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Immediate preoperative hyperglycemia correlates with complications in non-cardiac surgical cases

Sarah M. Dougherty[a,1], **Julie Schommer**[b,1], **Jorge L. Salinas**[c], **Barbara Zilles**[d], **Mary Belding-Schmitt**[a], **W. Kirke Rogers**[e], **Amal Shibli-Rahhal**[b], **Brian T. O'Neill**[b,f,g,*]

[a]Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, IA 52242, USA

[b]Divison of Endocrinology, Department of Medicine, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, IA 52242, USA

[c]Division of Infectious Disease, Department of Medicine, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, IA 52242, USA

[d]Program of Hospital Epidemiology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242, USA

[e]Department of Anesthesiology, University of Minnesota, Minneapolis, MN 55455, USA

[f]Fraternal Order of Eagles Diabetes Research Center and Division of Endocrinology and Metabolism, University of Iowa, Iowa City, IA 52242, USA

[g]Veterans Affairs Health Care System, Iowa City, IA 52242, USA

Abstract

Study objective: Assess for a relationship between immediate preoperative glucose concentrations and postoperative complications.

Design: Retrospective cohort study.

Setting: Single large, tertiary care academic medical center.

Patients: A five-year registry of all patients at our hospital who had a glucose concentration (plasma, serum, or venous/capillary/arterial whole blood) measured up to 6 h prior to a non-emergent surgery.

Interventions: The glucose registry was cross-referenced with a database from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP). We applied

*Corresponding author at: University of Iowa, 169 Newton Road, Iowa City, IA 52242, USA. brian-oneill@uiowa.edu (B.T. O'Neill).

[1] Authors contributed equally.

Author contributions

S.M.D. and J.Sch. wrote the IRB, obtained and researched the database, and wrote the manuscript. B.Z., M.B.S., and J. L. S. helped obtain data from the electronic health record and the ACS NSQIP database. A.S. R. helped design the study, performed all statistical analyses, and helped write the manuscript. W.K.R. helped design the study, obtain data, and helped write the manuscript. B.T.O. designed the study, helped research data, and helped write the manuscript.

Declaration of interest

None.

an outcomes review to the subset of patients for whom we had data from both registries (n = 1774).

Measurements: Preoperative glucose concentration in the full population as well as the subgroups of patients with or without diabetes were correlated with adverse postsurgical outcomes using 1) univariable analysis and 2) full multivariable analysis correcting for 27 clinical factors available from the ACS NSQIP database. Logistic regression analysis was performed using glucose level either as a continuous variable or as a categorical variable according to the following classifications: mild (≥140 mg/dL; ≥7.8 mmol/L), moderate (≥180 mg/dL; ≥10 mmol/L), or severe (≥250 mg/dL; ≥13.9 mmol/L) hyperglycemia. A third analysis was performed correcting for 7 clinically important factors (age, BMI, predicted duration of procedure, sex, CKD stage, hypoalbuminemia, and diabetic status) identified by anesthesiologists and surgeons as immediately available and important for decision making.

Main results: Univariable analysis of all patients and the subgroups of patients without diabetes or with diabetes showed that immediate preoperative mild or moderate hyperglycemia correlates with postoperative complications. Statistical significance was lost in most groups using full multivariable analysis, but not when correcting for the 7 factors available immediately preoperatively. However, for all patients with diabetes, moderate hyperglycemia (≥180 mg/dL; ≥10 mmol/L) continued to significantly correlate with complications even in the full multivariable analysis [odds ratio (OR) 1.79; 95% Confidence Intervals (CI) 1.10, 2.92], and with readmission/reoperation within 30 days [OR 1.93; 95% CI 1.18, 3.13].

Conclusions: Preoperative hyperglycemia within 6 h of surgery is a marker of adverse postoperative outcomes. Among patients with diabetes in our study, a preoperative glucose level ≥ 180 mg/dL (≥10 mmol/L) independently correlates with risk of postoperative complications and readmission/reoperation. These results should encourage future work to determine whether addressing immediate preoperative hyperglycemia can improve complication rates, or simply serves as a marker of higher risk.

Keywords

Hyperglycemia: complications; DM control: glycosylated Hgb; Perioperative insulin: effects; Outpatient surgery contraindications; Postoperative cardiac event: risk factors; Perioperative risk of MI

1. Introduction

Sustained or intermittent perioperative hyperglycemia (blood glucose concentration > 140 mg/dL; 7.8 mmol/L) is estimated to occur in 20–40% of non-cardiac surgery patients [1,2]. Such hyperglycemia has been suggested to be a modifiable, independent predictor of postsurgical complications in patients both with and without diabetes. Indeed, intensive insulin therapy and tight glycemic control in the postoperative period are, in some studies, associated with beneficial outcomes such as a decrease in postoperative infections [3–7].

Although there seems to be a correlation between poor outcomes and sustained hyperglycemia throughout the perioperative period, the predictive effect of immediate preoperative blood glucose levels on outcomes remains poorly studied. In fact, only a

limited number of studies have attempted to specifically estimate the risk of preoperative hyperglycemia on postoperative outcomes, and several include glucose values obtained well over 24 h prior to surgery. A large retrospective study with >61,000 individuals indicated that preoperative hyperglycemia (up to 1 month prior to surgery) strongly correlated with postoperative morbidity, but not after correction for preoperative comorbidities [8]. However, 1-year mortality remained significantly correlated with preoperative hyperglycemia in patients without diabetes, even after correction for comorbidities. Two other studies indicated that postoperative infections are highly correlated with preoperative hyperglycemia or both pre-and postoperative hyperglycemia, even after correction for comorbidities [4,9]. However, other studies did not find a correlation between preoperative glucose and surgical site infections after correction for comorbid conditions [10]. Therefore, target serum glucose levels and an optimal glucose management protocol during the immediate preoperative and perioperative periods are subjects of debate. For example, the Center for Disease Control (CDC) Guidelines for Prevention of Surgical Site infection recommend implementing “peri-operative glycemic control and [using] blood glucose target levels less than 200 mg/dL (11.1 mmol/L) in patients with and without diabetes” [11]; whereas the Society for Ambulatory Anesthesia (SAMBA), the Endocrine Society, the Joint British Diabetes Society, and the Society of Thoracic Surgeons (STS) Practice Guidelines recommend maintaining intraoperative blood glucose levels ≤180 mg/dL (≤10 mmol/L) [5,12–14]; and the Society of Critical Care Medicine (SCCM) advises that insulin treatment be triggered at blood glucose levels ≥150 mg/dL (>8.3 mmol/L) with a goal to maintain blood glucose below that level [15]. No guidelines give a clear threshold value of blood glucose at which postponement of elective surgery should be considered in the absence of severe dehydration, diabetic ketoacidosis, or hyperosmolar non-ketotic states [13], in part because the threshold at which increased risk based on immediate preoperative glucose is not known. Some expert authors have nonetheless strongly recommended that a threshold value of glucose >250 mg/dL (>13.9 mmol/L) warrants postponement of elective surgery [16] – without providing a clear justification for this particular threshold value.

We therefore undertook a study to evaluate whether immediate hyperglycemia (within 6 h prior to the start of anesthesia) before elective surgical procedures was associated with postoperative complications. We also attempted to identify threshold values of hyperglycemia that may inform clinical decision-making and future clinical practice guidelines. We hypothesized that a finding of moderate to severe hyperglycemia immediately prior to elective surgery – regardless of why a serum glucose level was checked, and regardless of whether or not attempts were made to correct the hyperglycemia – would be associated with an increased risk of adverse patient outcomes.

2. Methods

2.1. Study design and data sources

The study was approved by the University of Iowa Healthcare (UIHC) Institutional Review Board (IRB), and the requirement for written informed consent was waived by the IRB. This is a retrospective cohort study using the UIHC electronic health record (EHR, EPIC Systems, Verona, WI) and our local American College of Surgeons’ National Surgical

Quality Improvement Program (ACS NSQIP) database. The UIHC EHR contains complete demographic, clinical, laboratory, and medication data for all patients seen at UIHC – including time-stamped glucose concentrations from whole blood (venous, capillary and arterial), plasma, or serum. It also includes data from surgery, such as the time of induction of anesthesia, time of incision, and end of surgery. The local ACS NSQIP database is maintained by a dedicated Surgical Clinical Reviewer (SCR) nurse who audits all relevant patient charts every 30 days and enters patient-specific preoperative, intraoperative, and postoperative outcome variables for a variety of surgical case types [17]. The local ACS NSQIP database, like its national counterpart, does not include peri-operative glucose values. Thus we had to query the UIHC EHR to identify patients who had a plasma, serum, or whole blood (including capillary) glucose concentration obtained within 6 h of induction of anesthesia for their surgery. The NSQIP database does, however, include complication rates from all vascular and general surgery procedures as well as total hip arthroplasty, total knee arthroplasty and hip fracture repairs, and a sampling of other general surgical procedures performed at UIHC.

2.2. Patients

Using the UIHC EHR, we identified all patients admitted for a noncardiac surgical procedure between January 2015 and January 2020. The EHR was then queried to identify patients who had a plasma, serum, or whole blood glucose concentration obtained within 6 h of their surgery. This patient list was then cross-matched with our local ACS NSQIP database, and only patients who had both a glucose level recorded on the EHR within 6 h prior to the start of anesthesia, and who were included in the ACS NSQIP database, were selected for the study. Emergent surgeries were excluded. If an individual patient underwent multiple surgeries within 30 days, only the first surgery was used for analysis. If a patient had multiple glucose levels recorded within the 6 h preceding surgery, the highest glucose level was used for analysis. When possible, any missing data was filled in by individual EHR chart review.

2.3. Data elements

Relevant demographic and clinical information in the ACS NSQIP database includes, but is not limited to, patient age, sex, race, Body Mass Index (BMI), surgical specialty, elective status of the surgery, inpatient/outpatient status, whether or not the surgery required anesthesia, and American Society of Anesthesiologists (ASA) Physical Status classification. We analyzed only ASA Class I through IV patients, defined as follows – ASA I: healthy patient with no systemic disease; ASA II: mild systemic disease without substantive functional limitations; ASA III: severe systemic disease with substantive functional limitations; ASA IV: severe systemic disease that is a constant threat to life. There were no patients in our cohort with ASA of >IV, as these represent moribund patients who are receiving emergent surgery and are not expected to survive without the operation, or brain-dead patients undergoing organ donation. Full demographic and clinical information are summarized in Table 1 and under "Statistical analyses" listed below.

Lasty, patients were excluded if they did not have laboratory values for serum creatinine and albumin performed within 4 weeks of surgery (See Flow chart 1). Hypoalbuminemia

was defined in our study as an albumin level < 3.5 mg/dL. Chronic Kidney disease (CKD) stage was calculated by determining eGFR via the CKD-*epi* Creatinine equation (https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr#evidence).

2.3.1. Preoperative glucose and diabetes status—Patients were classified as having diabetes or not according to ACS NSQIP Guidelines: either a documented history of diabetes needed to appear on the medical record preoperatively, or the patient needed to have a documented use of oral hypoglycemic medication or insulin preoperatively. Patients with diabetes were subcategorized as not insulin dependent (DM - Ins) or insulin dependent (DM + Ins), although we were unable to further determine whether patients had Type 1 or Type 2 diabetes.

Hemoglobin A1C (HbA1C) percentage is not needed as a diagnostic criterion according the ACS NSQIP Guidelines and thus not routinely obtained for patients in the database. Therefore only a minority of patients in our combined dataset had HbA1C percentage values documented within 6 weeks of their surgical procedure (see Table 1). However, since HbA1C percentage is recognized by the American Diabetes Association (ADA) as the major tool for assessing long-term glycemic control, and has been demonstrated to have strong predictive value for diabetes complications [18] and potentially surgical outcomes [19–21], we did extract it from the EHR and included it in our analyses whenever possible.

2.3.2. Definitions of hyperglycemia and post-operative complications—Glycemic levels were divided into four categories, based on the ADA guidelines for glycemic targets in hospitalized patients [18]. In the most recent guidelines, hyperglycemia in the hospital is defined as >140 mg/dL and recommended optimal glycemic targets are <180 mg/dL, but can range from <140 mg/dL in cardiac surgical patients to <250 mg/dL in specialized cases (such as with severe comorbidities and when frequent glucose monitoring is challenging). These targets are mostly consistent with many other guidelines and expert opinion [11,12,14,15,20,21]. Glycemic levels were categorized as normal (≤140 mg/dL; ≤7.8 mmol/L), mild hyperglycemia (141–180 mg/dL; 7.8–10 mmol/L), moderate hyperglycemia (181–250 mg/dL; 10–13.9 mmol/L), and severe hyperglycemia (>250 mg/dL; >13.9 mmol/L). We also conducted a Receiver Operating Characteristics (ROC) analysis of pre-operative glucose as a predictor of overall post-operative complications. The analysis yielded an Area Under the Curve (AUC) of 0.6. The optimal cut-off glucose found through this analysis was 141 mg/dL (7.8 mmol/L), which was consistent the lowest cut-off chosen based on published literature.

A post-operative complication was defined according to ACS NSQIP criteria, and included any of the following: surgical site infection (SSI – this includes superficial SSI, Deep SSI, Organ space SSI and wound disruption), pneumonia, *Clostridioides difficile* infection, sepsis, septic shock, deep vein thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular accident, progressive renal insufficiency, acute renal failure, urinary tract infection, unplanned intubation, ventilator dependency for 48 h, and cardiopulmonary resuscitation. See Table 2 for numbers of complications in each group.

2.4. Statistical analyses

Statistical analyses were conducted using SAS for Windows, version 9.3 (SAS Institute Inc., Cary, NC, USA). All continuous variables were subjected to Shapiro Wilk's test of normality, and variables not found to be normally distributed were reported as median (Interquartile Range; IQR). We began by examining patient characteristics and evaluating the glucose distribution within the patient groups. We then performed 4 different logistic regression analyses for the following reasons:

1. A univariable simple analysis to evaluate the effect of preoperative glucose on postoperative complications, and to identify whether any relationship existed.

2. Full multivariable: analyses using the variables available in the NSQIP databases aligned with the patient's glucose for comparison: age (years), BMI (kg/m^2), duration of procedure (minutes), sex (Female/Male), CKD stage (1 to 5), hypoalbuminemia (present/absent), diabetic status (no diabetes or diabetes, and subcategorized as DM - Ins or DM + Ins), race (Asian, Black, Hispanic, White, Other), inpatient (87%) or outpatient (13%) status after procedure, elective surgery where the patient is brought from home for a non-urgent/non-emergent procedure (yes 72%/no 28%), type of anesthesia (general/other), ASA physical status (I to VI), functional status (independent 97%/partially dependent 2%/totally dependent 1%), smoking status within 1 year (yes/no), dyspnea (none 91%/dyspnea upon moderate exertion 8%/dyspnea at rest 1%), COPD (present/absent), ventilator dependency >48 h prior to procedure (yes 0.3%/no 99.7%), ascites within 30 days of surgery (present/absent), hypertension requiring medication (present/absent), new or acute exacerbation of congestive heart failure (CHF) within 30 days of surgery (present/absent), disseminated cancer (present/absent), bleeding disorder (present/absent), open wound (present/absent), immunosuppressant use for chronic condition (present/absent), 10% loss of body weight in 7 months prior to surgery (present 4%/absent 96%), transfused within 72 h of surgery (present/absent), and systemic inflammatory response syndrome (SIRS)/sepsis/septic shock within 48 h of surgery (present/absent). The full multivariable analyses were repeated for the following three outcomes: 1) composite infections (Superficial SSI, Deep SSI, Organ space SSI, Wound disruption, Pneumonia, *Clostridioides difficile* infection, Sepsis, Septic shock, Urinary Tract Infection (UTI)); 2) readmission or reoperation within 30 days; 3) death within 30 days.

3. Limited multivariable: This analysis used a limited number of predictor variables that were generated by a literature search and a survey of local surgeons and anesthesiologists to identify simple and easily accessible preoperative variables that were felt to be most relevant when determining the likelihood of perioperative complications. The variables in this analysis were: age (years), BMI (kg/m^2), duration of procedure (minutes), sex (Female/Male), CKD stage (1 to 5), hypoalbuminemia (present/absent), and diabetic status (no diabetes, DM - Ins, or DM + Ins). These variables were chosen and set prior to analysis to avoid bias.

4. Full multivariable with HbA1C within 1 month: analyses using the variables listed for the full multivariable in addition to HbA1C. We chose to conduct this analysis separately because only 649 patients had a HbA1C measurement within 1 month of surgery. We thought the additional data afforded by analyzing a model with HbA1C percentages would be useful even if less statistically powerful than the evaluation of the larger dataset which did not include these values.

We also conducted subgroup analyses on patients without diabetes and patients with diabetes, further subcategorized as not on insulin (DM - Ins) or on insulin (DM + Ins). For these analyses, we used the variables listed for the full multivariable analysis without "diabetes status" since the subgroups were defined based on this variable. This represented a different attempt to stratify patients with diabetes in the absence of adequate HbA1C values.

For each of the analyses listed above, serum glucose was studied as a continuous variable and as a categorical variable first to assess for the general presence of an association with postsurgical complications. If an association was detected, the analyses were repeated using serum glucose at the pre-specified cutoffs listed in "Definitions of hyperglycemia and post-operative complications" above. The purpose of the latter analyses was to try to define a practical glucose cut-off that could be used in the design of future interventional studies.

Using size effect estimates from existing literature [8,9] and G*Power software [22], a post-hoc power analysis for the full multivariable logistic regression was performed ($n = 1774$). The analysis yielded an estimated power of 0.86 for effect of hyperglycemia (defined both as a glucose of >140 mg/dL and > 180 mg/dL) on the composite post-operative complication end point.

3. Results

3.1. Demographics and serum glucose concentrations

Patient demographics and pre-surgical characteristics are presented in Table 1. While the different patient groups demonstrated statistically significant differences in some of their baseline clinical characteristics and post-surgical outcomes, it is important to note that these patient groups were not directly compared to each other in any of the subsequent outcome analyses, and that the multivariable regression analyses adjusted for baseline variables within each group. We were able to identify 3394 patients who both had a glucose value measured in the 6-h pre-surgical time frame and who were included in the ACS NSQIP database at the University of Iowa from January 2015 to January 2020. Prior to a recent quality improvement project and policy change at our hospital, immediate pre-operative glucose testing was not protocolized (levels could be checked at the discretion of anesthesiology, surgery, or pre-op nursing providers, and usually were drawn if the patient was known to have diabetes or there was other reason to suspect dysglycemia). 489 emergent surgical cases were then excluded from this study, and 1131 patients did not have a serum creatinine or albumin measured within 4 weeks of the procedure, resulting in a final study population of 1774 patients (see Flow chart 1).

The median age of the patient population was 64 years, and was slightly higher in patients with diabetes compared to patients without diabetes (Table 1). The median BMI was 31.8, with patients with diabetes having a higher BMI than patients without diabetes (34.9 versus 27.8, respectively). DM + Ins patients were more likely to have CKD stage 4–5 compared to DM - Ins (13.3% vs 4.7%, respectively). ASA physical status was also highest in the DM + Ins group. Lastly, HbA1C measured within 1 month of surgery was only available in 11% of patients without diabetes and in 57% of patients with diabetes, but the vast majority showed well-controlled diabetes with a median HbA1C of 7.2% even in the DM + Ins subgroup (Table 1). But, patients with reasonably controlled HbA1C levels did not always arrive with a well-controlled preoperative glucose. Among patients with a HbA1C ≤8.0% within 1 month of surgery, 10.4% had a glucose >180 mg/dL immediately prior to surgery. In addition, 49 of the 99 patients who had an HbA1C that was >8.0% had a glucose level < 180 mg/dL immediately prior to surgery.

Of the 1774 patients, most (n = 1254, 71%) had a pre-operative glucose less than 140 mg/dL (7.8 mmol/L) prior to surgery (Fig. 1A). Of the 520 patients with a pre-operative glucose greater than 140 mg/dL (7.8 mmol/L), 450 (87%) had a preoperative-diagnosis of diabetes. The median preoperative serum glucose concentration for purportedly nondiabetic patients was 103 mg/dL compared to 136 mg/dL for patients with known diabetes. Patients treated with insulin also showed higher median glucose levels: for DM - Ins it was 129 mg/dL, and for DM + Ins 147 mg/dL (Table 1). Of the 782 patients without diabetes, over 90% had a preoperative glucose concentration less than 140 mg/dL(7.8 mmol/L), whereas among the group with diabetes, 81% had a preoperative serum glucose concentration of less than 180 mg/dL (10 mmol/L) (Fig. 1B). Severe hyperglycemia (serum glucose greater than 250 mg/dL [13.9 mmol/L]) was noted in 57 (3.2%) patients, including 7 (0.9%) purportedly nondiabetic patients, 11 (1.9%) DM - Ins, and 39 (9.4%) DM + Ins.

3.2. Analyses of glucose as a continuous variable and within glycemic categories

Composite post-operative infections (SSI, pneumonia, *Clostridioides difficile*, UTI, sepsis, and septic shock) were the most common complication in our cohort (Table 2). But, given the low number of individual complications, analyses were performed with all complications combined. Univariable analyses of the entire cohort (n = 1774) revealed a positive correlation between glucose and postoperative complications, both with glucose as a continuous variable (Fig. 2A) and when classified into normal, mild, moderate, and severe glycemic categories (Fig. 2B). However, this correlation was lost with the full multivariable analysis whether HbA1C was included or not (Fig. 2). Interestingly, the association between glucose within glycemic categories remained significant when correcting for the subjectively chosen risk criteria of age, sex, BMI, diabetic status, low albumin, CKD stage, and duration of surgery (Table 3, limited multivariable analysis), indicating that these factors alone do not account for the increased risk in our patient population.

Table 3 shows the results for the subgroup analyses using glycemic categories. In individuals without diabetes, neither the full multivariable nor limited multivariable analyses showed a correlation between glycemic category and postoperative complications. By contrast, in individuals with diabetes, the limited multivariable analyses showed a significant association

between hyperglycemia and complications, but this correlation was lost with correction for all 27 factors in the full multivariable analysis. When individuals with diabetes were further subdivided into DM - Ins (n = 577) and DM + Ins (n = 415), the full multivariable analyses did not show correlations.

3.3. Analysis using individual glycemic categories

Given that our univariable analyses indicated a correlation between glycemic category and postoperative complications, we sought to determine whether a specific glucose cut-off (140, 180 or 250 mg/dL) best predicted post-operative complications in each of our individual subgroups. Shown in Fig. 3 are the results of these full multivariable logistic regression analyses using the previously described glycemic cutoffs.

In all patients, as well as patients with/without diabetes, a glucose concentration ≥ 140 mg/dL (≥7.8 mmol/L) showed no significant risk of postoperative complications when correcting for the 27 clinical factors in the full multivariable analysis (Fig. 3A). Similarly, if a glucose cutoff of ≥250 mg/dL (≥13.9 mmol/L) was used, there was no increased risk in the full cohort or subgroups (Fig. 3C). However, correlations between preoperative moderate hyperglycemia (≥180 mg/dL, ≥10 mmol/L) and postoperative complications were most striking in patients with diabetes. Even using the full multivariable analysis, patients with diabetes with a preoperative glucose level ≥ 180 mg/dL (≥10 mmol/L) showed a significant 1.79 (95% CI 1.10–2.92) odds ratio of having a postoperative complication (Fig. 3B). In subgroup analyses, the odds ratio of postoperative complications with moderate hyperglycemia in the DM - Ins (OR 2.00, CI 0.94–4.25) and DM + Ins (OR 1.68, CI 0.73–3.87) groups lost significance indicating that patients on noninsulin therapy and those treated with insulin both contribute to the increased risk.

In an effort to determine if the increased complication risk was restricted to infections or extended also to risk of reoperation/readmission or death within 30 days, we performed a secondary analysis using these outcomes. Full multivariable logistic regression analysis (excluding HbA1C) was performed using the prespecified glycemic cutoffs. Composite infections (Superficial SSI, Deep SSI, Organ space SSI, Wound disruption, Pneumonia, *Clostridioides difficile* infection, Sepsis, Septic shock, UTI) showed no correlation with mild or severe glycemia, although moderate hyperglycemia in patients with diabetes tended to increase correlation (Table 4). Moderate hyperglycemia (≥180 mg/dL) was significantly correlated with readmission or reoperation within 30 days in all patients and in just those patients with diabetes (Table 4). There were few deaths in our population and neither mild, moderate, nor severe hyperglycemia correlated with death within 30 days. These data demonstrate that immediate preoperative hyperglycemia is an indicator of higher risk for postoperative complications that can be used with other important preoperative clinical data. Furthermore, in our cohort, moderate hyperglycemia remains an independent risk factor for patients with diabetes when glucose levels are above ≥180 mg/dL (10 mmol/L).

3.4. Anesthesia type, CKD stage, duration of surgery and sepsis contribute to increased risk of complications

Other factors found to be significantly related to postoperative complications using the full multivariable analysis included Anesthesia type with odds ratio (OR) of 2.17 (CI 1.12, 4.19), CKD stage with OR of 1.24 (CI 1.03, 1.50), Duration of Surgery with OR of 1.004 (CI 1.003, 1.006), and Sepsis with OR of 2.81 (CI 1.73, 4.57).

4. Discussion

In this retrospective analysis of patients undergoing non-emergent, non-cardiac surgery, elevated glucose levels obtained in the immediate preoperative period (up to 6 h prior to induction of anesthesia) were associated with an increase in postoperative complications, as defined by the ACS NSQIP database. The most significant finding was that glucose levels equal to or above 180 mg/dL(10 mmol/L) in patients with diabetes independently correlated with increased risk of complications.

We hypothesized that hyperglycemia in the immediate pre-operative period would be associated with an increased risk of complications relative to patients who also had a glucose concentration checked but were not hyperglycemic. Indeed, our findings do show that *if* glucose concentration is evaluated (for whatever justification) in the immediate pre-operative period, a higher value is associated with an increased risk of complications relative to patients who also had their glucose level checked but were not found to be hyperglycemic. The fact that this association remained significant in the entire cohort when correcting for 7 subjectively chosen factors that surgeons and anesthesiologists felt were relevant indicates that hyperglycemia provides some added information about risk. However, the relationship was lost in a full multivariable analysis that included 27 patient factors used to judge severity of illness in the ACS NSQIP database.

To some degree, our findings suggest that fasting hyperglycemia already serves as a marker of “sicker” patients who are likely to have other illnesses or end-organ dysfunction that places them at higher risk of postoperative complications. We find support for such a theory in the multitude of studies demonstrating that HbA1C percentage levels – a marker of long-term diabetes control – correlate with the risk of postoperative complications [1,19,23], although this is not a universally identified finding [24]. Our study could suggest that HbA1C level may not fully capture the risk of hyperglycemia prior to surgery. Indeed, 10.4% of patients in our study with a HbA1C ≤8.0% arrived with a glucose ≥180 mg/dL immediately prior to surgery, indicating that a small but significant portion of patients with “good” glycemic control can arrive on the day of surgery with hyperglycemia. Furthermore, 49 of the 99 patients who had an HbA1C that was >8.0% actually had a glucose level < 180 mg/dL immediately prior to surgery, making it important for future studies to define whether immediate preoperative glucose imparts a separate risk beyond HbA1C. Unfortunately, due to the relatively small proportion of our population who HbA1C level measured within 1 month of surgery, we cannot fully evaluate this. Prior studies have suggested up to 20–30% of patients presenting for elective non-cardiac surgery have undiagnosed diabetes or pre-diabetes, and that such previously undiagnosed patients have higher fasting glucose levels compared with patients with diabetes [18,25]. It may therefore be that some of

our patients classified as “no diabetes” would have been recognized as belonging in the group with diabetes had a more rigorous screening regimen been performed, such as that recommended by the American Diabetes Association [18]. This may have also affected the apparent relationship between fasting hyperglycemia and postoperative outcomes in our study.

Guideline documents often use threshold values of glucose concentration. Logistic regression analyses in our study using individual glucose cutoffs in both the full cohort of patients and subgroups of patients as separated by diabetic status clearly identified 180 mg/dL (10 mmol/L) as a potential threshold for diabetic patients who have their serum glucose level checked pre-operatively, above which the risk of complications increases significantly. A previously published retrospective review showed that in non-cardiac, non-vascular surgery patients, preoperative blood glucose levels >200 mg/dL (11.1 mmol/L) were associated with a 2.1-fold increased risk in overall 30-day mortality [21]. In agreement with our results, a much larger retrospective analysis by Abdelmalek, et al., of >61,000 patients demonstrated that preoperative hyperglycemia (measured up to 1 month prior to surgery) is significantly correlated with postoperative complications – but not after correction for preoperative comorbidities. However, 1-year mortality after surgery was significantly related to preoperative blood glucose measured up to 1 month prior to surgery in this retrospective study [8]. The study by Abdelmalek, et al., further showed that a majority of this increased risk of postoperative complications came from patients without a known diagnosis of diabetes, which contradicts our own results. There are many differences in the populations studied which may account for the different results, including but not limited to lower rates of CHF, COPD, and cancer in our group of patients with diabetes. The findings of our study are also partially contradicted by a publication of 229 general and vascular surgery patients which demonstrated that preoperative blood glucose levels (measured up to 24 h before surgery) were not correlated with post-operative surgical site infections, whereas a preoperative HbA1C value >7% and a postoperative capillary glucose value ≥180 mg/dL (10 mmol/L) were associated [10]. Interestingly, in that study the odds ratio of SSI when preoperative glucose was ≥180 mg/dL was still 1.92 (CI 0.78–4.76) in elective procedures but did not reach significance, perhaps due to a lower sample number. Lastly, another study of patients *without* diabetes in the NSQIP database indicated that preoperative hyperglycemia was correlated with an increased risk of surgical site infections [9].

These prior studies, like our own, could not determine whether treatment of hyperglycemia will be beneficial or detrimental. Some previous studies in both surgical and non-surgical populations have shown that attempts at tight blood glucose control can perversely worsen outcomes (presumably by causing dangerous hypoglycemia) [23,26–28]. However, other studies indicate that coordinated preoperative care for diabetes by a clinical program focused on controlling glucose before and after surgery can reduce antibiotic use 24 h after surgery and reduce hypoglycemia in patients with diabetes [29]. Nonetheless, future research should focus on whether treating hyperglycemia – using insulin immediately pre-procedure to bring serum glucose levels below threshold values such as 140 mg/dL (7.8 mmol/L) or 180 mg/dL (10 mmol/L) – can change the risk of postoperative complications, or if preoperative hyperglycemia is simply a marker of unmodifiable risk.

Our study has many limitations, the most significant of which are that 1.) there was no standardized procedure for determining from which patients a serum, plasma, or whole blood glucose concentration would be obtained; 2.) the vast majority of elective surgical patients at our institution did not have an immediate preoperative glucose level available (n = 41,216); and 3.) we could not evaluate whether attempts were made to control hyperglycemia pre-, intra-, or postoperatively. We were also unable to obtain data on other important risk factors for infection or complication such as intraoperative hypothermia, specific type of procedure, history of coronary artery disease, or surgical approach. We are therefore unable to determine whether or how our sample subpopulation differs from all patients presenting for elective surgery at our institution. While we cannot use our data to make recommendations as to which patients should have a glucose concentration checked pre-operatively nor does this tell us whether treating hyperglycemia might affect patient outcomes, we do identify hyperglycemia ≥180 mg/dL as a significant marker of risk in patients with diabetes that is not accounted for by most other clinical factors.

In conclusion, our study demonstrates a clear association between hyperglycemia within 6 h of elective surgery and the risk of adverse postoperative outcomes in patients who had a glucose level measured for unknown reasons. In multivariable analyses, preoperative hyperglycemia by itself is not as predictive of adverse outcomes as other factors such as CKD stage and duration of surgery, but nonetheless, our data show that among patients with diabetes in our study, a preoperative glucose level ≥ 180 mg/dL (≥10 mmol/L) has a very high and statistically independent correlation with risk of postoperative complications and readmission/reoperation rates. Our study and others clearly identify preoperative hyperglycemia as a marker of postoperative complications that needs further investigation to clarify whether a precise glycemic cutoff indeed increases risk and may provide potential benefit from treatment. Our findings should prompt further studies that may help inform clinical decision-making on the day of surgery for patients with hyperglycemia and may be relevant for future guideline documents.

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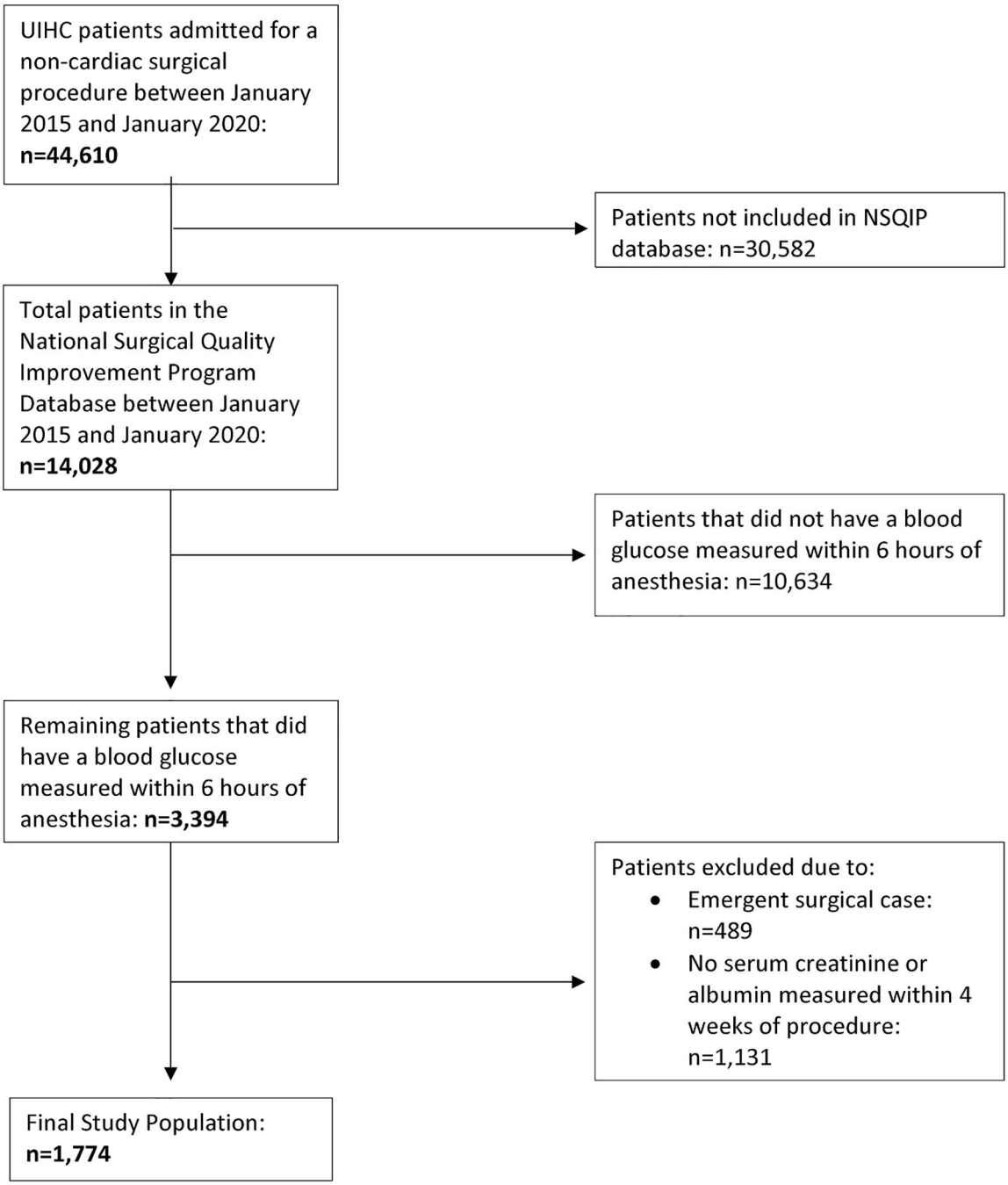

Flow chart 1.
Flow chart for inclusion of patients into the retrospective cohort study.

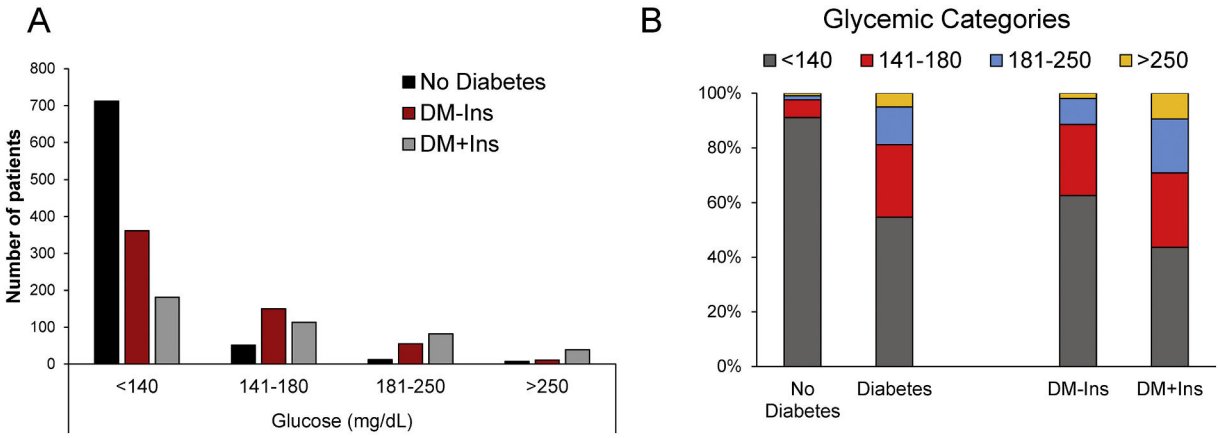

Fig. 1. Glycemia in the patient population and glycemic categories in subgroups.

(A) Number of patients with glucose levels separated into glycemic categories in No diabetes, DM - Ins, and DM + Ins subgroups. (B) Percent of patients in defined glycemic categories within each subgroup. (DM - Ins – patients with diabetes treated with medications other than insulin; DM + Ins – patients with diabetes treated with insulin).

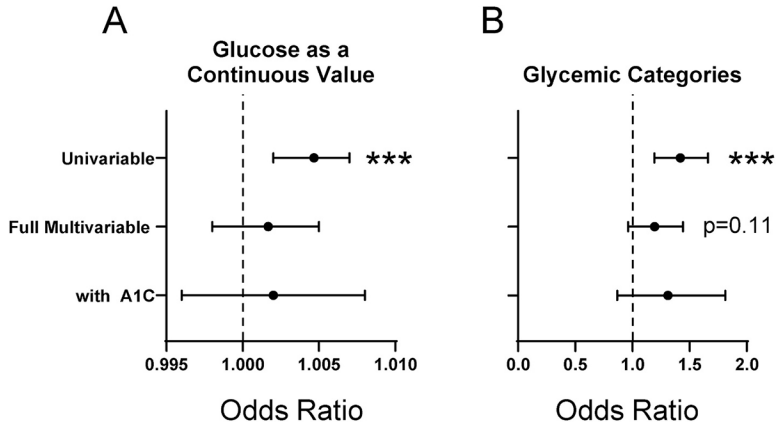

Fig. 2. Immediate preoperative hyperglycemia correlates with increased risk of postoperative complications.

Odds ratios from logistic regression analysis correlating glucose level drawn within 6 h of anesthesia as a continuous variable (A) or correlating glucose within specified categories (B) to postoperative complications. ***$p < 0.001$.

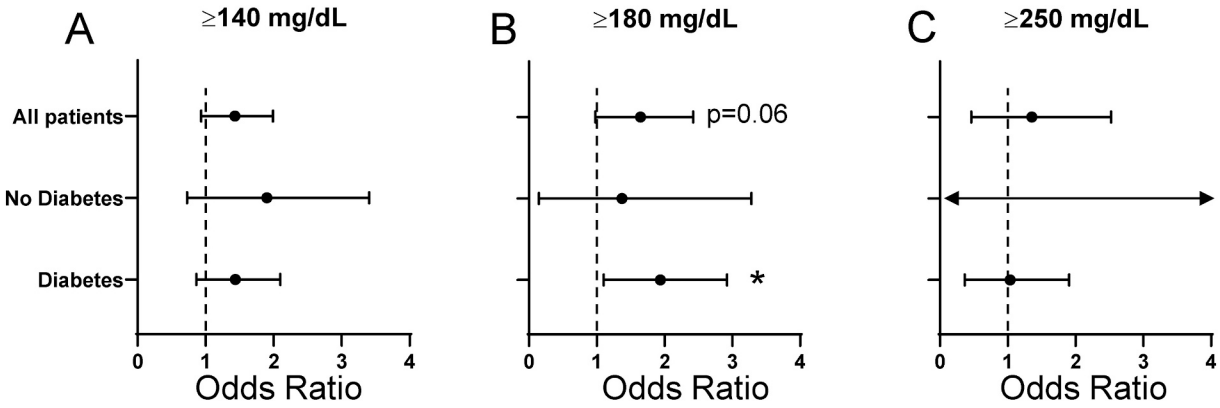

Fig. 3. Moderate (>180 mg/dL; >10 mmol/L) preoperative hyperglycemia correlates with postoperative complications in patients with diabetes.

Odds ratios from logistic regression analysis using glycemic cutoffs of mild ≥140 mg/dL (≥7.8 mmol/L)(A), moderate ≥180 mg/dL (≥10 mmol/L)(B), or severe ≥250 mg/dL (≥13.9 mmol/L)(C) in all patients, non-diabetic patients and patients with Diabetes using full multivariable analysis. *$p < 0.05$.

Table 1

Summary of preoperative patient characteristics.

Factor	All Patients (*n* = 1774)	No Diabetes (*n* = 782)	Diabetes (*n* = 992)	DM − Ins (n = 577)	DM + Ins (n = 415)
Glucose (mg/dL)	117 (48)	103 (27)	136 (57) *	129 (44)	147 (71)#
Age	64 (17)	63 (22)	65 (15) *	64 (16)	65 (14)
BMI	31.8 (12.6)	27.8 (9.8)	34.9 (11.6) *	35.7 (11.3)	34.1 (12.0)#
Female gender	57.2%	57.0%	57.3%	58.4%	55.7%
Race					
Caucasian	91.7%	90.9%	92.2%	93.4%	90.6%
African American	4.2%	4.6%	3.9%	3.1%	5.1%
Hispanic	2.5%	2.6%	2.4%	2.1%	2.9%
Asian	0.85%	0.89%	0.81%	0.69%	0.96%
Other	0.79%	1.02%	0.65%	0.69%	0.48%
Proportion with Hemoglobin A1C available	36.6%	11%	57% *	55%	59%
Hemoglobin A1C					
	6.7% (1.5)	6.0% (1.0)	6.8% (1.5) *	6.5% (1.4)	7.2% (1.8)#
Duration of Procedure (min)	152 (135)	157 (140)	146 (133)	146 (122)	148 (147)
General Anesthesia	81%	92%	73%	69%	77%
ASA Physical Status					
I	1.2%	2.8%	0% *	0%	0%
II	27.9%	35.4%	22.1% *	28.2%	13.3%#
III	63.9%	54.7%	71.1% *	68.5%	74.7%#
IV	7.0%	7.0%	7.0%	3.3%	12.0%#
V and VI	0%	0%	0%	0%	0%
CKD Stage					
1	34.7%	37.3%	32.6% *	35.7%	28.2%#
2	31.7%	32.9%	30.7%	34.3%	25.8%#
3	26.2%	23.4%	28.4% *	25.3%	32.8%#
4	4.7%	3.8%	5.3%	3.5%	8.0%#

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Factor	All Patients (*n* = 1774)	No Diabetes (*n* = 782)	Diabetes (*n* = 992)	DM − Ins (n = 577)	DM + Ins (n = 415)
5	2.8%	2.6%	2.9%	1.2%	5.3%#
Albumin < 3.5	19.7%	27.9%	13.3%*	9.0%	19.3%#
Smoker	15.4%	19.6%	12.2%*	10.7%	14.2%
COPD	6.3%	8.0%	4.8%*	4.3%	5.5%
Hypertension	67.1%	47.1%	83.0%*	83.2%	82.7%
CHF	1.4%	1.3%	1.4%	0.17%	3.1%#
ARF	0.23%	0.38%	0.1%	0%	0.24%
Ascites	1.5%	2.2%	0.9%*	0.35%	1.7%#
Cancer	8.8%	10.9%	7.2%*	7.1%	7.2%
Immunosuppressants	9.0%	12.3%	6.4%*	3.5%	10.4%#
Bleeding disorder	6.3%	6.5%	6.1%	4.3%	8.7%#
Transfused (pre-op)	1.4%	2.2%	0.7%*	0.3%	1.2%
SIRS/sepsis/septic shock	8.6%	13.8%	4.5%*	3.5%	6.0%

DM − Ins, Diabetes not treated with insulin; DM + Ins, Insulin-treated diabetes; see Methods for other abbreviations and ASA categories.

Values are presented as median (IQR) or percentages as appropriate. (*-$p < 0.05$ vs. No diabetes; #-p < 0.05 vs. DM − Ins. It is important to note that patient groups were not directly compared to each other in subsequent outcome analyses. Multivariable regression analyses adjusted for baseline variables within each group.)

Table 2

Summary of raw numbers of postoperative complications.

Postoperative complications	All Patients (n = 1774)	No Diabetes (n = 782)	Diabetes (n = 992)	DM − Ins (n = 577)	DM + Ins (n = 415)
Superficial SSI	44	25	19	9	10
Deep SSI	10	3	7	3	4
Organ space SSI	45	23	22	17	5
Wound disruption	7	2	5	3	2
Pneumonia	25	14	11	6	5
C. diff infection	20	10	10	4	6
Sepsis	34	12	22	11	11
Septic shock	15	6	9	4	5
UTI	32	10	22	9	13
Composite infections	232	105	127	66	61
DVT	23	15	8*	4	4
PE	15	8	7	5	2
MI	13	4	9	2	7#
CVA	8	2	6	3	3
Progressive renal insufficiency	16	6	10	4	6
ARF	13	4	9	4	5
Unplanned intubation	34	15	19	7	12
Ventilator dependency	22	11	11	5	6
CPR	9	2	7	2	5
Total complications	385	172	213	102	111
Reoperation/Readmission	234	96	138	73	65
Death	33	16	17	5	12

These included: surgical site infections (SSI), wound disruption, pneumonia, *Clostridioides difficile* (C. diff) infection, sepsis, septic shock, deep vein thrombosis (DVT) pulmonary embolism (PE), myocardial infarction (MI), cerebrovascular accident (CVA) progressive renal insufficiency, acute renal failure (ARF), urinary tract infection (UTI), unplanned intubation, ventilator dependency for 48 h and cardiopulmonary resuscitation (CPR). (*-$p < 0.05$ vs. No diabetes; #-$p < 0.05$ vs. DM − Ins. Patient groups were not directly compared to each other in any of the subsequent outcome analyses).

Table 3

Odds ratios for complications correlated to Glucose as a Categorical Variable (glucose levels were binned into 4 categories: normal, mild, moderate, or severe according to Methods section 2.3.2).

Analysis	All (n=1774)	No Diabetes (n=782)	Diabetes (n=992)	DM − Ins (n=577)	DM+Ins (n=415)
Univariable	**1.41 *** (1.19, 1.66)**	1.42 (0.93, 2.16)	**1.46 *** (1.19, 1.78)**	**1.48 * (1.06, 2.06)**	**1.35 * (1.04, 1.76)**
Limited Multivariable	**1.32 ** (1.09, 1.60)**	1.38 (0.90, 2.11)	**1.33 ** (1.08, 1.65)**	1.15 (0.79, 1.66)	**1.38 * (1.05, 1.83)**
Full Multivariable	1.18 (0.96, 1.44)	1.07 (0.65, 1.75)	1.23 (0.98, 1.55) p=0.07	1.06 (0.71, 1.59)	1.21 (0.88, 1.66)
Full Multivariable with HbA1C (n=649)	1.25 (0.87, 1.81)	ND	1.27 (0.86, 1.87)	1.93 (0.71, 5.26)	1.13 (0.68, 1.89)

Results presented as point estimate (confidence interval).

*-p < 0.05

**-*p* < 0.01

***-*p* < 0.001

ND - Not detectable with OR < 0.001.

Table 4

Odds ratio of composite infections, readmission or reoperation, or death related to mild, moderate, or severe hyperglycemia.

		Composite Infections	Readmission or Reoperation	Death
All Patients	≥140 mg/dL	1.29 (0.88, 1.89)	1.26 (0.88, 1.81)	0.79 (0.33, 1.91)
	≥180 mg/dL	1.54 (0.97, 2.45)	**1.80 ** (1.16, 2.78)**	0.36 (0.09, 1.39)
	≥250 mg/dL	0.97 (0.43, 2.20)	1.28 (0.62, 2.67)	ND
No Diabetes	≥140 mg/dL	1.11 (0.50, 2.50)	1.17 (0.54, 2.56)	0.07 (0.00, 2.75)
	≥180 mg/dL	0.67 (0.14, 3.13)	0.66 (0.14, 3.12)	ND
	≥250 mg/dL	ND	ND	ND
Diabetes	≥140 mg/dL	1.34 (0.85, 2.11)	1.19 (0.77, 1.82)	1.23 (0.40, 3.84)
	≥180 mg/dL	1.64 † (0.99, 2.72)	**1.93 ** (1.18, 3.13)**	0.39 (0.07, 2.13)
	≥250 mg/dL	1.14 (0.48, 2.69)	1.66 (0.76, 3.63)	1.75 (0.20, 15.3)

Results presented as point estimate (confidence interval).

† – $p = 0.053$

** -$p < 0.01$.

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