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Short Communication J Clin Med Res. 2023;15(5):268-273

# Timing of Postoperative Stroke and Risk of Mortality After Noncardiac Surgery: A Cohort Study

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## Abstract

**Background:** Postoperative stroke is a devastating complication of surgery, given its association with severe long-term disability and mortality. Previous investigators have confirmed the association of stroke with postoperative mortality. However, limited data exist regarding the relationship between the timing of stroke and survival. Addressing this knowledge gap will help clinicians develop tailored perioperative strategies to reduce the incidence, severity, and mortality associated with perioperative stroke. Therefore, our objective was to determine whether the timing of postoperative stroke influenced mortality risk.

**Methods:** We performed a retrospective cohort study of patients > 18 years who underwent noncardiac surgery and developed postoperative stroke during the first 30 days of surgery (National Surgical Quality Improvement Program Pediatrics 2010 - 2021). Our primary outcome was 30-day mortality following the occurrence of postoperative stroke. We subdivided patients into two mutually exclusive groups: early and delayed stroke. Early stroke was defined as the occurrence within 7 days following surgery, consistent with a previous study.

**Results:** We identified 16,750 patients who underwent noncardiac surgery and developed stroke within 30 days of surgery. Of these, 11,173 (66.7%) had an early postoperative stroke (≤ 7 days). Perioperative physiological status, operative characteristics, and preoperative comorbidities were generally comparable between patients with early and delayed postoperative stroke. Despite the comparability in these clinical characteristics, the mortality risk was 24.9% for early and 19.4% for delayed stroke. After adjusting for perioperative physiological status, operative characteristics, and preoperative comorbidities, early stroke was associated with an increased mortality risk (adjusted odds ratio: 1.39, confidence interval: 1.29 - 1.52, P-value < 0.001). In patients with an early postoperative stroke, the most common preceding complications were bleeding requiring transfusion (24.3%), followed by pneumonia (13.2%) and renal insufficiency (11.3%).

**Conclusions:** Postoperative stroke tends to occur within 7 days following noncardiac surgery. Such timing of postoperative stroke carries a higher mortality risk, suggesting that targeted efforts to prevent stroke should focus on the first week following surgery to reduce the incidence and mortality associated with this complication. Our findings contribute to the growing understanding of stroke after noncardiac surgery and may help clinicians develop tailored perioperative neuroprotective strategies to prevent or improve treatment and outcomes of postoperative stroke.

**Keywords:** Stroke; Mortality; Surgery

Manuscript submitted February 4, 2023, accepted March 16, 2023
Published online May 31, 2023

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doi: https://doi.org/10.14740/jocmr4877

## Introduction

Postoperative stroke is a devastating complication because it is associated with severe long-term disability, impaired quality of life, and postsurgical mortality [1, 2]. Previous studies of mortality associated with postoperative stroke have focused on events occurring within 30 days of surgery, thereby missing the significance of stroke occurring early in the post-surgery period [3-5]. Patients who suffer early postoperative stroke may have distinct perioperative profiles from those who develop stroke later in the postsurgical period [6]. For example, stroke occurring within a few days of surgery may reflect severe immediate perioperative physiological perturbations, while delayed postoperative stroke may have medical underpinning.

Despite the advances in medical technology and surgical practice over the past decades, surgery continues to carry a risk of major complications. Traditional metrics of surgical quality based on either surgical complications or mortality alone have progressively lost their discriminatory properties, especially because they fail to distinguish between high-performing institutions [7]. To overcome such limitations, quality improvement initiatives have relied on predicting mortality among the subset of patients developing major complications. Evaluating mortality following complication is more reliable to benchmark hospital performance and surgical care, especially when surgery continues to carry a risk of complications. Among major perioperative complications, stroke is of clinical significance because it is associated with an elevated risk of mortality and morbidity [3].

Despite the high fatality rates for perioperative stroke, we are unaware of a study identifying the clinical profile of patients at the greatest risk of failure to rescue following the occurrence of perioperative stroke. Addressing this knowledge gap is timely because it would inform the prognosis for the subset of patients who develop perioperative stroke. In addition, it would inform clinicians on factors requiring heightened attention and customize perioperative risk mitigation to individual surgical profile and cardiovascular risk factors.

Research has shown that, on average, perioperative stroke occurs within 7 days after surgery [8]. Whether stroke occurring within this time frame is associated with a higher risk of death compared to stroke occurring later has not been previously explored. A key aspect of perioperative care is understanding the timing of postoperative complications to develop early diagnosis and deploy prompt management. Identifying whether early stroke portends a poorer prognosis will provide healthcare workers with the empirical basis for developing tailored management, including aggressive perioperative stroke prevention strategies.

Therefore, our objective was to determine whether the timing of postoperative stroke influenced mortality risk. We hypothesized that early postoperative stroke carries a higher mortality risk compared to delayed stroke.

## Materials and Methods

### Study design

This was a retrospective cohort study using data from the American College of Surgeons (ACS) National Surgical Quality Improvement Program Pediatrics (NSQIP) participant user files from 2010 to 2021. This study was approved by the Institutional Review Board (IRB) of the Ohio State University; the IRB waived the requirement for written informed consent. ACS NSQIP is an internally validated ongoing data-driven quality management initiative that collects more than 300 perioperative variables, including biological and clinical characteristics and postoperative morbidity and mortality events. To ensure high-quality and standardized data collection, clinical reviewers who undergo structured continuing education and routine audits by the NSQIP committee collect patient data from medical records by adhering to standard definitions, resulting in low disagreement rates (most recently, 2%) [8]. Collection of data points uses a systematic sampling design to reduce selection bias and improve representation, allowing the NSQIP to be a complete and reliable surgical database. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

### Study population

Our study population included adults (age > 18 years) who developed postoperative stroke following surgery. Stroke was defined as an embolic, thrombotic, or hemorrhagic cerebrovascular event with motor, sensory, or cognitive dysfunction that persists for ≥ 24 h.

### Study outcomes

Our primary outcome was mortality among patients who developed postoperative stroke. To account for the timing of stroke, we subdivided patients into two mutually exclusive groups: early stroke and delayed stroke (referent group). Early stroke was defined as the occurrence of stroke within 7 days of surgery, consistent with a previous study [9].

### Statistical analyses

We presented categorical variables as frequency and column percentage. To test our hypothesis of whether early stroke carries a higher mortality risk, we used multivariable logistic regression models, with the results presented as odds ratio (OR) and 95% confidence intervals (CIs). We adjusted our analyses for variables that were selected based on a review of clinical research regarding perioperative stroke. The targeted patient characteristics included in the analysis were age (< 65, 65 -74, 75 - 84, ≥ 85), sex (male vs. female), body mass index (normal (18.5 - 24.9 kg/m$^2$), underweight (< 18.5 kg/m$^2$), overweight (25.0 - 29.9 kg/m$^2$), obese (≥ 30 kg/m$^2$)), American Society of Anesthesiologists (ASA) physical status class (≥ 3 vs. < 3), ventilator dependence (yes vs. no), emergency surgery (yes vs. no), systemic sepsis (none, systemic inflammatory response syndrome, sepsis, or septic shock) and other binary variables providing information about the patient's preoperative comorbidities including dialysis dependence, current tobacco use, diabetes mellitus (oral or insulin therapy), congestive heart failure within 30 days before surgery, history of chronic obstructive pulmonary disease requiring chronic bronchodilator therapy, history of myocardial infarction within 6 months before surgery, and hypertension requiring medication. We used Stata, version 16 (Stata-Corp) to perform statistical analysis, and P values ≤ 0.05 were considered statistically significant.

### Sample size estimation

We expected that early stroke would increase mortality risk by a minimum of 30% (OR: 1.3) [10]. We estimated that 2,423 observations are needed to test the difference in mortality risk between patients who developed early and delayed postoperative stroke, using a two-sided alpha level of 0.05 test with 80% power [11].

## Results

We identified 16,750 patients who underwent noncardiac sur-

**Table 1.** Characteristics of 16,750 Patients ≥ 18 Years of Age or Older Who Developed Stroke After Noncardiac Surgery (NSQIP 2010 - 2019)

| Characteristics | No. of patients (%) | | |
|---|---|---|---|
| | Overall | Early postoperative stroke (≤ 7 days following surgery) | Delayed postoperative stroke (> 7 days following surgery) |
| Study population | 16,750 (100.0) | 11,173 (66.7) | 5,577 (33.2) |
| Male sex | 8,122 (48.5) | 5,390 (48.2) | 2,732 (49) |
| Age | | | |
| < 65 | 4,939 (30.4) | 3,300 (30.4) | 1,639 (30.3) |
| 65 - 74 | 4,911 (30.2) | 3,280 (30.2) | 1,631 (30.2) |
| 75 - 84 | 4,209 (25.9) | 2,824 (26) | 1,385 (25.6) |
| ≥ 85 | 2,193 (13.5) | 1,441 (13.3) | 752 (13.9) |
| Body mass index (kg/m$^2$) | 27 (24 - 32) | 27 (23 - 32) | 28 (24 - 32) |
| ASA classification ≥ 3 | 14,762 (88.4) | 9,882 (88.7) | 4,880 (87.8) |
| Diabetes mellitus | | | |
| None | 11,823 (70.6) | 7,948 (71.1) | 3,875 (69.5) |
| Noninsulin | 2,409 (14.4) | 1,512 (13.5) | 897 (16.1) |
| Insulin | 2,518 (15) | 1,713 (15.3) | 805 (14.4) |
| Systemic sepsis | | | |
| None | 13,828 (82.7) | 9,243 (82.9) | 4,585 (82.4) |
| Systemic inflammatory response syndrome | 1,463 (8.7) | 992 (8.9) | 471 (8.5) |
| Sepsis | 795 (4.8) | 492 (4.4) | 303 (5.4) |
| Septic shock | 635 (3.8) | 429 (3.8) | 206 (3.7) |
| Smoker within 1 year of surgery | 3,663 (21.9) | 2,457 (22) | 1,206 (21.6) |
| Ventilator-dependent | 732 (4.4) | 538 (4.8) | 194 (3.5) |
| Emergency case | 3,354 (22.3) | 2,287 (22.7) | 1,067 (21.4) |
| On dialysis prior to surgery | 667 (4) | 398 (3.6) | 269 (4.8) |
| Functional dependency | 2,016 (12.1) | 1,280 (11.6) | 736 (13.3) |
| Congestive heart failure | 776 (4.6) | 487 (4.4) | 289 (5.2) |
| History of severe COPD | 1,770 (10.6) | 1,155 (10.3) | 615 (11) |
| Hypertension requiring medication | 12,468 (74.4) | 8,272 (74) | 4,196 (75.2) |
| Weight loss prior to surgery | 533 (3.5) | 322 (3.2) | 211 (4.2) |
| Transfusion 72 h before surgery | 758 (4.5) | 514 (4.6) | 244 (4.4) |
| Ascites | 176 (1.1) | 102 (0.9) | 74 (1.3) |
| Renal failure | 286 (1.9) | 179 (1.8) | 107 (2.1) |

ASA: American Society of Anesthesiologists; COPD: chronic obstructive pulmonary disease.

gery and developed stroke following surgery (mean number of days between surgery and stroke = 7 days). Of these, 11,173 (66.7%) had an early postoperative stroke (≤ 7 days). Less than half of the patients were male (48.5%); the median body mass index (BMI) was 27 (interquartile range (IQR) 24 - 32). Thirty percent of patients were younger than 65, and 13.5% were ≥ 85. Most patients had an ASA classification ≥ 3 at the time of surgery. The most common comorbidity was hypertension (74.4%). These perioperative physiological statuses, operative characteristics, and preoperative comorbidities were generally comparable between patients with early and delayed postoperative stroke (Table 1).

Table 2 summarizes the associations between the timing of stroke and survival. The overall surgical mortality rate was 23.1% (n = 3,868). The mortality risk was 24.9% for early and 19.4% for delayed stroke. After adjusting for perioperative physiological status, operative characteristics, and preoperative comorbidities, early stroke was associated with an increased mortality (adjusted OR: 1.39, CI: 1.29 - 1.52, P-value < 0.001).

**Table 2.** Associations Between Timing of Stroke and Surgical Mortality Among 16,750 Patients Who Developed Postoperative Stroke After Non-Cardiac Surgery

| | Mortality n/N (%) | Crude | | Multivariable | |
|---|---|---|---|---|---|
| | | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Delayed postoperative stroke | 1,083/5,577 (19.4) | Reference | | Reference | |
| Early postoperative stroke | 2,785/11,173 (24.9) | 1.38 (1.27, 1.49) | <0.01 | 1.39 (1.29, 1.52) | <0.01 |

Adjusted analyses were controlled for age, sex, body mass index, American Society of Anesthesiologists (ASA) physical status class, ventilator dependence, emergency surgery, systemic sepsis and other binary variables providing information about the patient's preoperative comorbidities including dialysis dependence, current tobacco use, diabetes mellitus, congestive heart failure within 30 days before surgery, history of chronic obstructive pulmonary disease requiring chronic bronchodilator therapy, history of myocardial infarction within 6 months before surgery, and hypertension requiring medication. OR: odds ratio; CI: confidence interval.

## Discussion

In this retrospective study of patients who underwent major surgical procedures, we identified (for the first time) the critical impact of the timing of postoperative stroke on surgical mortality. Specifically, we found that early postoperative stroke (stroke within 7 days of surgery) was more common than delayed postoperative stroke. We also observed that stroke within the first week of surgery was associated with a 1/4 likelihood of postsurgical mortality. Taken together, these suggest that targeted efforts to prevent stroke should focus on the first seven postoperative days to reduce incidence and mortality associated with postsurgical stroke. Finally, we identified a few perioperative factors (age > 85 years, systemic sepsis, acute renal failure, bleeding requiring transfusion, and postoperative pneumonia) that when present, significantly increased the risk of stroke-related mortality among patients with early stroke compared to those who developed delayed stroke.

Stroke remains one of the leading causes of death in the United States [1, 2]. Postoperative stroke is particularly devasting given that stroke survivors not only have to contend with recovery from surgery, but they may be left with profound neurological deficits and reduced quality of life. Reports on postoperative stroke have paid little emphasis on its timing [4]. Our finding that timing of postoperative stroke is not only important because majority of cerebrovascular events occurred withing the first week of surgery, but also that stroke within this time frame carried higher risk of postsurgical death than delayed stroke. These findings may help design perioperative approaches to reduce the risk of postoperative stroke and mitigate its occurrence as well as improve outcomes through appropriate allocation of resources. Implementing appropriate treatment after complications is a critical component of patient rescue and, thus, quality of surgical care [12]. Given that patients who suffered postoperative stroke must have had a variable period of normal neurological function after surgery and anesthesia, it is imperative to deploy intensive stroke preventions strategies during the early postoperative period [13].

The mortality rate of 24.3% for early stroke in the current study is higher than the risk of mortality associated with postoperative myocardial infarction (19.3%) and is near the upper limit of mortality rates found in a study incorporating 37 high-volume centers (0.0-25.0%) [14, 15]. The high mortality associated with early postoperative stroke may be a reflection of severe physiological perturbation during surgery and the early postsurgical period. Delayed recognition of stroke due to the residual effects of general anesthesia and postoperative analgesia may also be contributory. Our findings highlight the need for further research to improve perioperative techniques and therapies geared toward reduction of postoperative stroke especially with targeted efforts within the first week of surgery.

### Limitations

Interpreting the results of this study requires consideration of its limitations. In this study, postoperative stroke was defined as an embolic, a thrombotic, or a hemorrhagic cerebrovascular event with motor, sensory, or cognitive dysfunction occurring after surgery [16]. This definition overlooks silent cerebral infarctions, which may be more important than previously realized. Also, the retrospective design of this study means that causality can only be inferred, not proven. This design is also likely to introduce heterogeneity into our findings, especially since identification and recording of complications were within the sole purview of NSQIP. Consequently, the database does not contain information that may be relevant to the risk of postoperative strokes, such as genetics, exposure to environmental factors, and socioeconomic status. Also worthy of noting is that the NSQIP database does not contain information relevant to intraoperative factors, such as aortic access sites, incidence of hemodynamic variability, nor the detailed record of blood and medication administration. Furthermore, not all CPT codes across all surgical specialties are captured by NSQIP; our assessment was based on the available codes in this dataset. Finally, the NSQIP does not report information on the site of care, precluding us from understanding the role of hospital factors on mortality risk across subpopulation defined by the timing of stroke. Despite these limitations, the NSQIP database is one of the most rigorously collected and complete clinical databases in the United States. Furthermore, the use of data from multiple centers across the nation improves the generalizability of our findings.

### Conclusion

Based on large multi-institutional data, we conclude that early postoperative stroke is more common and more lethal than delayed stroke. Future investigations are necessary to identify and develop diagnostic and therapeutic measures to reduce the incidence of early postoperative stroke.

## Acknowledgments

This work was presented at the 2021 annual ASA meeting.

## Financial Disclosure

Internal departmental funds.

## Conflict of Interest

None to declare.

## Informed Consent

IRB waived the requirement for written informed consent.

## Author Contributions

Dr. Christian Mpody and Dr. Olubukola Nafiu helped with the idea conception, study design, critical review of literature, data acquisition and analyses, and manuscript preparation and revision. Dr. Onaopepo Kola-Kehinde, Dr. Hamdy Awad, Dr. Sujatha Bhandary, Dr. Michael Essandoh, Dr. Demicha Rankin, Dr. Antolin Flores, and Dr. Ronald Harter helped with the idea conception, interpretation of the data and provided critical revisions for important scientific contents. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## Data Availability

The authors declare that data supporting the findings of this study are available within the article.

## Abbreviations

ACS: American College of Surgeons; CI: confidence interval; NSQIP: National Surgical Quality Improvement Program Pediatrics; OR: odds ratio

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