.2	0.85	0.6

Data are presented as number (percentage), mean±SD, or median (interquartile range). ECMO indicates extracorporeal membranous oxygenation; ESA, European Society of Anaesthesiology; ESC, European Society of Cardiology; HbA1c, hemoglobin A1c; IPW, inverse probability weighting; and SMD, standardized mean difference.

*Preoperative HbA1c was not retained in multivariable or IPW adjustments.

these limitations, this is the first study to compare the incidence and relevant outcomes of MINS in patients according to glucose and HbA1c levels. The results of the present study may reinforce evidence for future guidelines of glucose control in patients undergoing noncardiac surgery.

Table 4. Incidence of MINS and Mortalities, According to Preoperative HbA1c Level

Variable	HbA1c ≤6.5% (N=1849)	HbA1c >6.5% (N=2524)	Unadjusted OR/HR (95% CI)	*P* Value	Adjusted OR/HR (95% CI)	*P* Value	IPW OR/HR (95% CI)	IPW *P* Value
MINS	470 (25.4)	537 (21.3)	0.79 (0.69–0.91)	<0.001	1.01 (0.86–1.20)	0.89	0.98 (0.85–1.14)	0.8
30-d Mortality	57 (3.1)	64 (2.5)	0.82 (0.57–1.17)	0.28	1.19 (0.81–1.76)	0.38	1.13 (0.78–1.65)	0.52
Cardiovascular death	14 (0.8)	17 (0.7)	0.89 (0.44–1.80)	0.74	1.49 (0.65–3.38)	0.34	1.56 (0.71–3.45)	0.27
Noncardiovascular death	43 (2.3)	47 (1.9)	0.80 (0.53–1.21)	0.29	1.11 (0.91–1.73)	0.66	1.02 (0.66–1.58)	0.92

Data are presented as number (percentage). Multivariable analysis included age, diabetes mellitus, chronic kidney disease, history of coronary artery disease, active cancer, high surgical risk, emergency operation, preoperative intensive care unit treatment, intraoperative packed red blood cell transfusion, and intraoperative inotropic agent use. Diabetes mellitus was retained into multivariable analysis after IPW adjustment. MINS was presented with OR, and mortalities were presented as HR. HbA1c indicates hemoglobin A1c; HR, hazard ratio; IPW, inverse probability weighting; MINS, myocardial injury after noncardiac surgery; and OR, odds ratio.

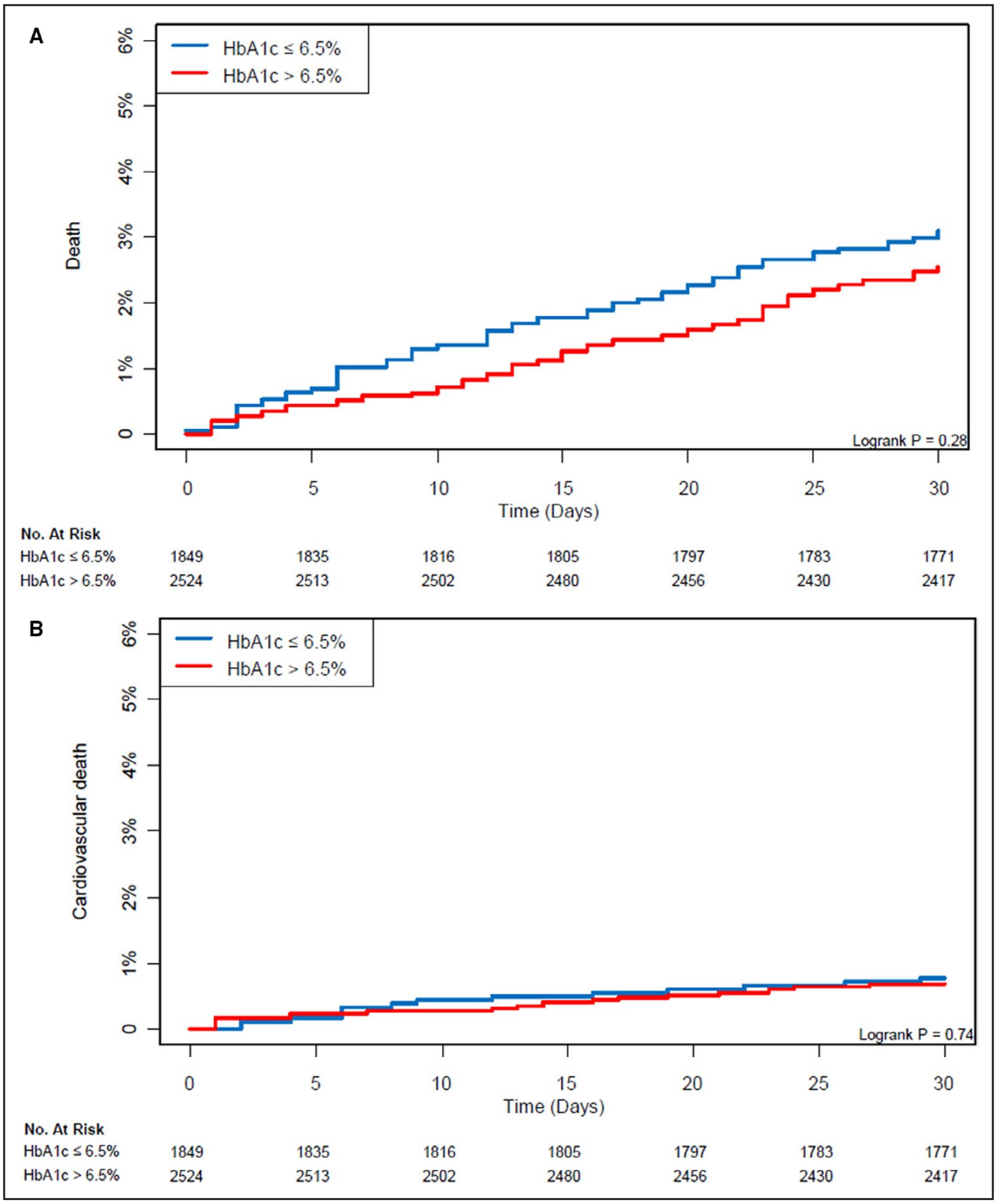

Figure 4. Kaplan-Meier curves of cumulative all-cause mortality (A) and cardiovascular mortality (B) during 30 days after surgery, according to preoperative hemoglobin A1c (HbA1c) level.

CONCLUSIONS

Preoperative hyperglycemia was associated with increased MINS and 30-day mortality, whereas HbA1c was not. Immediate glucose control may be more crucial than long-term glucose control in patients undergoing noncardiac surgery.

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None.

Supplementary Material

Tables S1–S4
Figure S1

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Supplemental Material

Table S1. Types of surgery.

	Normal (N=8,324)	Hyperglycemia (N=3,980)
Vascular	624 (7.5)	318 (8.0)
Orthopedic	1203 (14.5)	513 (12.9)
Neuro	2062 (24.8)	981 (24.6)
Breast or Endo	198 (2.4)	99 (2.5)
Plastic or Otolaryngeal or Eye	291 (3.5)	129 (3.2)
Transplantation	556 (6.7)	181 (4.5)
Gynecology or Urology	577 (6.9)	173 (4.3)
Gastrointestinal	2333 (28.0)	1310 (32.9)
Noncardiac thoracic	453 (5.4)	254 (6.4)
Others	27 (0.3)	22 (0.6)

Table S2. Sensitivity analysis on odds ratio of poorly controlled preoperative blood glucose level for myocardial injury after noncardiac surgery in inverse probability weighting analysis.

	OR (95% CI)	P-value
Patients stratified by fasting glucose (n=7,718)	1.40 (1.25-1.57)	<0.001
Patients stratified by random glucose (n=4,586)	1.21 (1.03-1.41)	<0.001
Patients with diabetes (n=9,440)	1.26 (1.13-1.39)	<0.001
Patients without diabetes (n=2,864)	1.43 (1.17-1.75)	<0.001
Patients with preoperative intensive care unit treatment (n=962)	1.30 (1.01-1.68)	0.04
Patients without preoperative intensive care unit treatment (n=11,342)	1.32 (1.20-1.46)	<0.001

OR, odds ratio; CI, confidence interval

Table S3. Effect of an unmeasured confounder on odds ratio of poorly controlled preoperative blood sugar test level for myocardial injury after noncardiac surgery in inverse probability weighting analysis.

		$OR_{ZY\|X}$					
		1.5	2	2.5	3	3.5	4
	0.3	1.97 (1.80-2.17)	2.20 (2.00-2.42)	2.42 (2.19-2.66)	2.63 (2.38-2.91)	2.84 (2.57-3.15)	3.06 (2.76-3.40)
	0.4	1.88 (1.71-2.06)	2.04 (1.86-2.24)	2.19 (1.99-2.41)	2.33 (2.12-2.57)	2.47 (2.24-2.73)	2.60 (2.36-2.88)
OR_{zx}	0.5	1.82 (1.66-1.99)	1.93 (1.76-2.12)	2.04 (1.86-2.24)	2.14 (1.95-2.36)	2.24 (2.03-2.46)	2.33 (2.12-2.57)
	0.6	1.77 (1.62-1.94)	1.86 (1.70-2.04)	1.94 (1.77-2.12)	2.01 (1.83-2.21)	2.08 (1.89-2.28)	2.14 (1.95-2.36)
	0.7	1.74 (1.59-1.90)	1.80 (1.64-1.97)	1.86 (1.69-2.03)	1.91 (1.74-2.09)	1.96 (1.79-2.15)	2.01 (1.83-2.21)

Prevalence of unmeasured confounder = 40%

Numbers represent ORs (including 95% CIs).

OR, odds ratio; X: dichotomous exposure measure, y dichotomous outcome measure, z: potential dichotomous confounder.

OR_{ZX} indicates the association (OR) between the unmeasured confounder and poorly controlled preoperative blood glucose level.

|$OR_{ZY|X}$ indicates the association (OR) between the unmeasured confounder and myocardial injury after noncardiac surgery.

Table S4. Baseline characteristics and outcomes of patients with and without HbA1c.

	Without HbA1c (N=7,931)	With HbA1c (N=4,373)	P-value
Male	4478 (56.5)	2597 (59.4)	0.002
Age	62.1 (±14.0)	65.9 (±11.9)	<0.001
Diabetes	5381 (67.8)	4059 (92.8)	<0.001
Hypertension	4765 (60.1)	3515 (80.4)	<0.001
Chronic kidney disease	484 (6.1)	794 (18.2)	<0.001
Current smoking	960 (12.1)	416 (9.5)	<0.001
Current alcohol	1620 (20.4)	708 (16.2)	<0.001
Previous disease			
Coronary artery disease	1149 (14.5)	1148 (26.3)	<0.001
Heart failure	126 (1.6)	157 (3.6)	<0.001
Stroke	674 (8.5)	453 (10.4)	0.001
Arrhythmia	486 (6.1)	404 (9.2)	<0.001
Heart valve disease	91 (1.1)	61 (1.4)	0.27
Active cancer	3220 (40.6)	1410 (32.2)	<0.001
Preoperative inhospital care			
Insulin use	1676 (21.1)	883 (20.2)	0.23
Intensive care unit	656 (8.3)	306 (7.0)	0.01
ECMO	0	0	
Continuous renal replacement therapy	45 (0.6)	22 (0.5)	0.74
Ventilator	122 (1.5)	67 (1.5)	>0.99
Operative variables			
ESC/ESA surgical high risk	1505 (19.0)	873 (20.0)	0.19
Emergency operation	2447 (30.9)	926 (21.2)	<0.001
General anesthesia	7138 (90.0)	3564 (81.5)	<0.001
Operation duration, hours	3.11 (±2.19)	2.95 (±2.15)	<0.001
Packed red blood cell transfusion	712 (9.0)	496 (11.3)	<0.001
Continuous infusion of inotropics	2630 (33.2)	1241 (28.4)	<0.001
Outcomes			
MINS	1645 (20.7)	1007 (23.0)	0.003
30-day mortality	249 (3.1)	121 (2.8)	0.27

Data are presented as n (%), mean (±standard deviation) or median (interquartile range)
HbA1c, hemoglobin A1c; ECMO, extracorporeal membranous oxygenation; ESC, European Society of Cardiology; ESA, European Society of Anaesthesiology; MINS, myocardial injury after noncardiac surgery

Figure S1. Association between poorly controlled preoperative blood sugar test level and myocardial injury after noncardiac surgery according to the type of surgery.

Surgery type	Patients number	Odds ratio (95% CI)	P-value	P for interaction
Vascular	942	1.34 (1.00 - 1.78)	0.047	
Orthopedic	1716	1.76 (1.40 - 2.22)	< 0.001	
Neurosurgery	3043	3.14 (2.55 - 3.86)	< 0.001	
Breast, endocrine	297	1.51 (0.86 - 2.63)	0.146	
Plastic, ENT, eye	420	1.33 (0.80 - 2.16)	0.262	
Transplantation	737	1.60 (1.14 - 2.25)	0.006	0.003
OBGY, Urology	750	1.83 (1.23 - 2.69)	0.003	
Gastrointestinal	3643	1.58 (1.33 - 1.88)	< 0.001	
Thoracic	707	1.12 (0.81 - 1.56)	0.483	
Etc.	49	1.98 (0.61 - 6.61)	0.256