The Effect of Enhanced Recovery After Surgery (ERAS®) on Individuals with Diabetes

by

Zaina Harb Albalawi

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

Department of Medicine
University of Alberta

Abstract

Individuals with diabetes experience higher postoperative morbidity and mortality. This thesis aims to evaluate the effect of a multimodal care pathway package; the Enhanced Recovery after Surgery (ERAS®) program, on those with diabetes. The first section systematically evaluated the state of the evidence, and found a lack of robust evidence assessing the impact of ERAS® in the diabetes population.

To address a knowledge gap, the second section of this thesis focused on analyzing the "real-world" findings of implementing ERAS® program on length of stay (LOS) and postoperative outcomes in the province of Alberta in a retrospective cohort of *all* colorectal surgical patients and the diabetes subgroup while accounting for secular trends overtime utilizing an interrupted time series (ITS) model. The diabetes subgroup did not demonstrate any benefit post implementation of ERAS® for 12 months, but reassuringly, no harm was observed in any of the postoperative outcomes. Future intervention studies are still required to improve postoperative outcomes in colorectal surgical patients with diabetes. On the other hand, despite a lower LOS post ERAS® in the full cohort, the ITS analysis found this to be secondary to a background trend predicted by the 12-month period preceding ERAS® and may not be directly attributable to ERAS® program implementation. This unexpected finding is contrary to the ERAS® literature and necessitates further evaluation of the impact of ERAS® program in real world settings, using robust study designs.

Preface

Chapter 2 of this thesis has been published as Albalawi Z, Laffin M, Gramlich L, Senior P, McAlister FA, "Enhanced Recovery After Surgery (ERAS$^{(®)}$) in Individuals with Diabetes: A Systematic Review," World Journal of Surgery, vol. 41, issue 8, 1927-1934. I was responsible for the concept formation, data collection and manuscript composition; F.A McAlister, L. Gramlich, P. Senior contributed to study design, and manuscript edits. M. Laffin assisted with data collection.

The research project in Chapter 3 received research ethics approval from the University of Alberta Research Ethics Board, Study Title "The effect of introducing Enhanced Recovery After Surgery (ERAS) protocol on outcomes in patients with diabetes in Alberta: An interrupted time series analysis", No. Pro00058134 and Pro00058134_AME2, July 2016. A manuscript from Chapter 3 has been published as Albalawi Z, Gramlich L, Nelson G, Senior P, Youngson E, McAlister FA, "The Impact of the Implementation of the Enhanced Recovery After Surgery (ERAS$^{®}$) Program in an Entire Health System: A Natural Experiment in Alberta, Canada," World Journal of Surgery, 2018 Mar 12. doi: 10.1007/s00268-018-4559-0. [Epub ahead of print]. F.A McAlister and myself were responsible for concept formation, analysis design, and manuscript composition. Erik Youngson contributed to analysis design and conducted the analysis, and F.A McAlister was the supervisory author. L. Gramlich, G. Nelson and P. Senior contributed to manuscript edits.

Dedication

This work is dedicated to all my patients with diabetes and their families.

Acknowledgement

I would like to thank my supervisor, Dr. Finlay McAlister, for his guidance and efforts in making this work come to light. I am sincerely grateful for his endless support and dedication throughout this process, his patience and investment in revising manuscripts, and teachings on how to develop robust study designs and meaningful research. His mentorship has been invaluable. I would also like to extend my thanks to my co-supervisors, Dr. Leah Gramlich; for her unconditional support, enthusiasm and encouragement from the very beginning, her role was instrumental in facilitating this work, and Dr. Peter Senior; a special debt of gratitude for his support, personal guidance and thoughtful advice throughout this journey. His encouragement to pursue new opportunities was what sparked the beginning of this work.

I am grateful for Erik Youngson and Jeff Bakal for their valuable help with the statistical planning and analysis, as well as Edwin Rogers for his work in establishing case definitions that facilitated analysis of the administrative database.

Finally, my deepest gratitude goes out to my family: my parents (Sanaa & Harb) for their constant support in so many ways and their belief in me, my sisters and brothers who were always there for me to push me forward when I needed it the most, and my wonderful children (Jude, Jassem and Noor) for their understanding. Last but by no means least, to Mohammad, my friend, my supporter and my amazing husband.

1 Table of Contents

List of Tables

List of Figures

1 Chapter 1: Introduction

Literature Review

1.1.1 Surgical Risk in Individuals with Diabetes

Epidemiology

The prevalence of diabetes in surgical patients is estimated to be 10-15%, and up to 40% in some specialties such as bariatric surgery.(1–3) People with diabetes are more likely to require surgery compared to those without diabetes, and with the prevalence of diabetes in adults estimated at 8.8% worldwide [425 million people] and an expected rise in these numbers over the upcoming decades, the surgical burden of this population is expected to increase as well.(4) Furthermore, extensive evidence suggests diabetes to be an independent risk factor for developing colorectal cancer, the 2nd most common cancer worldwide for which colorectal surgery remains a cornerstone of management, and this becomes relevant at a population level given the prevalence of diabetes.(5–10)

Surgical Morbidity and Mortality

It is well recognized that individuals with diabetes are a high-risk surgical population with longer hospital stays, higher health care resource utilization, and greater perioperative morbidity and mortality.(9,11–15) Substantial evidence supports the association between diabetes and postoperative infections.(16–20) Among surgical patients, surgical site infections (SSI) are the most common cause of nosocomial infections and are associated with longer hospital stays and postoperative morbidity. They are also one of the leading causes of morbidity in colorectal surgery.(21,22) Ata and colleagues reported the incidence of SSI in colorectal surgery as 11.6% (95% CI, 11.1–12.2%) compared to a lower incidence in general surgery (3.3%, 95% CI, 3.2–3.4%), and

the incidence of SSI was significantly higher in individuals with diabetes (15.4% vs. 11.0%, $p < 0.001$).(18)

It is also worth noting that diabetes impacts prognosis of colorectal cancer;(23) a common underlying disease in colorectal surgery patients.(24,25) In addition to an observed increase in 30-day mortality –adjusted hazard ratio HR; 1.17, 95% CI 1.01-1.35, P = 0.03,(26) - overall mortality is also increased in the presence of diabetes. In a meta-analysis evaluating the association between diabetes and colorectal cancer all-cause mortality, cancer specific mortality and disease-free survival, 21 observational studies with 216,981 colorectal cancer patients were included. All-cause mortality was found to be higher with a relative risk (RR)=1.17; 95% CI: 1.09-1.25, cancer specific mortality RR = 1.12; 95% CI: 1.01-1.24, and disease-free survival was found to be lower (RR=1.54; 95% CI: 1.08-2.18) in the diabetes group. In the same meta-analysis, excluding metastatic disease revealed an even stronger association between diabetes and mortality: all-cause mortality (RR=1.32; 95% CI: 1.21-1.44) and cancer-specific mortality (RR=1.27; 95% CI: 1.06-1.52).(9) Whether the association found between diabetes and mortality is in part influenced by the surgical risk is unclear.

Pathophysiology and Mechanisms Impacting Morbidity and Mortality in Diabetes

Hyperglycemia, a hallmark of diabetes, is one of the main underlying mediators of postoperative morbidity. An association between hyperglycemia and infections – particularly surgical site infections- is well established.(15) Chronic and acute hyperglycemia cause a relative state of immunosuppression mediated through neutrophil and monocyte dysfunction (27-29). Disruption in inflammatory cytokine cascades with

an increase in IL-6 and TNF-α in response to hyperglycemia has also been identified resulting in oxidative stress, endothelial dysfunction and a prothrombotic state.(27–30) Whether the pathophysiological mechanisms underlying type 2 diabetes are independent risk factors for overall mortality and cancer-specific mortality observed is still unclear, however hyperinsulinema, and altered insulin-like growth factor I (IGF-I) signalling and its binding proteins may have a role in tumorigenesis and metastasis with the expression of insulin and IGF-1 receptors on most cancer cells.(6,7,9,31–36)

1.1.2 Evolution of Surgical Care and Enhanced Recovery Protocols

Background

Since the introduction of the concept of "fast track surgery" by Kehlet in Denmark in the 1990s,(37) the approach to improving surgical outcomes has evolved from single interventions to multimodal pathways involving multidisciplinary teams.(37–39) Over the past 2 decades, the evolution in understanding the physiological stress incurred during surgery and its association with postoperative outcomes has led to advancements in interventions focused on modifying the underlying surgical stress response to impact postoperative outcomes. Although enhanced recovery protocols have been used across different surgical specialties, colorectal surgery has been the leading specialty to apply and evaluate enhanced recovery protocols, hence the abundance of evidence seen in this area, particularly in colorectal cancer surgery.(38) Multiple enhanced recovery protocols have been developed and evaluated, and various terms are used to describe them such as enhanced recovery after surgery (ERAS), fast-track, multimodal, rapid or accelerated recovery programs.(40) These various enhanced recovery protocols share the same objective of implementing a multimodal protocol designed to reduce surgical stress with elements targeting the preoperative, intraoperative

and postoperative periods.(40) The objective of these enhanced recovery protocols is to speed up recovery, decrease postoperative morbidity, and to allow early discharge from acute care settings without an increase in 30-day readmission rates.

With the divergence between actual practice and best practice based on the available evidence, and the increase in heterogeneous enhanced recovery protocols, a group of academic surgeons established the Enhanced Recovery After Surgery (ERAS®) Study Group in 2001.(38) The ERAS® Study Group –currently known as the ERAS® Society- developed and published the first ERAS® colonic surgery protocol in 2005, with the latest update released in 2012.(41,42) Multiple ERAS® protocols followed expanding across various surgical specialties,(43) and the ERAS® Interactive Audit System (EIAS) developed by the ERAS® Society allows monitoring adherence and auditing of the implementation program for ongoing improvements.(38)

The ERAS® Program

The ERAS® program includes 22 components of preoperative, intraoperative and postoperative care, which have been evaluated using The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework and found to have a strong recommendation.(41,44,45) The *preoperative ERAS elements* include: preadmission counseling, fluid and carbohydrate loading, no prolonged fasting, no/selective bowel preparation, antibiotic prophylaxis, thromboprophylaxis, no premedication; *intraoperative elements:* short-acting anesthetic agents, mid-thoracic epidural anesthesia/analgesia, no drains, avoidance of salt and water overload, maintenance of normothermia (body warmer/warm intravenous fluids; and *postoperative elements:* mid-thoracic epidural (anesthesia/analgesia), no nasogastric tubes, prevention

of nausea and vomiting, avoidance of salt and water overload, early removal of catheter, early oral nutrition, non-opioid oral analgesia, early mobilization, stimulation of gut motility, audit of compliance and outcome.(42) The evidence base and recommendations for each of these individual elements are outlined in the ERAS® guidelines.(42,45) A structured implementation program, ongoing audit, and adherence to ERAS® >70% have been shown to be associated with a reduction in LOS and postoperative complications in the largest ERAS® registry analyses to date, and sustaining those benefits overtime.(24,25,46,47)

ERAS® vs. Other Enhanced Recovery Protocols

There are multiple surgical protocols other than ERAS® such as fast track and enhanced recovery protocols that have been evaluated in surgical patients.(40,48) Most of these studies are limited by the heterogeneity and significant variation in the completeness of descriptions of their protocols.(48) ERAS® is distinguished among other protocols with its structured perioperative care program –including the implementation program and the ERAS® Interactive Audit System audit tool. Additionally, multiple centers have reported cost savings after ERAS® implementation,(49–56) and to our knowledge it is the only enhanced recovery program thus far to report an increase in 5-year cancer-specific survival after colorectal cancer surgery.(57) Controversy however remains on whether all the ERAS® components are necessary to have an impact on postoperative outcomes, and results of studies attempting to identify a shorter list have been inconsistent.(58–62) Nonetheless, within the ERAS® literature "adherence" to the ERAS® program and laparoscopic approach have been consistent findings associated with improved postoperative outcomes, highlighting the advantages of implementing the whole package.(24,25,56,57,63)

The Evidence Base For The ERAS® Program

The evidence base for ERAS® is incomplete. To date, there are no randomized controlled trials evaluating the ERAS® program developed by the ERAS® Society in colorectal surgery. Frequently reported outcomes in the literature on the magnitude of effect of ERAS program (as it relates to reductions in postoperative LOS, complications and 30 day events) were extrapolated from meta-analyses of RCTs examining enhanced recovery protocols other than that developed by the ERAS® Society (i.e. ERAS®), or uncontrolled observational studies of ERAS®. Examining a recent systematic review and meta-analysis with the largest number of RCTs included (16 RCTs, N=2,376), revealed that the protocols utilized were heterogeneous, and the mean number of elements included in each protocol was 10 (range 4 to 13), and 9 of the included RCTs were rated to have moderate to high risk of bias.(40,64) All except two of the included trials were from single centers,(58,65) and over half had small sample sizes (<100 patients). Publication bias was not identified. ERAS was found in this systematic review to shorten LOS by -2.28 days (95 % CI -3.09 to -1.47), without increasing readmission rates. A significant reduction in overall morbidity was also observed RR=0.60, (95 % CI 0.46-0.76). Several systematic reviews on the effectiveness of enhanced recovery programs in colorectal surgery have been published, however majority of included trials were of poor quality, used heterogeneous protocols and varying definitions of morbidity which precludes determining reliability and external validity of these findings.(66–70)

1.1.3 Diabetes and ERAS®

Effectiveness of ERAS® in Individuals with Diabetes

To our knowledge it is unknown whether individuals with diabetes would benefit from an ERAS® program. Despite the reported benefits of ERAS® implementation on postoperative outcomes, extremely limited evidence exists about its effect in individuals with diabetes.(40) Previous trials have excluded those with diabetes perhaps due to concerns about aspiration risk (due to diabetic gastroparesis) or severe hyperglycemia.(71–76) A systematic review, presented in chapter 2 of this thesis, reviews the entirety of the evidence for ERAS® in individuals with diabetes.(77) Whether patients with diabetes should be included in ERAS® has been a controversial issue resulting in varying clinical practice and guideline recommendations.(42,78–82)

Controversial Element of the ERAS® Program: Carbohydrate Loading Preoperatively

Carbohydrate loading is in the form of a drink consumed up to 2 hours preoperatively, this is to counteract metabolic stress, insulin resistance, and protein catabolism resulting from fasting overnight, which has been linked to worse postoperative outcomes.(71,83–87) Both surgery and general anesthesia cause a neuroendocrine stress response resulting in hyperglycemia and a catabolic metabolic profile.(82) Recommendations supporting the safety of a carbohydrate load preoperatively in individuals *without* diabetes are based on meta-analyses of RCTs where gastric volumes were found to be small, and gastric pH high following a carbohydrate drink; a desirable effect indicating rapid gastric emptying of the carbohydrate drink and a lower risk of aspiration pneumonia.(88,89) Furthermore, an analysis from an

international multicenter ERAS® registry of 2,352 surgical patients identified carbohydrate and fluid loading to be associated with a shorter hospital stay (OR=0.89, p=0.001).(24) In individuals with diabetes enrolled in an ERAS® program, an uncontrolled analysis of a prospective cohort of 106 consecutive patients undergoing colorectal surgery at one of the Alberta surgical sites was conducted to evaluate the impact of consumption of a preoperative carbohydrate load on preoperative glycemic control and postoperative outcomes. Compliance with the carbohydrate drink was only 43%, and there was no significant difference in mean preoperative glucose levels between those who were compliant and those who were not (8.3mmol/l [SD=3.2] vs. 8.1mmol/l [SD=3.1] respectively; LOS was also similar between both groups (median 5 days (IQR 2-7) vs. 4 days (IQR 2-10.5); p=0.96) respectively. The authors of this prospective non-inferiority study concluded that consumption of a preoperative carbohydrate drink was non-inferior to overnight fasting.(81)

However, there are potential risks to carbohydrate loading in individuals with diabetes such as higher risks of aspiration pneumonia due to delayed gastric emptying. Hyperglycemia and its sequelae is another concern in individuals with diabetes, as the underlying insulin resistance and altered insulin secretion -which is inherent to type 2 diabetes pathophysiology-, and insulin deficiency –inherent to type 1 diabetes- would hinder a normal physiological response to a carbohydrate load. It is uncertain whether the abnormal response to a carbohydrate load may negate any beneficial effects from the other elements of ERAS®. An additional consideration is the heterogeneous response to a carbohydrate load within each subtype of diabetes (i.e. long duration of type 2 diabetes and poor glycemic control on insulin might suggest progressive disease and inability to tolerate a carbohydrate load. Similarly, individuals with poorly-controlled and brittle type

1 diabetes might not be able to safely account for a carbohydrate load preoperatively without subsequent hyper- or hypoglycemia). Whether carbohydrate loading is essential or possibly detrimental for those with diabetes requires further investigation (a trial is currently underway in Alberta to address this).

1.1.4 **ERAS® Implementation in Alberta: A natural experiment**

Alberta Health Services (AHS); a single provincial health care system, adopted the new standard of care at a system-level in surgical care for patients undergoing elective colorectal surgery: the ERAS® program. Implementation was initially for colorectal surgery patients at two sites in 2013, and then spread to include four more sites with high annual colorectal surgery volumes; all six sites collectively perform >75% of colorectal surgeries in the province. A pre-ERAS® cohort at each of the 6 sites was analyzed prior to implementation with enrollment of 50 patients (range 50-80 patients per site).(90) Implementation then followed utilizing the ERAS® Society's Implementation Program (EIP) which provided tailored training and involved forming an implementation team, along with regular auditing of the data for adherence using the ERAS® Interactive Audit System (EIAS) -a data entry and analysis system-, through which data was collected prospectively. Analysis of the cohort at the two lead sites 15 months into ERAS® implementation revealed a significant reduction in mean LOS (9.8 days [SD=11.7] pre-ERAS® vs. 6.7 days [SD=6.4] post-ERAS®; $p<0.0001$), and postoperative complications (11% reduction; 95 % CI 2.5–21.0, $p=0.0139$) with no increase in 30-day readmissions.(90) Median adherence to the protocol increased from 39% pre-ERAS® to 60% post-ERAS® implementation.(91) As part of the system wide implantation initiative, all patients including those with diabetes were included which resulted in a diverse, "real-

life" multicenter cohort.

Clinical Equipoise

Due to lack of robust evidence, a knowledge gap exists on whether ERAS® impacts postoperative outcomes in individuals with diabetes. There is also no consensus among professional associations on recommendations for this population. The absence of clear recommendations has hindered ERAS® evaluation and implementation in individuals with diabetes.(45,79,82,89)

1.1.5 Significance

It is important to identify and address this knowledge gap about the effect of ERAS® on postoperative outcomes in individuals with diabetes given the high postoperative morbidity in this population. With the increasing incidence and prevalence of diabetes, the burden of this population is expected to continue to grow. ERAS® implementation continues to be expanded across multiple sites and surgical specialties, and evidence is needed to inform national and international health care policies and guidelines about whether to include individuals with diabetes in the ERAS® program. Furthermore, the observed outcomes with ERAS® would be expected to impact patients' quality of life and return to independent activities of daily living post surgery with the ERAS® components that target early feeding and mobilization postoperatively. These are patient-centered outcomes, and addressing this knowledge gap would help advance science in the area of surgical care in individuals with diabetes.

Research Questions

1.1.6 Hypotheses

1. There is no robust evidence that ERAS® impacts postoperative outcomes in individuals with diabetes undergoing elective surgery.
2. ERAS® implementation improves postoperative outcomes by reducing LOS, postoperative complications and 30-day readmission rates in individuals with diabetes.

1.1.7 Objectives

1. To systematically evaluate the evidence on whether ERAS® impacts postoperative outcomes in individuals with diabetes.
2. To evaluate the association of ERAS® implementation and postoperative outcomes in individuals with and without diabetes in Alberta, Canada.

1.1.8 Research Questions and Designs

The following study designs will be used to address the research questions:

1. Systematic Review presented in chapter 2 of this study; published manuscript.
2. Interrupted time series analysis presented in chapter 3 of this study. A brief introduction is presented followed by the methods, results, and discussion; published manuscript.

This thesis aims to systematically evaluate the effect of ERAS® on individuals with diabetes. It also aims to evaluate the impact of ERAS® implementation on individuals with and without diabetes in Alberta, Canada. The results will help inform current clinical practice, and guide future clinical research to advance care in this high-risk surgical population.

Bibliography

1. Awad S, Carter S, Purkayastha S, Hakky S, Moorthy K, Cousins J, et al. Enhanced recovery after bariatric surgery (ERABS): clinical outcomes from a tertiary referral bariatric centre. Obes Surg. 2014 May;24(5):753–8.

2. Dogan K, Kraaij L, Aarts EO, Koehestanie P, Hammink E, van Laarhoven CJHM, et al. Fast-track bariatric surgery improves perioperative care and logistics compared to conventional care. Obes Surg. 2015 Jan;25(1):28–35.

3. Hahl T, Peromaa-Haavisto P, Tarkiainen P, Knutar O, Victorzon M. Outcome of Laparoscopic Gastric Bypass (LRYGB) with a Program for Enhanced Recovery After Surgery (ERAS). Obes Surg. 2016 Mar;26(3):505–11.

4. IDF diabetes atlas - Home [Internet]. [cited 2018 Mar 23]. Available from: http://www.diabetesatlas.org/

5. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. Am J Clin Nutr. 2007 Sep;86(3):s836-842.

6. Berster JM, Göke B. Type 2 diabetes mellitus as risk factor for colorectal cancer. Arch Physiol Biochem. 2008 Feb;114(1):84–98.

7. Aleksandrova K, Boeing H, Jenab M, Bas Bueno-de-Mesquita H, Jansen E, van Duijnhoven FJB, et al. Metabolic syndrome and risks of colon and rectal cancer: the European prospective investigation into cancer and nutrition study. Cancer Prev Res Phila Pa. 2011 Nov;4(11):1873–83.

8. Sun L, Yu S. Diabetes mellitus is an independent risk factor for colorectal cancer. Dig Dis Sci. 2012 Jun;57(6):1586–97.

9. Mills KT, Bellows CF, Hoffman AE, Kelly TN, Gagliardi G. Diabetes mellitus and colorectal cancer prognosis: a meta-analysis. Dis Colon Rectum. 2013 Nov;56(11):1304–19.

10. Holden SE. Diabetes and Cancer. Endocr Dev. 2016;31:135–45.

11. Bower WF, Jin L, Underwood MJ, Lee JF, Lee KF, Lam YH, et al. Overt diabetes mellitus adversely affects surgical outcomes of noncardiovascular patients. Surgery. 2010 May;147(5):670–5.

12. Frisch A, Chandra P, Smiley D, Peng L, Rizzo M, Gatcliffe C, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. Diabetes Care. 2010 Aug;33(8):1783–8.

13. Korol E, Johnston K, Waser N, Sifakis F, Jafri HS, Lo M, et al. A systematic review of risk factors associated with surgical site infections among surgical patients. PloS One. 2013;8(12):e83743.

14. Yeh C-C, Liao C-C, Chang Y-C, Jeng L-B, Yang H-R, Shih C-C, et al. Adverse outcomes after noncardiac surgery in patients with diabetes: a nationwide population-based retrospective cohort study. Diabetes Care. 2013 Oct;36(10):3216–21.

15. Martin ET, Kaye KS, Knott C, Nguyen H, Santarossa M, Evans R, et al. Diabetes and Risk of Surgical Site Infection: A Systematic Review and Meta-analysis. Infect Control Hosp Epidemiol. 2016 Jan;37(1):88–99.

16. Neumayer L, Hosokawa P, Itani K, El-Tamer M, Henderson WG, Khuri SF. Multivariable predictors of postoperative surgical site infection after general and vascular surgery: results from the patient safety in surgery study. J Am Coll Surg. 2007 Jun;204(6):1178–87.

17. Ata A, Lee J, Bestle SL, Desemone J, Stain SC. Postoperative hyperglycemia and surgical site infection in general surgery patients. Arch Surg Chic Ill 1960. 2010 Sep;145(9):858–64.

18. Ata A, Valerian BT, Lee EC, Bestle SL, Elmendorf SL, Stain SC. The effect of diabetes mellitus on surgical site infections after colorectal and noncolorectal general surgical operations. Am Surg. 2010 Jul;76(7):697–702.

19. Lawson EH, Hall BL, Ko CY. Risk Factors for Superficial vs Deep/Organ-Space Surgical Site Infections: Implications for Quality Improvement Initiatives. JAMA Surg. 2013 Sep 1;148(9):849–58.

20. Silvestri M, Dobrinja C, Scomersi S, Giudici F, Turoldo A, Princic E, et al. Modifiable and non-modifiable risk factors for surgical site infection after colorectal surgery: a single-center experience. Surg Today. 2018 Mar;48(3):338–45.

21. Kobayashi M, Mohri Y, Inoue Y, Okita Y, Miki C, Kusunoki M. Continuous follow-up of surgical site infections for 30 days after colorectal surgery. World J Surg. 2008 Jun;32(6):1142–6.

22. Wick EC, Vogel JD, Church JM, Remzi F, Fazio VW. Surgical site infections in a "high outlier" institution: are colorectal surgeons to blame? Dis Colon Rectum. 2009 Mar;52(3):374–9.

23. Zhu B, Wu X, Wu B, Pei D, Zhang L, Wei L. The relationship between diabetes and colorectal cancer prognosis: A meta-analysis based on the cohort studies. PloS One. 2017;12(4):e0176068.

24. ERAS Compliance Group. The Impact of Enhanced Recovery Protocol Compliance on Elective Colorectal Cancer Resection: Results From an International Registry. Ann Surg. 2015 Jun;261(6):1153–9.

25. Gustafsson UO, Hausel J, Thorell A, Ljungqvist O, Soop M, Nygren J, et al. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. Arch Surg Chic Ill 1960. 2011 May;146(5):571–7.

26. Fransgaard T, Thygesen LC, Gögenur I. Increased 30-day mortality in patients with diabetes undergoing surgery for colorectal cancer. Colorectal Dis Off J Assoc Coloproctology G B Irel. 2016 Jan;18(1):O22-29.

27. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation. 2002 Oct 15;106(16):2067–72.

28. Kim S-H, Park K-W, Kim Y-S, Oh S, Chae I-H, Kim H-S, et al. Effects of acute hyperglycemia on endothelium-dependent vasodilation in patients with diabetes mellitus or impaired glucose metabolism. Endothel J Endothel Cell Res. 2003;10(2):65–70.

29. Turina M, Miller FN, Tucker CF, Polk HC. Short-term hyperglycemia in surgical patients and a study of related cellular mechanisms. Ann Surg. 2006 Jun;243(6):845-851; discussion 851-853.

30. Blondet JJ, Beilman GJ. Glycemic control and prevention of perioperative infection. Curr Opin Crit Care. 2007 Aug;13(4):421–7.

31. Sandhu MS, Dunger DB, Giovannucci EL. Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. J Natl Cancer Inst. 2002 Jul 3;94(13):972–80.

32. Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Macdonald JS, Benson AB, et al. Impact of diabetes mellitus on outcomes in patients with colon cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2003 Feb 1;21(3):433–40.

33. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, et al. Insulin, insulin-like growth factor-I, endogenous estradiol, and risk of colorectal cancer in postmenopausal women. Cancer Res. 2008 Jan 1;68(1):329–37.

34. Huang Y-C, Lin J-K, Chen W-S, Lin T-C, Yang S-H, Jiang J-K, et al. Diabetes mellitus negatively impacts survival of patients with colon cancer, particularly in stage II disease. J Cancer Res Clin Oncol. 2011 Feb;137(2):211–20.

35. Chi F, Wu R, Zeng Y, Xing R, Liu Y. Circulation insulin-like growth factor peptides and colorectal cancer risk: an updated systematic review and meta-analysis. Mol Biol Rep. 2013 May 1;40(5):3583–90.

36. Chan YX, Alfonso H, Paul Chubb SA, Ho KKY, Gerard Fegan P, Hankey GJ, et al. Higher IGFBP3 is associated with increased incidence of colorectal cancer in older men independently of IGF1. Clin Endocrinol (Oxf). 2018 Feb;88(2):333–40.

37. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth. 1997 May;78(5):606–17.

38. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. JAMA Surg. 2017 Mar 1;152(3):292–8.

39. Carmichael JC, Keller DS, Baldini G, Bordeianou L, Weiss E, Lee L, et al. Clinical Practice Guidelines for Enhanced Recovery After Colon and Rectal Surgery From the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal and Endoscopic Surgeons. Dis Colon Rectum. 2017 Aug;60(8):761–84.

40. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced Recovery Program in Colorectal Surgery: A Meta-analysis of Randomized Controlled Trials. World J Surg. 2014 Jun 1;38(6):1531–41.

41. Fearon KCH, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CHC, Lassen K, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. Clin Nutr Edinb Scotl. 2005 Jun;24(3):466–77.

42. Gustafsson U o., Scott M j., Schwenk W, Demartines N, Roulin D, Francis N, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. Clin Nutr. 2012 Dec;31(6):783–800.

43. List of Guidelines [Internet]. Eras. [cited 2018 Mar 18]. Available from: http://erassociety.org/guidelines/list-of-guidelines/

44. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26;336(7650):924–6.

45. Nygren J, Thacker J, Carli F, Fearon K c. h., Norderval S, Lobo D n., et al. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. Clin Nutr. 2012 Dec;31(6):801–16.

46. Gillissen F, Hoff C, Maessen JMC, Winkens B, Teeuwen JHFA, von Meyenfeldt MF, et al. Structured synchronous implementation of an enhanced recovery program in

elective colonic surgery in 33 hospitals in The Netherlands. World J Surg. 2013 May;37(5):1082–93.

47. Gillissen F, Ament SMC, Maessen JMC, Dejong CHC, Dirksen CD, van der Weijden T, et al. Sustainability of an enhanced recovery after surgery program (ERAS) in colonic surgery. World J Surg. 2015 Feb;39(2):526–33.

48. Day RW, Fielder S, Calhoun J, Kehlet H, Gottumukkala V, Aloia TA. Incomplete reporting of enhanced recovery elements and its impact on achieving quality improvement. Br J Surg. 2015 Dec;102(13):1594–602.

49. Sammour T, Zargar-Shoshtari K, Bhat A, Kahokehr A, Hill AG. A programme of Enhanced Recovery After Surgery (ERAS) is a cost-effective intervention in elective colonic surgery. N Z Med J. 2010 Jul 30;123(1319):61–70.

50. Roulin D, Donadini A, Gander S, Griesser A-C, Blanc C, Hübner M, et al. Cost-effectiveness of the implementation of an enhanced recovery protocol for colorectal surgery. Br J Surg. 2013 Jul;100(8):1108–14.

51. Lemanu DP, Singh PP, Stowers MDJ, Hill AG. A systematic review to assess cost effectiveness of enhanced recovery after surgery programmes in colorectal surgery. Colorectal Dis Off J Assoc Coloproctology G B Irel. 2014 May;16(5):338–46.

52. Lee L, Mata J, Ghitulescu GA, Boutros M, Charlebois P, Stein B, et al. Cost-effectiveness of Enhanced Recovery Versus Conventional Perioperative Management for Colorectal Surgery. Ann Surg. 2015 Dec;262(6):1026–33.

53. Simpson JC, Moonesinghe SR, Grocott MPW, Kuper M, McMeeking A, Oliver CM, et al. Enhanced recovery from surgery in the UK: an audit of the enhanced recovery partnership programme 2009-2012. Br J Anaesth. 2015 Oct;115(4):560–8.

54. Stone AB, Grant MC, Pio Roda C, Hobson D, Pawlik T, Wu CL, et al. Implementation Costs of an Enhanced Recovery After Surgery Program in the United States: A Financial Model and Sensitivity Analysis Based on Experiences at a Quaternary Academic Medical Center. J Am Coll Surg. 2016 Mar;222(3):219–25.

55. Thanh NX, Chuck AW, Wasylak T, Lawrence J, Faris P, Ljungqvist O, et al. An economic evaluation of the Enhanced Recovery After Surgery (ERAS) multisite implementation program for colorectal surgery in Alberta. Can J Surg. 2016 Dec;59(6):415–21.

56. Li L, Jin J, Min S, Liu D, Liu L. Compliance with the enhanced recovery after surgery protocol and prognosis after colorectal cancer surgery: A prospective cohort study. Oncotarget. 2017 Aug 8;8(32):53531–41.

57. Gustafsson UO, Oppelstrup H, Thorell A, Nygren J, Ljungqvist O. Adherence to the ERAS protocol is Associated with 5-Year Survival After Colorectal Cancer Surgery: A Retrospective Cohort Study. World J Surg. 2016;40(7):1741–7.

58. Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). Ann Surg. 2011 Dec;254(6):868–75.

59. Ament SMC, Gillissen F, Moser A, Maessen JMC, Dirksen CD, von Meyenfeldt MF, et al. Identification of promising strategies to sustain improvements in hospital practice: a qualitative case study. BMC Health Serv Res. 2014 Dec 16;14:641.

60. Nicholson A, Lowe MC, Parker J, Lewis SR, Alderson P, Smith AF. Systematic review and meta-analysis of enhanced recovery programmes in surgical patients. Br J Surg. 2014 Feb;101(3):172–88.

61. Messenger DE, Curtis NJ, Jones A, Jones EL, Smart NJ, Francis NK. Factors predicting outcome from enhanced recovery programmes in laparoscopic colorectal surgery: a systematic review. Surg Endosc. 2017;31(5):2050–71.

62. Kim BJ, Aloia TA. What Is "Enhanced Recovery," and How Can I Do It? J Gastrointest Surg Off J Soc Surg Aliment Tract. 2018 Jan;22(1):164–71.

63. Aarts M-A, Rotstein OD, Pearsall EA, Victor JC, Okrainec A, McKenzie M, et al. Postoperative ERAS Interventions Have the Greatest Impact on Optimal Recovery: Experience With Implementation of ERAS Across Multiple Hospitals. Ann Surg. 2018 Jan 4;

64. Delaney CP, Zutshi M, Senagore AJ, Remzi FH, Hammel J, Fazio VW. Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. Dis Colon Rectum. 2003 Jul;46(7):851–9.

65. Muller S, Zalunardo MP, Hubner M, Clavien PA, Demartines N, Zurich Fast Track Study Group. A fast-track program reduces complications and length of hospital stay after open colonic surgery. Gastroenterology. 2009 Mar;136(3):842–7.

66. Varadhan KK, Neal KR, Dejong CHC, Fearon KCH, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr Edinb Scotl. 2010 Aug;29(4):434–40.

67. Adamina M, Kehlet H, Tomlinson GA, Senagore AJ, Delaney CP. Enhanced recovery pathways optimize health outcomes and resource utilization: a meta-analysis of randomized controlled trials in colorectal surgery. Surgery. 2011 Jun;149(6):830–40.

68. Spanjersberg WR, van Sambeeck JDP, Bremers A, Rosman C, van Laarhoven CJHM. Systematic review and meta-analysis for laparoscopic versus open colon surgery with or without an ERAS programme. Surg Endosc. 2015 Dec;29(12):3443–53.

69. Lv L, Shao Y-F, Zhou Y. The enhanced recovery after surgery (ERAS) pathway for patients undergoing colorectal surgery: an update of meta-analysis of randomized controlled trials. Int J Colorectal Dis. 2012 Dec;27(12):1549–54.

70. Paton F, Chambers D, Wilson P, Eastwood A, Craig D, Fox D, et al. Initiatives to reduce length of stay in acute hospital settings: a rapid synthesis of evidence relating to enhanced recovery programmes [Internet]. Southampton (UK): NIHR Journals Library; 2014 [cited 2018 Mar 17]. (Health Services and Delivery Research). Available from: http://www.ncbi.nlm.nih.gov/books/NBK259855/

71. Crowe PJ, Dennison A, Royle GT. The effect of pre-operative glucose loading on postoperative nitrogen metabolism. Br J Surg. 1984 Aug;71(8):635–7.

72. Soop M, Nygren J, Myrenfors P, Thorell A, Ljungqvist O. Preoperative oral carbohydrate treatment attenuates immediate postoperative insulin resistance. Am J Physiol Endocrinol Metab. 2001 Apr;280(4):E576-583.

73. Henriksen MG, Hessov I, Dela F, Hansen HV, Haraldsted V, Rodt SA. Effects of preoperative oral carbohydrates and peptides on postoperative endocrine response, mobilization, nutrition and muscle function in abdominal surgery. Acta Anaesthesiol Scand. 2003 Feb;47(2):191–9.

74. Yuill KA, Richardson RA, Davidson HIM, Garden OJ, Parks RW. The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively--a randomised clinical trial. Clin Nutr Edinb Scotl. 2005 Feb;24(1):32–7.

75. Noblett SE, Watson DS, Huong H, Davison B, Hainsworth PJ, Horgan AF. Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial. Colorectal Dis Off J Assoc Coloproctology G B Irel. 2006 Sep;8(7):563–9.

76. Yagci G, Can MF, Ozturk E, Dag B, Ozgurtas T, Cosar A, et al. Effects of preoperative carbohydrate loading on glucose metabolism and gastric contents in patients undergoing moderate surgery: a randomized, controlled trial. Nutr Burbank Los Angel Cty Calif. 2008 Mar;24(3):212–6.

77. Albalawi Z, Laffin M, Gramlich L, Senior P, McAlister FA. Enhanced Recovery After Surgery (ERAS(®)) in Individuals with Diabetes: A Systematic Review. World J Surg. 2017 Mar 20;

78. Søreide E, Eriksson LI, Hirlekar G, Eriksson H, Henneberg SW, Sandin R, et al. Pre-operative fasting guidelines: an update. Acta Anaesthesiol Scand. 2005 Sep;49(8):1041–7.

79. Dhatariya K, Levy N, Kilvert A, Watson B, Cousins D, Flanagan D, et al. NHS Diabetes guideline for the perioperative management of the adult patient with diabetes. Diabet Med J Br Diabet Assoc. 2012 Apr;29(4):420–33.

80. Farrukh A, Higgins K, Singh B, Gregory R. Can pre-operative carbohydrate loading be used in diabetic patients undergoing colorectal surgery? Br J Diabetes. 2014 Sep 12;14(3):102–4.

81. Laffin MR, Li S, Brisebois R, Senior PA, Wang H. The Use of a Pre-operative Carbohydrate Drink in Patients with Diabetes Mellitus: A Prospective, Non-inferiority, Cohort Study. World J Surg. 2017 Dec 27;

82. Hill LT, Miller MGA. Carbohydrate loading in the preoperative setting. South Afr Med J Suid-Afr Tydskr Vir Geneeskd. 2015 Mar;105(3):173–4.

83. Thorell A, Efendic S, Gutniak M, Häggmark T, Ljungqvist O. Insulin resistance after abdominal surgery. Br J Surg. 1994 Jan;81(1):59–63.

84. Ljungqvist O. Modulating postoperative insulin resistance by preoperative carbohydrate loading. Best Pract Res Clin Anaesthesiol. 2009 Dec;23(4):401–9.

85. Thorell A, Alston-Smith J, Ljungqvist O. The effect of preoperative carbohydrate loading on hormonal changes, hepatic glycogen, and glucoregulatory enzymes during abdominal surgery. Nutr Burbank Los Angel Cty Calif. 1996 Oct;12(10):690–5.

86. Thorell A, Nygren J, Ljungqvist O. Insulin resistance: a marker of surgical stress. Curr Opin Clin Nutr Metab Care. 1999 Jan;2(1):69–78.

87. Smiley DD, Umpierrez GE. Perioperative glucose control in the diabetic or nondiabetic patient. South Med J. 2006 Jun;99(6):580-589; quiz 590-591.

88. American Society of Anesthesiologists Committee. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. Anesthesiology. 2011 Mar;114(3):495–511.

89. Merchant R, Chartrand D, Dain S, Dobson G, Kurrek MM, Lagacé A, et al. Guidelines to the practice of anesthesia--revised edition 2015. Can J Anaesth J Can Anesth. 2015 Jan;62(1):54–67.

90. Nelson G, Kiyang LN, Crumley ET, Chuck A, Nguyen T, Faris P, et al. Implementation of Enhanced Recovery After Surgery (ERAS) Across a Provincial Healthcare System: The ERAS Alberta Colorectal Surgery Experience. World J Surg. 2016 May 1;40(5):1092–103.

91. Gramlich LM, Sheppard CE, Wasylak T, Gilmour LE, Ljungqvist O, Basualdo-Hammond C, et al. Implementation of Enhanced Recovery After Surgery: a strategy to transform surgical care across a health system. Implement Sci IS. 2017 May 19;12(1):67.

2 Chapter 2: Enhanced Recovery After Surgery (ERAS®) in Individuals with Diabetes: A Systematic Review[1]

Zaina Albalawi, MD

Michael Laffin, MD

Leah Gramlich, MD

Peter Senior, MBBS PhD

Finlay A. McAlister, MD MSc

[1] A version of this chapter has been published [Albalawi Z, Laffin M, Gramlich L, Senior P, McAlister FA. World J Surg. 2017 Aug;41(8):1927–34]

Introduction

The Prevalence of diabetes in surgical patients is 10-40%.(1–6) It is well recognized that individuals with diabetes have higher rates of complications, and longer stays in-hospital compared to patients without diabetes.(7–9) ERAS® is an evidence-based multimodal surgical care pathway that improves postoperative complications and length of stay –Table 1. (10–15) It is unclear whether individuals with diabetes were included in enhanced recovery studies; they were not explicitly excluded and not reported. This study was conducted to systematically evaluate the state of the evidence base for the use of ERAS® protocol in individuals with diabetes undergoing surgery. To the best of our knowledge, this is the first systematic review addressing this question.

Methods

As per the recommendations of the Cochrane Effective Practice and Organization of Care Group (EPOC) for evaluating healthcare interventions, we included randomized controlled trials (RCTs), subgroups of RCTs in individuals with diabetes undergoing elective surgery, and non-randomized studies with more robust methodology including non-randomized controlled trials (NRCT), controlled before-after (CBA) studies, interrupted-time-series (ITS), and cohort studies with concurrent controls.(16) The intervention was the full suite of all 22 elements of ERAS®. Non-ERAS protocols were excluded (e.g. fast-track, enhanced recovery program) due to lack of standardization of these protocols and heterogeneity.

2.1.1 **Outcomes**

Our primary outcome of interest was Length of stay (LOS) in-hospital. Secondary outcomes included postoperative complications, 30-day readmission and complication rates, episodes of hyperglycemia (glucose >14mmol/l preoperatively or postoperatively, since this level has been shown to be associated with higher rates of postoperative infections in individuals with diabetes undergoing non-cardiac surgery).(17)

2.1.2 **Search methods for identification of studies**

Electronic searches: studies were identified by searching MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials June 2016, EMBASE 1996 to 2016 Week 25. There was no language restriction –Table 2. The Search was run in Ovid Databases on June 22 2016, and duplicates were removed. Searches were limited from year 2000 to the current year, as the first ERAS protocol was not published until 2005.(10)

Other resources: additional studies were identified and included by searching conference proceedings of surgical and anaesthesiology societies, and the bibliographies of review articles and trials of identified studies. Experts in the area were contacted, and www.clinicaltrials.gov was also searched for ongoing trials.

2.1.3 **Data collection and analysis**

All retrieved study titles were scanned independently for inclusion by two authors; Zaina Albalawi (ZA) and Michael Laffin (ML), using a standardized form. Disagreement was solved by consensus between them, and full articles were retrieved for those thought to be potentially relevant. Abstracts from conference proceedings were included if the authors were able to provide details for the full study. RevMan (version 5.3) was used. For NRS, additional data would be collected using the data collection form developed by the Cochrane Collaboration.(18) This provides a standardized tool for collecting data on study designs, potential sources of confounding, and risk of bias.(19,20)

Results

The electronic search yielded 437 references. After removing duplicates, 376 remained for screening for eligibility. Searching bibliographies of reviews, conference proceedings and ERAS guidelines identified additional 8 references. Searching www.clinicaltrials.gov yielded 59 references. Contacting experts in the field identified no further studies. The study flow diagram illustrates the search results (Figure 1).(21) Fourteen full articles were retrieved, and subsequently excluded as they used an intervention other than ERAS® (n= 10), they did not include patients with diabetes (n= 2) or used an uncontrolled before-after design (n= 2). One of the latter studies included subjects with diabetes among others without diabetes.(22) This included 8 subjects (10.4%) with diabetes in the ERAS intervention group, and 15 (13.8%) in the conventional care group. The author was contacted to provide individual data to further analyze this group, but we were unable to obtain this.

Discussion

This review did not identify any randomized controlled trials or observational studies meeting the EPOC criteria, which evaluated the effects of ERAS® in patients with diabetes. To the best of our knowledge, this is the first systematic review addressing this question. It highlights the lack of evidence in this area, which has lead to varying practices at sites where ERAS® is implemented.(23) It is likely that all potentially relevant studies were identified in this review with the sensitive search strategy used, as well as the methods utilized to identify grey literature.

Individuals with diabetes constitute on average 15% of surgical patients, and up to 40% in bariatric surgery.(1–6) With the predicted increase in prevalence of diabetes, this proportion is likely to increase further.(24) The question that remains unanswered is whether patients with diabetes enrolled in ERAS® would observe similar improvements in postoperative outcomes as those reported in trials of patients without diabetes, or whether those would be negated by the potential risks of hyperglycemia and delayed gastric emptying from the carbohydrate load. It is also unknown whether implementing ERAS® and monitoring adherence would be cost effective in individuals with diabetes.(11,25) On the contrary, it is well recognized (and supported by an extensive body of evidence) that individuals with diabetes are at higher risk for morbidity and mortality postoperatively across various types of surgeries.(7,8,26–31) Within the context of enhanced recovery programs, results from a small number of observational studies in individuals with diabetes are inconsistent. The only study using ERAS® was Luther and colleagues where they analyzed 18 patients in the diabetes group and 125 in the non-diabetes group. Both groups were scheduled to undergo an elective major colorectal

procedure and were enrolled in ERAS®. They found the median length of stay in the diabetes group to be significantly longer at 7 days with an interquartile range of 5-15.5 days compared to 5 days in the non-diabetes group (Interquartile range 4–7.5 days) P = 0.041.(32) It is unknown as well -given the study design- whether the 7-day LOS observed in the diabetes group is different than the expected LOS outside of ERAS implementation. This study was excluded because the control arm did not include individuals with diabetes and was not "conventional care". The second study used a fast-track protocol in primary total hip and total knee arthroplasty, and found no association between diabetes and postoperative morbidity.(33)

Revisiting the *Clinical Significance* of Gastroparesis Preoperatively in Individuals with Diabetes

Although gastroparesis is one of the main potential barriers to carbohydrate loading -and including individuals with diabetes in ERAS®-, it is not as common as previously thought.(34–37) In a recent population-based study, gastroparesis was found to be relatively uncommon with a cumulative incidence of %1 in patients with type 2 diabetes vs. 0.2% in controls over 10 years.(38) Previously reported prevalence of gastroparesis of 30-50% was an overestimate, biased by the cohorts from tertiary centers.(39,40) Recent studies have found this to be only 5-12%, and the most common cause is in fact idiopathic in over one-third of patients.(36,41) Even in the presence of gastroparesis, slower movement of solid food from the stomach is the hallmark of this condition radiologically, and to much less extent liquids.(35,36,42) Two studies have assessed a liquid carbohydrate load in individuals with diabetes, and their results would suggest that harm is unlikely given complete gastric emptying at ≤180 min: **1)** Jones et al administered a liquid drink containing 15g of dextrose in subjects with variable diabetes

control (n=86, median HbA1c 9.3% (3.6-16%)); majority on insulin. Gastric half-emptying time (T50) was not delayed in 72% of the participants, and all participants had emptied the liquid by about 60 minutes compared to about 40 minutes in healthy controls,(43) **2)** The second study by Gustafsson and colleagues used a 50g carbohydrate drink in a better controlled group (n=25, mean HbA1c 5.6% and 6.8% in non-insulin and insulin treated subjects respectively). They found no signs of delayed gastric emptying (T50 49.8±2 min compared to 58.6±3.7 min), and gastric emptying was complete by 180 min.(44) This would suggest the acceptable 2-3 hour time frame for consumption of a liquid load preoperatively by modern fasting guidelines and ERAS®. Furthermore, for passive regurgitation and pulmonary aspiration to occur, gastric content needs to be >200 ml.(45,46) With the current volumes of carbohydrate delivered at a maximum of 400 ml, and T50 reported at < 1 hour from the previous studies, the suggested 2-3 hour time frame is conservative. It should also be highlighted that there are other risk factors for aspiration preoperatively, which are far more common than diabetes: anaesthesia and airway management.(47) Therefore, in a setting where those two latter factors are controlled (i.e. ERAS®), the risk of aspiration with the carbohydrate load of 400 ml is expected to be low, even in individuals with diabetes *and* delayed gastric emptying.

ERAS® or other Fast-Track Programs?

The *ERAS® Care System* comprises three components, and has been tested and implemented in about 40 leading hospitals in Europe and North America. These components include the 1) *ERAS® Protocol*; the 2) *ERAS® Implementation Program*; a change management program specifically developed for the perioperative team of surgical clinics performing major operations, and the 3) *ERAS® Interactive Audit System*

(EIAS); a software program designed to ensure compliance to the protocol, maintain tight control of patient information at every step, and monitor the results.(48)

There are multiple surgical protocols other than ERAS® such as fast-track protocols and enhanced recovery (ERP) protocols that have been evaluated in patients.(33,49,50) There is controversy on whether all the ERAS® components are needed to impact postoperative outcomes, or whether a refined "shorter list" would suffice and result in better adherence and ease of implementation and uptake.(51–54) Studies however have been inconsistent, and are limited by the heterogeneity of these protocols, types of surgery, surgical technique, and study design. However, a recent international, multicenter ERAS® registry data analysis (including 13 centers from 6 countries between 2008-2013) demonstrated that increasing compliance with the ERAS® program and the use of laparoscopic surgery independently improve outcomes.(48) ERAS® stands out among other protocols with its structured perioperative Care System - described earlier- developed by the ERAS® Society to facilitate consistent hospital implementation, and maintenance of the ERAS® pathway to achieve the desired outcomes. More importantly, adherence to ERAS® has recently been shown to be associated with increased 5-year cancer specific survival after colorectal cancer surgery,(55) not reported with any other fast-track or enhanced recovery program.

Implications for practice

Currently, there is a lack of evidence demonstrating benefit or harm from enrolling surgical patients with diabetes in ERAS®. There is no robust evidence to support a specific recommendation for this population. Thus, there is a clear need to rigorously evaluate the outcomes for any diabetic patients enrolled in ERAS® for elective surgery. Clinical judgment (and close monitoring of glucose levels and diabetic

medication management) will be required on a case-to-case basis until further evidence is available to inform this decision.

Implications for research

A randomized controlled trial is needed to examine the impact of ERAS® implementation on patients with diabetes. If this is not feasible, then one of the following NRS would be preferred: NRCT, CBA, or an ITS. The ITS design has been recognized as "one of the most effective and powerful of all quasi-experimental designs",(56) and is the best next step if randomization is not possible.(57) It has the advantage of using multiple pre and post time points to control for secular trends in outcomes, and would provide an unbiased estimate of the impact of ERAS® implementation. It allows for statistical investigation of cyclical or seasonal effects, random fluctuations, and autocorrelation. Ramsay et al provides an outline of quality criteria for ITS studies.(58) Although uncontrolled before-after designs are appealing for their simplicity, their use is discouraged due to their tendency to overestimate benefits of new interventions.(59) Alternatively, a CBA design can be used to compare the before-after effect of implementation of ERAS to a concurrent control group to adjust for trends over time.

Conclusion

In conclusion, this rigorous systematic review highlights the lack of evidence on the effects of ERAS® for surgical patients with diabetes. A policy change in ERAS® implementation is suggested to encourage evaluation when ERAS® is used in individuals with diabetes, and guidance on study designs is provided to direct future research to inform care in this high-risk population.

Table 1 Enhanced Recovery After Surgery (ERAS®)

Protocol Elements [16,17,20,21]

Operative Stage	ERAS elements
Preoperative	1-Pre-admission counselling 2-Fluid and carbohydrate loading 3-No prolonged fasting 4-No/selective bowel preparation 5-Antibiotic prophylaxis 6-Thromboprophylaxis 7-No premedication
Intraoperative	1-Short-acting anaesthetic agents 2-Mid-thoracic epidural anaesthesia/analgesia 3-No drains 4-Avoidance of salt and water overload 5-Maintenance of normothermia (body warmer/warm intravenous fluids)
Postoperative	1-Mid-thoracic epidural (anaesthesia/analgesia) 2-No nasogastric tubes 3-Prevention of nausea and vomiting 4-Avoidance of salt and water overload 5-Early removal of catheter 6-Early oral nutrition 7-Non-opioid oral analgesia/NSAIDs 8-Early mobilization 9-Stimulation of gut motility 10-Audit of compliance and outcomes

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs

Table 2 Database Search

Search Run June 22 2016

1 MEDLINE Search Strategy: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

1. exp Diabetes Mellitus/
2. (diabet* or mody or niddm or t2d*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. 1 or 2
4. (enhanced recovery or fast track or eras or erp or erabs).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5. 3 and 4 **(174 results)**

6. limit 5 to yr="2000 -Current" **(136 results)**

2 EMBASE Search Strategy: Ovid Embase 1996 to 2016 Week 25

1. exp *Diabetes Mellitus/
2. (diabet* or mody or niddm or t2d*).ti,ab.
3. 1 or 2
4. (enhanced recovery or fast track or eras or erp or erabs).ti,ab.
5. 3 and 4 **(306 results)**

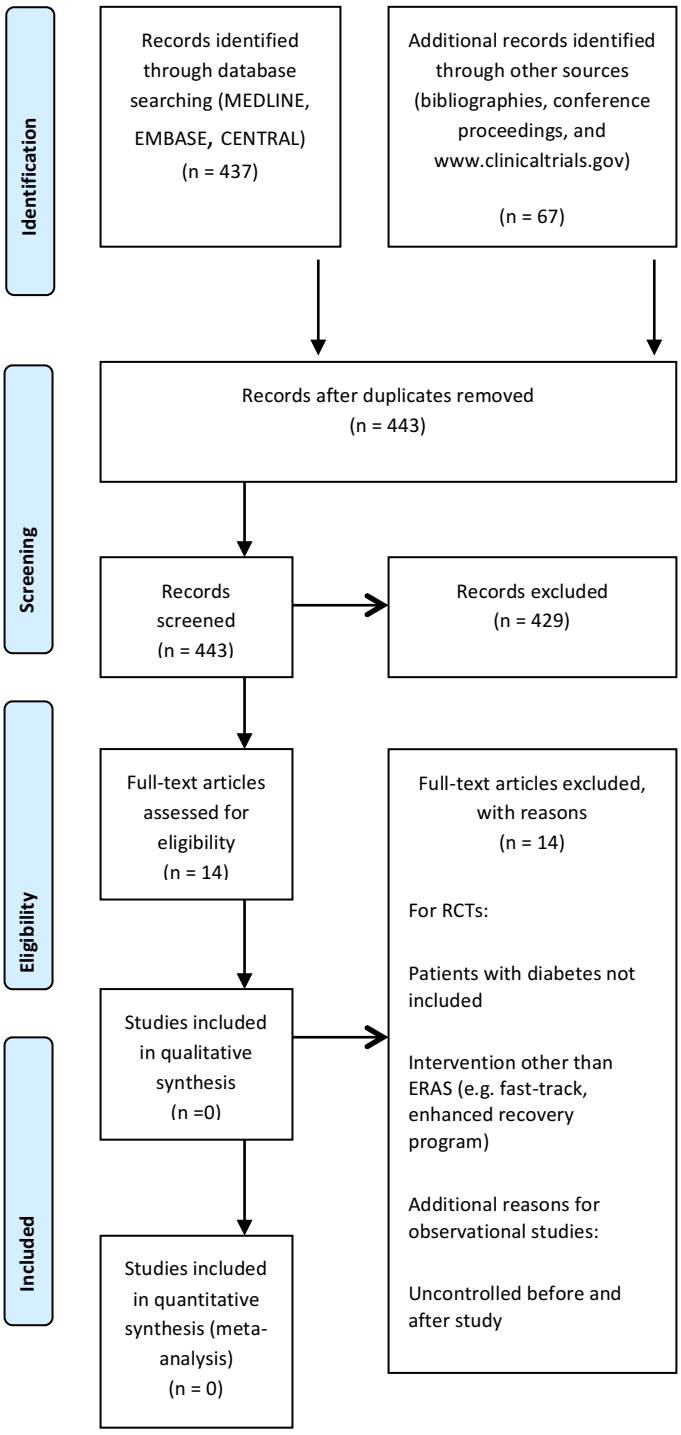
6. limit 5 to yr="2000 -Current" **(292 results)**

3 CENTRAL Search Strategy: Ovid EBM Reviews - Cochrane Central Register of Controlled Trials June 2016

1. exp Diabetes Mellitus/
2. (diabet* or mody or niddm or t2d*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. 1 or 2
4. (enhanced recovery or fast track or eras or erp or erabs).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5. 3 and 4 **(9 results)**

4 www.clinicaltrials.gov
(diabetes OR diabetics OR diabetic) AND Surgery AND (ERAS OR enhanced OR recovery) **(59 results)**

Figure 1 PRISMA study flow diagram [38]



Bibliography

1. Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, et al. Management of diabetes and hyperglycemia in hospitals. Diabetes Care. 2004 Feb;27(2):553–91.

2. Smiley DD, Umpierrez GE. Perioperative glucose control in the diabetic or nondiabetic patient. South Med J. 2006 Jun;99(6):580–9; quiz 590–1.

3. Hoffman RL, Bartlett EK, Ko C, Mahmoud N, Karakousis GC, Kelz RR. Early discharge and readmission after colorectal resection. J Surg Res. 2014 Aug 1;190(2):579–86.

4. Awad S, Carter S, Purkayastha S, Hakky S, Moorthy K, Cousins J, et al. Enhanced recovery after bariatric surgery (ERABS): clinical outcomes from a tertiary referral bariatric centre. Obes Surg. 2014 May;24(5):753–8.

5. Dogan K, Kraaij L, Aarts EO, Koehestanie P, Hammink E, van Laarhoven CJHM, et al. Fast-track bariatric surgery improves perioperative care and logistics compared to conventional care. Obes Surg. 2015 Jan;25(1):28–35.

6. Hahl T, Peromaa-Haavisto P, Tarkiainen P, Knutar O, Victorzon M. Outcome of Laparoscopic Gastric Bypass (LRYGB) with a Program for Enhanced Recovery After Surgery (ERAS). Obes Surg. 2016 Mar;26(3):505–11.

7. Malone DL, Genuit T, Tracy JK, Gannon C, Napolitano LM. Surgical site infections: reanalysis of risk factors. J Surg Res. 2002 Mar;103(1):89–95.

8. Bower WF, Jin L, Underwood MJ, Lee JF, Lee KF, Lam YH, et al. Overt diabetes mellitus adversely affects surgical outcomes of noncardiovascular patients. Surgery. 2010 May;147(5):670–5.

9. Korol E, Johnston K, Waser N, Sifakis F, Jafri HS, Lo M, et al. A systematic review of risk factors associated with surgical site infections among surgical patients. PloS One. 2013;8(12):e83743.

10. Fearon KCH, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CHC, Lassen K, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. Clin Nutr Edinb Scotl. 2005 Jun;24(3):466–77.

11. Sammour T, Zargar-Shoshtari K, Bhat A, Kahokehr A, Hill AG. A programme of Enhanced Recovery After Surgery (ERAS) is a cost-effective intervention in elective colonic surgery. N Z Med J. 2010 Jul 30;123(1319):61–70.

12. Varadhan KK, Neal KR, Dejong CHC, Fearon KCH, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr Edinb Scotl. 2010 Aug;29(4):434–40.

13. Lv L, Shao Y-F, Zhou Y. The enhanced recovery after surgery (ERAS) pathway for patients undergoing colorectal surgery: an update of meta-analysis of randomized controlled trials. Int J Colorectal Dis. 2012 Dec;27(12):1549–54.

14. Gustafsson U o., Scott M j., Schwenk W, Demartines N, Roulin D, Francis N, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. Clin Nutr. 2012 Dec;31(6):783–800.

15. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced Recovery Program in Colorectal Surgery: A Meta-analysis of Randomized Controlled Trials. World J Surg. 2014 Jun 1;38(6):1531–41.

16. Reeves BC, Deeks JJ, Higgins JPT, Wells GA. Chapter 13: Including non-randomized studies. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org. In.

17. King JT, Goulet JL, Perkal MF, Rosenthal RA. Glycemic control and infections in patients with diabetes undergoing noncardiac surgery. Ann Surg. 2011 Jan;253(1):158–65.

18. Effective Practice and Organisation of Care (EPOC) (2013) How to prepare a risk of bias table for reviews that include more than one study design. EPOC Resources for review authors. Oslo: Norwegian Knowledge Centre for the Health Services. Available at: http://epoc.cochrane.org/sites/epoc.cochrane.org/files/public/uploads/Resources-for-authors2017/how_to_prepare_a_risk_of_bias_table_for_reviews_that_include_more_than_one_study_design.pdf.

19. Effective Practice and Organisation of Care (EPOC) (2015) Suggested risk of bias criteria for EPOC reviews. EPOC Resources for review authors. Oslo: Norwegian Knowledge Centre for the Health Services. Available at: http://epoc.cochrane.org/sites/epoc.cochrane.org/files/public/uploads/Resources-for-authors2017/suggested_risk_of_bias_criteria_for_epoc_reviews.pdf.

20. Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011, Available from www.cochrane-handbook.org. In.

21. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009 Oct;62(10):1006–12.

22. Haverkamp MP, de Roos M a. J, Ong KH. The ERAS protocol reduces the length of stay after laparoscopic colectomies. Surg Endosc. 2012 Feb;26(2):361–7.

23. Laffin MR, Li S, Brisebois R, Senior PA, Wang H. The Use of a Pre-operative Carbohydrate Drink in Patients with Diabetes Mellitus: A Prospective, Non-inferiority, Cohort Study. World J Surg. 2017 Dec 27;

24. International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium: International Diabetes Federation, 2017. http://www.diabetesatlas.org.

25. Roulin D, Donadini A, Gander S, Griesser A-C, Blanc C, Hübner M, et al. Cost-effectiveness of the implementation of an enhanced recovery protocol for colorectal surgery. Br J Surg. 2013 Jul;100(8):1108–14.

26. Juul AB, Wetterslev J, Kofoed-Enevoldsen A. Long-term postoperative mortality in diabetic patients undergoing major non-cardiac surgery. Eur J Anaesthesiol. 2004 Jul;21(7):523–9.

27. Bolognesi MP, Marchant MH, Viens NA, Cook C, Pietrobon R, Vail TP. The impact of diabetes on perioperative patient outcomes after total hip and total knee arthroplasty in the United States. J Arthroplasty. 2008 Sep;23(6 Suppl 1):92–8.

28. Gil-Bona J, Sabaté A, Pi A, Adroer R, Jaurrieta E. [Mortality risk factors in surgical patients in a tertiary hospital: a study of patient records in the period 2004-2006]. Cirugia Espanola. 2009 Apr;85(4):229–37.

29. Jämsen E, Nevalainen P, Eskelinen A, Huotari K, Kalliovalkama J, Moilanen T. Obesity, diabetes, and preoperative hyperglycemia as predictors of periprosthetic joint infection: a single-center analysis of 7181 primary hip and knee replacements for osteoarthritis. J Bone Joint Surg Am. 2012 Jul 18;94(14):e101.

30. Fei Q, Li J, Lin J, Li D, Wang B, Meng H, et al. Risk Factors for Surgical Site Infection After Spinal Surgery: A Meta-Analysis. World Neurosurg. 2016 Nov;95:507–15.

31. Martin ET, Kaye KS, Knott C, Nguyen H, Santarossa M, Evans R, et al. Diabetes and Risk of Surgical Site Infection: A Systematic Review and Meta-analysis. Infect Control Amp Hosp Epidemiol. 2016 Jan;37(1):88–99.

32. Luther A, Panteleimonitis S, Kang P, Evans J. Tu1759 Diabetic Patients Take Longer to Recover Than Non-Diabetics Within an Enhanced Recovery Programme. Gastroenterology. 2012 May 1;142(5):S-1092.

33. Jørgensen CC, Madsbad S, Kehlet H, Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group. Postoperative morbidity and mortality in type-2 diabetics after fast-track primary total hip and knee arthroplasty. Anesth Analg. 2015 Jan;120(1):230–8.

34. Loo FD, Palmer DW, Soergel KH, Kalbfleisch JH, Wood CM. Gastric emptying in patients with diabetes mellitus. Gastroenterology. 1984 Mar;86(3):485–94.

35. Wright RA, Clemente R, Wathen R. Diabetic gastroparesis: an abnormality of gastric emptying of solids. Am J Med Sci. 1985 Jun;289(6):240–2.

36. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L, American College of Gastroenterology. Clinical guideline: management of gastroparesis. Am J Gastroenterol. 2013 Jan;108(1):18–37; quiz 38.

37. Horváth VJ, Izbéki F, Lengyel C, Kempler P, Várkonyi T. Diabetic gastroparesis: functional/morphologic background, diagnosis, and treatment options. Curr Diab Rep. 2014;14(9):527.

38. Choung RS, Locke GR, Schleck CD, Zinsmeister AR, Melton LJ, Talley NJ. Risk of gastroparesis in subjects with type 1 and 2 diabetes in the general population. Am J Gastroenterol. 2012 Jan;107(1):82–8.

39. Horowitz M, Wishart JM, Jones KL, Hebbard GS. Gastric emptying in diabetes: an overview. Diabet Med J Br Diabet Assoc. 1996 Sep;13(9 Suppl 5):S16-22.

40. Kong MF, Horowitz M, Jones KL, Wishart JM, Harding PE. Natural history of diabetic gastroparesis. Diabetes Care. 1999 Mar;22(3):503–7.

41. Parkman HP, Yates K, Hasler WL, Nguyen L, Pasricha PJ, Snape WJ, et al. Similarities and differences between diabetic and idiopathic gastroparesis. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2011 Dec;9(12):1056–64; quiz e133-134.

42. Kashyap P, Farrugia G. Diabetic gastroparesis: what we have learned and had to unlearn in the past 5 years. Gut. 2010 Dec;59(12):1716–26.

43. Jones KL, Horowitz M, Wishart MJ, Maddox AF, Harding PE, Chatterton BE. Relationships between gastric emptying, intragastric meal distribution and blood glucose concentrations in diabetes mellitus. J Nucl Med Off Publ Soc Nucl Med. 1995 Dec;36(12):2220–8.

44. Gustafsson UO, Nygren J, Thorell A, Soop M, Hellström PM, Ljungqvist O, et al. Pre-operative carbohydrate loading may be used in type 2 diabetes patients. Acta Anaesthesiol Scand. 2008 Aug;52(7):946–51.

45. Tryba M, Zenz M, Mlasowsky B, Huchzermeyer H. [Does a stomach tube enhance regurgitation during general anaesthesia?]. Anaesthesist. 1983 Aug;32(8):407–9.

46. Ljungqvist O, Søreide E. Preoperative fasting. Br J Surg. 2003 Apr;90(4):400–6.

47. Søreide E, Eriksson LI, Hirlekar G, Eriksson H, Henneberg SW, Sandin R, et al. Pre-operative fasting guidelines: an update. Acta Anaesthesiol Scand. 2005 Sep;49(8):1041–7.

48. ERAS Compliance Group. The Impact of Enhanced Recovery Protocol Compliance on Elective Colorectal Cancer Resection: Results From an International Registry. Ann Surg. 2015 Jun;261(6):1153–9.

49. Jia Y, Jin G, Guo S, Gu B, Jin Z, Gao X, et al. Fast-track surgery decreases the incidence of postoperative delirium and other complications in elderly patients with colorectal carcinoma. Langenbecks Arch Surg. 2014 Jan;399(1):77–84.

50. Kobayashi S, Ooshima R, Koizumi S, Katayama M, Sakurai J, Watanabe T, et al. Perioperative care with fast-track management in patients undergoing pancreaticoduodenectomy. World J Surg. 2014 Sep;38(9):2430–7.

51. Lassen K, Soop M, Nygren J, Cox PBW, Hendry PO, Spies C, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. Arch Surg Chic Ill 1960. 2009 Oct;144(10):961–9.

52. Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). Ann Surg. 2011 Dec;254(6):868–75.

53. Ahmed J, Khan S, Lim M, Chandrasekaran TV, MacFie J. Enhanced recovery after surgery protocols - compliance and variations in practice during routine colorectal surgery. Colorectal Dis Off J Assoc Coloproctology G B Irel. 2012 Sep;14(9):1045–51.

54. Nicholson A, Lowe MC, Parker J, Lewis SR, Alderson P, Smith AF. Systematic review and meta-analysis of enhanced recovery programmes in surgical patients. Br J Surg. 2014 Feb;101(3):172–88.

55. Gustafsson UO, Oppelstrup H, Thorell A, Nygren J, Ljungqvist O. Adherence to the ERAS protocol is Associated with 5-Year Survival After Colorectal Cancer Surgery: A Retrospective Cohort Study. World J Surg. 2016;40(7):1741–7.

56. Shadish WR, Cook TD, Campbell DT. Experimental and Quasi-Experimental Designs for Generalized Causal Inference. 2 edition. Boston: Wadsworth Publishing; 2001. 656 p.

57. Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. BMJ. 2015 Jun 9;350:h2750.

58. Ramsay CR, Matowe L, Grilli R, Grimshaw JM, Thomas RE. Interrupted time series designs in health technology assessment: lessons from two systematic reviews of behavior change strategies. Int J Technol Assess Health Care. 2003;19(4):613–23.

59. Goodacre S. Uncontrolled before-after studies: discouraged by Cochrane and the EMJ. Emerg Med J EMJ. 2015 Jul;32(7):507–8.

3 Chapter 3: The Impact of the Implementation of the Enhanced Recovery After Surgery (ERAS®) Program in an Entire Health System: A Natural Experiment in Alberta, Canada[2]

Zaina H. AlBalawi Z, MD

Leah Gramlich, MD

Gregg Nelson, MD PhD

Peter A. Senior, MBBS PhD

Erik Youngson, MMath, A.Stat.

McAlister FA, MD MSc

[2] A version of this chapter has been published [Albalawi Z, Gramlich L, Nelson G, Senior P, Youngson E, McAlister FA. The Impact of the Implementation of the Enhanced Recovery After Surgery (ERAS®) Program in an Entire Health System: A Natural Experiment in Alberta, Canada World J Surg. 2018 Mar 12. doi: 10.1007/s00268-018-4559-0. [Epub ahead of print]

Introduction

A multimodal care approach to improve surgical outcomes (the Enhanced Recovery After Surgery [ERAS®] program) has demonstrated promising results, and is being implemented across many centers worldwide.[1,2] The ERAS protocol includes 22 components distributed among pre-, intra- and postoperative care.[3,4] A meta-analysis of 16 randomized controlled trials (RCTs) of enhanced recovery programs (including, but not limited to ERAS) demonstrated an approximately 40% reduction in postoperative complications and a 2.3 day reduction in length of stay (LOS) without any increase in readmission rates.[5] Earlier met-analyses reported up to 50% reduction in postoperative complications, but these included non-randomized studies, and were of poor quality.[6–8] However, as adherence to the ERAS program elements is a key driver of outcomes[9] and is likely to vary outside of the controlled setting of an RCT, it is important to confirm the benefits seen in RCTs do translate into clinical practice in real-world hospitals. Moreover, although they comprise a substantial proportion of the surgical population, patients with diabetes have not been included in previous trials of enhanced recovery programs and it is unclear whether they would obtain similar benefits compared to patients without diabetes.[10]

In the Canadian province of Alberta, ERAS® was implemented at the main colorectal surgical sites starting in 2013 for all patients, including those with diabetes, thereby precluding conducting an RCT. However, this allows us to evaluate the impact of ERAS on postoperative LOS and outcomes (postoperative complications and 30-day death, readmission, or ED visits after discharge) in an entire health care system and for those individuals with diabetes using an interrupted time series (ITS) analysis: a quasi-

experimental design that allows the evaluation of system-wide effectiveness accounting for any underlying secular trends.[11]

Hypothesis

Implementation of the ERAS program in colorectal surgical patients results in a reduction in postoperative length of stay, and postoperative complications (gastrointestinal, wounds, infections, renal and endocrine, cardiovascular, pulmonary, and neurological), with no increase in 30-day events after discharge (death/readmission/or ED visits).

Objectives

To evaluate the impact of ERAS program implementation on patients with and without diabetes who underwent elective colorectal surgery in Alberta. The outcomes of interest include acute length of stay (aLOS), postoperative complications (gastrointestinal, wounds, infections, renal and endocrine, cardiovascular, pulmonary, and neurological), 30-day death/readmission, 30-day death/ED visits, and 30-day death/readmission/ED visits.

Methods

Setting

The province of Alberta has a single integrated healthcare system, providing universal coverage for 4.2 million people. The six hospitals where ERAS was implemented are located in Calgary (2 hospitals; A and B) and Edmonton (4 hospitals; C-F). This study was approved by the Health Research Ethics Board at the University of

Alberta, and de-identified linked data from the Discharge Abstract Database (DAD; which captures acute care hospitalizations including admission and discharge dates, patient demographics, most responsible diagnosis and up to 24 other diagnoses, and procedure details), the National Ambulatory Care Reporting System (NACRS; which captures visits to emergency departments and in-hospital clinics including visit dates, most responsible diagnosis, and any procedure details), and the provincial registry which tracks the vital status of Albertans.

Cohort

All elective hospitalizations of adults (age ≥18 years) for colorectal surgery at one of the six major hospitals in the province of Alberta were identified in the 12 months pre and post ERAS implementation: Hospital A: Sep 2013 to Sep 2015, Hospital B: Oct 2012 to Oct 2014, Hospital C: Sep 2013 to Sep 2015, Hospital D: Sep 2012 to Sep 2014, Hospital E: Jul 2013 to Jul 2015, Hospital F: Jul 2013 to Jul 2015. Procedures had to be performed by a general surgeon, and on the same day of admission to eliminate patients already in-hospital for other medical conditions that have the potential to independently influence the outcomes of this study. For patients who met the criteria multiple times, only their first hospitalization was included. Patients from out of province were excluded because their postoperative outcomes could not be captured. All patients undergoing elective colorectal surgery in participating hospitals were approached at the time of their preoperative anesthesia assessment and those who consented to involvement in ERAS were actively followed by ERAS case managers during their hospitalization. Surgical ward nurses and attending surgical physician teams delivered inpatient care; the ERAS case managers monitored for complications via chart review and telephone follow-up

(note that complications captured in DAD are also collected via chart review by trained nosologists using the same procedures pre/post ERAS).

Covariates

Comorbidities were defined using International Classification of Disease ICD-10 codes from the index hospitalization and all hospitalizations, ED visits or ambulatory care visits in the 2 years prior to their index admission, using definitions previously validated in Alberta databases.[12,13] For example, our case definition of diabetes required a physician-assigned diagnosis of diabetes (ICD-10 codes E10-E14) in at least one hospitalization or ED visit in the prior 2 years. The Charlson Comorbidity score was defined using the above comorbidities and using original weights.[14,15] Rural residence was also captured from the patients' home postal codes and included as a covariate given the well-recognized association between location, socioeconomic status and colorectal cancer outcomes.[16]

Outcomes

Our primary outcome was Index Acute LOS, which was considered to be the number of days in acute care during the index hospitalization, but not counting any transfers to other hospitals or rehabilitation facilities within the same episode of care. Secondary outcomes included total LOS (all days during index hospitalization plus all days in transfer hospitals); postoperative complications (ICD-10 and Canadian Classification of Health Intervention (CCI) codes listed in **Appendix 1**); these have been shown to be sensitive for detecting Clavien class III or greater postoperative complications[17–19] –i.e. those that are most clinically relevant); 30-day death/readmission; 30-day death/ED visits; and 30-day death/readmission/ED visits after discharge from the

index hospitalization.[17] Hospitalizations were considered a readmission if they occurred within 30 days of discharge and were coded as 'urgent' rather than “elective”. Death was captured during the index hospitalization, as well as within 30 days of discharge from the index episode of care.

Analysis

Patient characteristics were summarized using proportions and means and compared between the pre and post ERAS periods (for all 6 sites combined) using Chi-Square tests and t-test, respectively. To evaluate the effect of ERAS on the outcomes of interest, we first conducted univariate analysis comparing outcomes in the pre and post ERAS periods, as well as the adjusted change (odds ratios for binary outcomes and difference in means for continuous outcomes), adjusting for age, sex, Charlson score, procedure type, surgical approach (laparoscopic or open), and hospital.

Finally, because the pre/post analyses does not account for secular trends we conducted an ITS analysis to further evaluate the impact of ERAS implementation. A time series was created using the 12 months prior and the 12 months after the month of implementation at each hospital (the month of implementation was excluded because implementation happened on different days of the month at each hospital and to give ward staff some time to “get up to speed” with all 22 components of ERAS). Note that due to implementation in different months across the hospitals, the time points are relative to month of implementation, rather than calendar month. Outcomes were summarized using bimonthly periods to reduce the variability due to small sample size within each month, resulting in 6 time points pre ERAS and 6 time points post ERAS implementation. Autoregressive integrated moving average (ARIMA) models were

initially considered, however stationarity was confirmed using the augmented Dickey-Fuller test and visual inspection of the autocorrelation, partial autocorrelation, and inverse autocorrelation plots suggested no autoregressive or moving average components were required. The lack of autocorrelation was further confirmed using the Durbin-Watson statistic. Thus, our final interrupted time series analysis was modeled using linear regression and including terms for a) pre ERAS intercept, b) pre ERAS slope, c) level change (intercept) post ERAS, and d) change in slope post ERAS. The analysis was repeated in the subset of patients with diabetes. In a sensitivity analysis, we re-ran the analysis using monthly data (12 time points pre ERAS and 12 time points post ERAS) and the results did not appreciably change.

In addition to the primary "intention to treat" analysis described above, three further sensitivity analyses were conducted: an "on-treatment analysis", a "higher-risk cohort analysis", and an "on-treatment-higher-risk cohort analysis". For the "on-treatment analysis", only data for patients in the post-ERAS phase who were clearly identified by the Alberta Health Services ERAS team as having consented to and received the ERAS program were analyzed (intended to maximize any potential benefit signal for ERAS). Note that other patients managed on the same wards may have also received elements of the ERAS program but as they were not followed by the ERAS case managers we could not be certain and thus they were only included in our primary "intention to treat" analysis. In the second "higher-risk cohort analysis", patients undergoing revision surgery in either timeframe were excluded (to focus on patients felt to be undergoing more complicated surgeries, again intended to maximize any benefit signal for ERAS). The third analysis was a combination of both analyses described above.

All statistical analysis was performed using SAS version 9.4 (Cary, NC) and R version 3.3.3 (Vienna, Austria).

Results

Our cohort consisted of 2,714 patients (mean age 60.4 years, 55% men) who underwent elective colorectal surgery in the 12 months before and after implementation of ERAS at the 6 teaching hospitals in Alberta where colorectal surgery is carried out (Figure 2). Patient demographics and comorbidity profiles were very similar in the pre/post ERAS time periods (Table 3), although there were more colon and laparoscopic surgeries done in the post ERAS phase and more revision surgery in the pre ERAS phase. The 428 patients with diabetes in our cohort were older and had higher comorbidity profiles than the patients without diabetes, but there were no appreciable differences between diabetic patients enrolled pre- or post ERAS implementation (Table 4). The baseline characteristics within each hospital were similar in the pre and post ERAS phases (Table 5, Table 6). There were minor differences between the patient profiles in the 6 hospitals we studied; laparoscopic approach was significantly higher in the post ERAS phase in hospitals A to D, and rural residence was higher in the pre-ERAS phase in hospital B only. Hospital F primarily performed open surgeries in both pre and post ERAS phases (92.8% and 92.6% respectively). For the diabetes group, no significant differences were present.

Length of Stay

For all elective colorectal surgery patients, LOS was significantly shorter in the post ERAS phase (Acute LOS 8.5 days vs. 9.5 days, p=0.01; Total LOS 9.4 days vs. 10.8

days, p=0.03), and these differences persisted after adjustment for age, sex, Charlson score, procedure type, surgical approach and hospital (-0.84 days [95%CI -.04 to -1.64 days) for Acute LOS and -1.15 days [95%CI 0.13 days to -2.44 days) for Total LOS - Table 7**.** However, this appeared to be due to a secular trend rather than implementation of ERAS since the interrupted time series demonstrated no significant level change (p=0.30 for Acute LOS and p=0.42 for Total LOS) or change in slope (p=0.63 and p=0.91 respectively) with ERAS implementation (Table 8, Figure 3, Figure 4). Individuals with diabetes had a longer LOS but no significant difference between post- and pre ERAS (Acute LOS 10.7 vs. 11.6 days, p=0.53; Total LOS 12.0 vs. 13.4 days, p=0.42; adjusted differences -0.63 and -0.84 days respectively with non-significant confidence intervals,(Table 7) and interrupted time series level changes p=0.56 and p=0.28 and slope changes p=0.66 and p=0.25) (Table 1, Figure 5, Figure 6).

Complications and 30-day Events

There were no significant differences in 30-day death/readmission rates (14.3% post vs. 13.5% pre ERAS, aOR 1.12, 95% CI 0.89 to 1.40), 30-day death/ED visit (27.2% post vs. 30.0% pre, aOR 0.93, 95% CI 0.78 to 1.10), or 30-day death/readmission/ED visit in all patients (27.8% post vs. 30.6% pre, aOR 0.93, 95% CI 0.78 to 1.10) – Table 7. The interrupted time series confirmed that ERAS implementation was not associated with any level changes in these three outcomes (p values 0.09, 0.26, and 0.22 respectively) – Table 8, Figure 7, Figure 8, **Figure 9**. The only statistically significant change observed with the ITS was a change in the slope of the trend line for 30-day death/readmission rates and the composite death/readmission/ED visits in all patients post ERAS demonstrating a more pronounced decline than would have been expected based on the

secular trend to that point in time (β -1.31; SE=0.37; p-value=0.008) and β -1.63; SE=0.64; p-value=0.035 respectively) –Table 8**,** Figure 7**,** Figure 8**.** This was present for all patients, but not for the subgroup with diabetes (where the pre/post slopes were nearly identical – p=0.89, p=0.51 respectively) –Figure 10, Figure 11, Figure 12.

Complications during the index hospitalization were higher after ERAS implementation (38.8% vs. 36.1%, aOR 1.22, 95% CI 1.03 to 1.43) **(**Table 7) largely due to increases in the proportion of patients with postoperative intestinal obstruction (10.2% vs. 7.9% or peritoneal adhesions (9.8% vs. 6.7%) –Table 10**.** However, this was not significantly associated with ERAS implementation (p=0.60 for a level change and p=0.18 for a slope change) **(**Table 8**,** Figure 13**)** and appeared to be due to changes in types of surgery over time as excluding revision surgeries in both timeframes ameliorated the apparent hazard (38.4% post vs. 38.3% pre, aOR 1.12, 95%CI 0.94 to 1.34) –Table 11**.** While the diabetes patients exhibited higher event rates for all 4 outcomes **(**Table 7), there were no statistically significant differences between the post- and pre ERAS timeframes. Postoperative complications however, approached clinical significance (adjusted OR 1.49 (0.98-2.27)) (Table 7) and were mainly due to an increase in postoperative intestinal obstruction (11.2% vs. 8.0% or peritoneal adhesions (10.2% vs. 5.6%) **-**Table 10**.** The interrupted time series confirmed no level changes (p values 0.99, 0.13, 0.07 and 0.85 respectively) –Table 9**,** Figure 10, Figure 11, Figure 12, **Figure 14**.

Mortality

Mortality within 30 days of admission was not significantly different between the pre and post ERAS phases; in all patients there were 14 (1%) vs. 20 (1.5%) deaths respectively (p=0.27), and in the diabetes group 3 (1.4%) vs. 4 (1.9%) p=0.71. In-

hospital mortality also did not differ post vs. pre (1.0% vs. 0.6% overall and 1.4% vs. 0.5% in the diabetes subgroup).

Sensitivity Analyses

The first sensitivity analysis (the "on-treatment analysis") was restricted to the 83% of patients definitely identified by the Alberta ERAS Program as having received ERAS in the post-ERAS timeframe. There appeared to be a selection bias in that those patients explicitly enrolled in ERAS were less sick than patients not listed as "ERAS patients" by the case managers (mean Charlson 2.7 vs. 3.8 preoperatively, 56.2% (626) open surgical procedure vs. 73.8% (166), 0 in-hospital deaths vs. 5.8% (13) in-hospital deaths, and 35.5% (396) perioperative complication rate vs. 55.1% (124) - Table 12. However, even those patients identified by Alberta Health Services as receiving ERAS did not demonstrate a statistically significant improvement in outcomes compared to the pre-ERAS phase in multivariate analysis or interrupted time series: 30-day death/readmission (12.5% post vs. 13.5% pre-ERAS, aOR 0.97, 95%CI 0.76-1.24, ITS p-value 0.90), 30-day death/ED visit (25.7% post vs. 30.0% pre, aOR 0.86, 95%CI 0.72-1.04, ITS p-value 0.21), or 30-day death/readmission/ED visit (26.2% post vs. 30.6% pre, aOR 0.87, 95%CI 0.72-1.04, ITS p-value 0.18). Although acute LOS was 1.2 (95%CI 0.4 to 2.1) days shorter for those patients definitely identified by the case managers as being exposed to the ERAS protocol in the post-phase, the ITS confirmed this was not statistically significant after accounting for underlying temporal trends (ITS p-value 0.37) -Table 13**,** Table 14**,** Table 15**.**

The second sensitivity analysis excluding patients undergoing revision surgery in either timeframe (the "high risk cohort analysis"), also did not identify any significant

association between ERAS implementation and better outcomes -Table 16**,** Table 17**,** Table 18**.** In fact, while 30-day rates of death/ED visit (26.7% post vs. 30.1% pre, aOR 0.91, 95%CI 0.75-1.09, ITS p-value 0.38), or 30-day death/readmission/ED visit (27.4% post vs. 30.8% pre, aOR 0.91, 95%CI 0.76-1.10, ITS p-value 0.38) did not change appreciably, the 30-day death/readmission rate was higher in the post-ERAS timeframe (14.6% post vs. 13.7% pre-ERAS, aOR 1.16, 95%CI 0.91 to 1.47, ITS p- value 0.008 as this represented a level increase when the background trend was declining) –Table 11, Table 17, Figure 15.

The final sensitivity analysis excluding revision surgeries in both timeframes *and* excluding those who were not part of the ERAS program post implementation resulted in comparable groups pre and post-ERAS, albeit a higher risk group pre-ERAS (Charlson comorbidity score 3.0 vs. 2.8 post-ERAS, p value 0.03) and more laparoscopic procedures done post-ERAS (46.9% vs. 34.3% pre-ERAS, p value <0.0001) **-**Table 18**.** Findings in all patients were similar to those seen in previous analyses with a significantly shorter LOS observed post-ERAS –but more pronounced-; 1.5 days shorter (95%CI -2.42 to -0.58), and no significant changes in postoperative complications or 30-day events post ERAS -Table 19. Interrupted time series similarly confirmed that this was not statistically significant after accounting for underlying temporal trends (ITS p-values 0.37, 0.32, 0.53, 0.22, and 0.2 respectively) -Table 20, **Figure 16**, Figure 17**,** Figure 18**,** Figure 19**,** Figure 20. For the diabetes subgroup, the same sensitivity analysis did not demonstrate statistically significant improvements post-ERAS in acute LOS (adjusted difference -2.06 days (95%CI -5.27 to 1.16, ITS p-value 0.37) **-**Figure 21**,** or outcomes compared to the pre-ERAS phase in multivariate analysis or interrupted time series: postoperative complications (35.3 % post vs. 38.3% pre-ERAS, aOR 1.03, 95%CI 0.86 to

1.24, ITS p-value 0.32) -Figure 22, 30-day death/readmission (12.6% post vs. 14.9% pre-ERAS, aOR 0.82, 95%CI 0.43-1.59, ITS p-value 1.0), 30-day death/ED visit (25.8% post vs. 32.2% pre, aOR 0.74, 95%CI 0.45-1.23, ITS p-value 0.43), or 30-day death/readmission/ED visit (26.4% post vs. 33.3% pre, aOR 0.73, 95%CI 0.44-1.21, ITS p-value 0.47) Table 19, Table 21, Figure 23, Figure 24, **Figure 25**.

Discussion

Although we found a significant decrease in LOS over time in Albertan adults undergoing colorectal surgery, this appeared to be a secular trend and was not related to ERAS implementation. We have seen similar declines in LOS for hospitalizations on medicine wards in Alberta in recent years too (likely attributable to more ready access to diagnostic imaging resources and better outpatient resources to enable sooner transitioning of patients including home intravenous therapy teams, wound care teams, and extra homecare capacity.[20] On the other hand, we observed non-significant decreases in post-discharge deaths/readmissions/or ED visits post vs. pre ERAS with no evidence of increased risk associated with ERAS implementation. We found that patients with diabetes were higher risk group, with longer LOS and higher event rates for all outcomes, but there were no significant differences in any outcomes after ERAS implementation. The higher risk of complications during the index hospitalization, driven largely by gastrointestinal complications, is worth noting, both within the overall population and the diabetic subgroup.

Interpreting the results within the existing literature:

There have been no RCTs evaluating ERAS® per se, but RCTs evaluating *other*

enhanced recovery and fast-track programs that overlap with ERAS® have demonstrated consistent results with reduction in LOS and postoperative complications without an increase in 30-day readmissions.[5,21–23] The majority of RCTs included in the previously published meta-analyses were small (2,376 participants in 16 RCTs) and more than half were at moderate to high risk of bias.[5,21–23] Support for ERAS® is extrapolated from those RCTs with the reasoning that the common element is minimizing surgical-metabolic stress and improving the patient's response to this stress.[24,25] Mean LOS in the largest meta-analysis was 5.8 days in the enhanced recovery group and 8 days in the control group [Weighted mean differences = - 2.28 days (- 3.09, - 1.47), $p<0.001$; heterogeneity $p<0.001$, I^2 =86 %], and no publication bias was identified.[5] Development of the initial ERAS® protocol for colorectal surgery stemmed from recognizing the need to optimize outcomes using standardized evidence-based components, and to support models for implementation of best perioperative practices with consistent audit tools.[24] Since the publication of the ERAS® protocol for colorectal surgery in 2005, several observational studies have demonstrated its effectiveness in reducing LOS and postoperative complications.[2,26,27] Those have been before-after studies and prospective cohorts without control groups which carry substantial inherent risks of bias, and cannot be used to infer causality.

Length of Stay

A recent uncontrolled before-after study of the first 15 months experience with ERAS® in 2 Alberta hospitals reported a mean LOS of 9.8 days (n=130) pre ERAS, compared to 7.5 days (n=697) post-ERAS ($p<0.0001$).[27] This is comparable to the acute LOS observed in our analysis of all 6 sites. The 2-site audit demonstrated that compliance

with ERAS elements increased within the first 3 months of implementation and then stayed constant thereafter with median compliance of 60% 15 months out at those 2 early adopter sites. On the other hand, median LOS in multicenter international ERAS® registries was 6 days -much shorter than that observed in our cohort- but compliance with components of ERAS was higher.[2,26] Lower compliance with components of the ERAS protocol could explain the apparent lack of effect of ERAS implementation in Alberta (either overall or even in the "on-treatment" analysis of those patients identified as having received the ERAS program) given that a dose-response relationship between compliance with ERAS elements and reduction in postoperative outcomes has been suggested in several studies; optimal outcomes were observed when compliance was >70%.[2,9,28]

Complications

In the large multicenter international ERAS® registry[2], postoperative complications were found to be 40.3%, comparable to those observed in our cohort (38.8% in all patients and 41.9% in the diabetes subgroup). Enhanced recovery processes in general have been shown to reduce complications by 10% to 20%, and in some meta-analyses up to 50%.[5–8,21–24,29] Although no reduction was observed in our study, this might be related to lower compliance to the ERAS® protocol (which was not captured in our analysis but was only 60% in the analysis of the 2 hospitals who were early adopters of ERAS in Alberta – one would expect adherence rates to be highest in early adopters)[27], or the predominance of open surgical approaches in Alberta (about 2/3 of colorectal surgeries compared to 53% in the largest case series completed to date).[2] Alternatively,

this might suggest that previously reported figures in trial participants may not be attainable in actual clinical practice.

Diabetes Subgroup

Evidence is scarce examining the impact of ERAS in individuals with diabetes.[10] Small observational studies have demonstrated inconsistent results; Luther et al reported a shorter LOS than our analysis; a median LOS of 7 days (n=18, IQR=5-15.5) post elective colorectal surgery in those with diabetes which was significantly longer than the 5 days observed in the non-diabetes group (n=125, IQR=4-7.5) p=0.04. No other outcomes relating to ERAS were reported.[30] On the other hand, Jorgenson et al demonstrated similar LOS in individuals with and without diabetes within a fast-track protocol –however in lower risk surgeries (i.e. primary total hip and knee arthroplasty)- and found that type 2 diabetes had limited influence on postoperative morbidity with both groups having an adjusted LOS <4days.[31] Both studies had small sample sizes.

An unexpected strong trend towards an excess in postoperative complications was observed in the diabetes group post ERAS implementation, although not statistically significant (adjusted OR = 1.49 (0.98 to 2.27). This was related to higher gastrointestinal complications: peritoneal adhesions (12 [5.6%] pre ERAS vs. 22 [10.2%] post ERAS) and small bowel obstructions (17 [8%] vs. 24 [11.2%]) with the latter associated with ileus in 96% of the cases. This was unexpected given that these particular complications have been shown to occur less frequently with early nutrition postoperatively, removal of gastric tubes, less use of opioids and early mobility– all key components of the ERAS program.[32] Whether carbohydrate loading preoperatively -part of the ERAS- has an

impact is unknown, and whether hyperglycemia perioperatively had an influence needs to be investigated further in an RCT (which we have initiated in Alberta). Another potential explanation may be a progressive increase in reporting of complications over time (i.e. "up-coding" where there isn't a change in actual complication rates, just an increase in recognition and/or mention in discharge summaries). The other variable that could have explained this harm signal would have been use of an open surgical approach -a well established risk factor for ileus and small bowel obstruction[33,34]- but despite the predominance of this surgical approach in the diabetes group, there was no significant increase in the post ERAS phase, in fact these were less. Prospective safety data is collected by the ERAS® audit system for all enrolled patients, and this would need to be further analyzed to determine potential contributors.

Strengths and Limitations

The strengths of this study include that the intervention of interest, ERAS®, occurred independent of other changes over time, and by using routinely collected administrative health data there was no influence of ERAS or our study on data collection for the outcomes of interest and no possibility of a Hawthorne effect. The primary outcomes examined were objective and derived from routinely collected health data using validated ICD-10 codes in both the pre and post-ERAS periods. This also allowed capturing 100% of subjects at each data point. Given that this study was undertaken in a real-world setting, it carries stronger external validity compared to an RCT and allows an assessment of the longitudinal impact of ERAS®. Our analysis also meets criteria for a high quality interrupted time series design[35] and ITS has been recognized by the Cochrane Effective Practice and Organization of Care methods group

(http://epoc.cochrane.org/) as the strongest study design after RCTs for evaluation of organizational interventions in health care services.

A number of limitations however need to be considered when interpreting the results. First and foremost, individual patient data on adherence to the ERAS program was not available precluding an examination of whether the lack of apparent effect was due to non-adherence or true negative effects. However, no signal was detected in either the primary "intention to treat" or the sensitivity "on-treatment" analyses. Second, our ITS is not as robust as an RCT design, and residual confounding cannot be excluded. However, we also conducted multivariate analyses adjusting for baseline characteristics and type of surgery to compare post vs. pre-outcomes, and the fact that there were no significant changes in baseline characteristics between the pre and post-ERAS periods is reassuring for our ITS, as is the fact our results were similar in the "high risk cohort" analysis where differences would be most likely to be seen. Identification of covariates was based on the ICD codes which, although validated in Alberta[12,13] are subject to potential misclassification bias. Our ITS had 12 data points in total, and this may result in less power to detect an effect; however, these were equally distributed pre and post-ERAS, there was no autocorrelation, and the reported effect in the published RCTs was large, suggesting that our study was adequately powered.[36,37] Regardless, repeating this analysis in a couple of years with additional patients and as the hospitals optimize adherence to ERAS might detect a treatment effect too small to find in this study.

Future research and policy implications

We recommend analyzing prospectively collected ERAS® data using robust study designs (i.e. interrupted time series analysis where appropriate), and discourage

exclusively relying on uncontrolled before after studies to determine the effectiveness of ERAS® implementation. It is important to evaluate whether our results are replicated in other ERAS® cohorts, or whether these findings are specific to Alberta's surgical population. This would be best pioneered by the ERAS® Society to provide guidance and methodological support for analyzing their central database with data linkage to local administrative databases.

Further work is required to address the gap in perioperative care in individuals with diabetes. Analyzing this subgroup within ERAS® databases will help guide the design of RCTs utilizing diabetes-specific protocols; taking into account the higher preoperative risk and need for surgical prehabilitation, perioperative glycemic control, and adopting routine use of laparoscopy.

Conclusion

This robust study design demonstrated little change in LOS or perioperative outcomes in Alberta attributable to ERAS implementation. Further efforts are required to improve ERAS adherence before expecting the benefits suggested in RCTs to be accrued in routine clinical practice. Moreover, our data illustrate that individuals with diabetes remain at high risk, even within an ERAS program. Our study highlights the importance of prospectively evaluating any changes in care delivery models at a system level and the need for further interventions to improve perioperative outcomes for patients with diabetes undergoing colorectal surgery.

Acknowledgement: This work was supported by the Alberta Strategy for Patient Oriented Research Support Unit Data Platform. The authors thank Mr. Edwin Rogers,

M.A. (Senior Analyst, Clinical Analytics, Alberta Health Services) for assistance with colorectal surgery case definitions and logic, as well as access to the patient lists maintained by the ERAS team for cross-validation with our administrative data. They also extend their thanks to Jeff Bakal, PhD., P.Stat (Alberta SPOR Support Unit, University of Alberta) for assistance with study design and statistical methods and Peter Faris, PhD (Director, Research Facilitation, Analytics, DIMR, Alberta Health Services) for statistical review. Zaina Albalawi and Erik Youngson had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. None of the authors have any conflict of interest relating to this study.

.

Table 3 Patient characteristics pre and post ERAS implementation for all patients

Characteristic	Pre-ERAS N = 1375	Post-ERAS N = 1339	P-value
Age, mean (SD)	59.7 (15.0)	60.7 (14.6)	0.080
Male	738 (53.7)	748 (55.9)	0.252
Rural residence	158 (11.5)	150 (11.2)	0.813
Hospital			0.011
A	264 (19.2)	264 (19.7)	
B	267 (19.4)	324 (24.2)	
C	176 (12.8)	167 (12.5)	
D	203 (14.8)	190 (14.2)	
E	271 (19.7)	205 (15.3)	
F	194 (14.1)	189 (14.1)	
Procedure type			<.0001
Colon	645 (46.9)	739 (55.2)	
Rectal	457 (33.2)	478 (35.7)	
Revision	273 (19.9)	122 (9.1)	
Surgical approach			<.0001
Laparoscopic	396 (28.8)	547 (40.9)	
Open	979 (71.2)	792 (59.1)	
Charlson comorbidity score, mean (SD)	2.9 (2.6)	2.9 (2.5)	0.933
Myocardial infarction	68 (4.9)	50 (3.7)	0.122
Congestive heart failure	44 (3.2)	29 (2.2)	0.096
Peripheral vascular disease	32 (2.3)	23 (1.7)	0.260
Cerebrovascular disease	36 (2.6)	34 (2.5)	0.897
Dementia	12 (0.9)	14 (1.0)	0.644
Chronic pulmonary disease	156 (11.3)	114 (8.5)	0.014
Rheumatologic disease	28 (2.0)	25 (1.9)	0.750
Peptic ulcer disease	37 (2.7)	27 (2.0)	0.247
Mild liver disease	36 (2.6)	29 (2.2)	0.441
Diabetes without chronic complications	128 (9.3)	127 (9.5)	0.875
Diabetes with chronic complications	85 (6.2)	88 (6.6)	0.677
Hemiplegia or paraplegia	10 (0.7)	9 (0.7)	0.863
Renal disease	45 (3.3)	38 (2.8)	0.511
Any malignancy, including leukemia and lymphoma	538 (39.1)	606 (45.3)	0.001
Moderate or severe liver disease	5 (0.4)	7 (0.5)	0.532
Metastatic solid tumor	337 (24.5)	316 (23.6)	0.580
AIDS/HIV	0 (0.0)	1 (0.1)	0.311

Values are displayed as n(%) unless specified otherwise
ERAS Enhanced Recovery After Surgery; *SD* Standard Deviation; *AIDS* Acquired Immune Deficiency Syndrome; *HIV* Human Immunodeficiency Virus

Table 4 Patient characteristics pre and post ERAS implementation for patients with diabetes

Characteristic	Pre-ERAS N = 213	Post-ERAS N = 215	P-value
Age, mean (SD)	66.7 (11.3)	66.0 (9.9)	0.529
Male	134 (62.9)	142 (66.0)	0.498
Rural residence	37 (17.4)	27 (12.6)	0.163
Hospital			0.089
A	36 (16.9)	44 (20.5)	
B	37 (17.4)	52 (24.2)	
C	24 (11.3)	23 (10.7)	
D	25 (11.7)	33 (15.3)	
E	53 (24.9)	36 (16.7)	
F	38 (17.8)	27 (12.6)	
Procedure type			0.054
Colon	107 (50.2)	115 (53.5)	
Rectal	67 (31.5)	78 (36.3)	
Revision	39 (18.3)	22 (10.2)	
Surgical approach			0.288
Laparoscopic	65 (30.5)	76 (35.3)	
Open	148 (69.5)	139 (64.7)	
Charlson comorbidity score, mean (SD)	4.6 (2.5)	4.4 (2.4)	0.405
Myocardial infarction	20 (9.4)	15 (7.0)	0.362
Congestive heart failure	20 (9.4)	8 (3.7)	0.018
Peripheral vascular disease	8 (3.8)	4 (1.9)	0.235
Cerebrovascular disease	9 (4.2)	12 (5.6)	0.516
Dementia	4 (1.9)	3 (1.4)	0.694
Chronic pulmonary disease	42 (19.7)	28 (13.0)	0.061
Rheumatologic disease	1 (0.5)	4 (1.9)	0.181
Peptic ulcer disease	10 (4.7)	8 (3.7)	0.616
Mild liver disease	7 (3.3)	8 (3.7)	0.807
Diabetes without chronic complications	128 (60.1)	127 (59.1)	0.829
Diabetes with chronic complications	85 (39.9)	88 (40.9)	0.829
Hemiplegia or paraplegia	2 (0.9)	3 (1.4)	0.660
Renal disease	11 (5.2)	9 (4.2)	0.632
Any malignancy, including leukemia and lymphoma	116 (54.5)	115 (53.5)	0.840
Moderate or severe liver disease	2 (0.9)	1 (0.5)	0.557
Metastatic solid tumor	51 (23.9)	51 (23.7)	0.957
AIDS/HIV	0 (0.0)	0 (0.0)	n/a

Values are displayed as n(%) unless specified otherwise
ERAS Enhanced Recovery After Surgery; *SD* Standard Deviation; *AIDS* Acquired Immune Deficiency Syndrome; *HIV* Human Immunodeficiency Virus

Table 5 Patient characteristics pre and post ERAS implementation by hospital, for all patients

	Hospital A			Hospital B			Hospital C			Hospital D			Hospital E			Hospital F		
Characteristic	Pre-ERAS N = 264	Post-ERAS N = 264	P-value	Pre-ERAS N = 267	Post-ERAS N = 324	P-value	Pre-ERAS N = 176	Post-ERAS N = 167	P-value	Pre-ERAS N = 203	Post-ERAS N = 190	P-value	Pre-ERAS N = 271	Post-ERAS N = 205	P-value	Pre-ERAS N = 194	Post-ERAS N = 189	P-value
Age, mean (SD)	56.9 (15.2)	58.8 (14.9)	0.150	59.9 (15.1)	60.6 (13.9)	0.553	62.6 (13.2)	61.6 (15.3)	0.530	62.7 (13.7)	63.2 (13.7)	0.756	60.5 (14.3)	61.8 (13.4)	0.295	56.4 (16.8)	59.0 (16.3)	0.122
Male	139 (52.7)	152 (57.6)	0.255	136 (50.9)	188 (58.0)	0.085	93 (52.8)	94 (56.3)	0.522	104 (51.2)	99 (52.1)	0.863	152 (56.1)	107 (52.2)	0.398	114 (58.8)	108 (57.1)	0.749
Rural residence	16 (6.1)	22 (8.3)	0.312	34 (12.7)	25 (7.7)	0.043	25 (14.2)	24 (14.4)	0.965	11 (5.4)	18 (9.5)	0.124	45 (16.6)	29 (14.1)	0.464	27 (13.9)	32 (16.9)	0.414
Procedure type			0.001			<.000			0.000			0.002			0.016			0.019
Colon	132 (50.0)	166 (62.9)		102 (38.2)	169 (52.2)		86 (48.9)	87 (52.1)		86 (42.4)	111 (58.4)		133 (49.1)	113 (55.1)		106 (54.6)	93 (49.2)	
Rectal	74 (28.0)	69 (26.1)		111 (41.6)	132 (40.7)		61 (34.7)	74 (44.3)		78 (38.4)	61 (32.1)		84 (31.0)	71 (34.6)		49 (25.3)	71 (37.6)	
Revision	58 (22.0)	29 (11.0)		54 (20.2)	23 (7.1)		29 (16.5)	6 (3.6)		39 (19.2)	18 (9.5)		54 (19.9)	21 (10.2)		39 (20.1)	25 (13.2)	
Surgical approach			0.009			0.000			<.000			0.007			0.307			0.043
Laparoscopic	54 (20.5)	80 (30.3)		118 (44.2)	192 (59.3)		66 (37.5)	108 (64.7)		57 (28.1)	78 (41.1)		87 (32.1)	75 (36.6)		14 (7.2)	14 (7.4)	
Open	210 (79.5)	184 (69.7)		149 (55.8)	132 (40.7)		110 (62.5)	59 (35.3)		146 (71.9)	112 (58.9)		184 (67.9)	130 (63.4)		180 (92.8)	175 (92.6)	
Charlson comorbidity score, mean (SD)	3.4 (2.8)	3.6 (2.8)	0.459	2.7 (2.5)	2.6 (2.2)	0.372	2.5 (2.2)	2.5 (2.1)	0.965	2.9 (2.6)	3.3 (2.5)	0.159	3.1 (2.8)	2.7 (2.5)	0.139	2.4 (2.4)	2.6 (2.3)	0.414
Myocardial infarction	9 (3.4)	2 (0.8)	0.033	11 (4.1)	7 (2.2)	0.168	3 (1.7)	7 (4.2)	0.171	11 (5.4)	14 (7.4)	0.429	22 (8.1)	10 (4.9)	0.162	12 (6.2)	10 (5.3)	0.707
Congestive heart failure	9 (3.4)	2 (0.8)	0.033	9 (3.4)	5 (1.5)	0.146	3 (1.7)	7 (4.2)	0.171	5 (2.5)	6 (3.2)	0.676	10 (3.7)	4 (2.0)	0.266	8 (4.1)	5 (2.6)	0.425

(Continued)

	Hospital A			Hospital B			Hospital C			Hospital D			Hospital E			Hospital F		
Characteristic	Pre-ERAS N = 264	Post-ERAS N = 264	P-value	Pre-ERAS N = 267	Post-ERAS N = 324	P-value	Pre-ERAS N = 176	Post-ERAS N = 167	P-value	Pre-ERAS N = 203	Post-ERAS N = 190	P-value	Pre-ERAS N = 271	Post-ERAS N = 205	P-value	Pre-ERAS N = 194	Post-ERAS N = 189	P-value
Peripheral vascular disease	2 (0.8)	4 (1.5)	0.412	7 (2.6)	6 (1.9)	0.525	2 (1.1)	2 (1.2)	0.958	10 (4.9)	5 (2.6)	0.236	5 (1.8)	2 (1.0)	0.435	6 (3.1)	4 (2.1)	0.540
Cerebrovascular disease	7 (2.7)	4 (1.5)	0.361	7 (2.6)	8 (2.5)	0.907	3 (1.7)	2 (1.2)	0.695	8 (3.9)	5 (2.6)	0.468	9 (3.3)	5 (2.4)	0.573	2 (1.0)	10 (5.3)	0.017
Dementia	0 (0.0)	3 (1.1)	0.08	3 (1.1)	1 (0.3)	0.22	3 (1.7)	2 (1.2)	0.69	0 (0.0)	4 (2.1)	0.03	4 (1.5)	2 (1.0)	0.62	2 (1.0)	2 (1.1)	0.97
Chronic pulmonary disease	17 (6.4)	10 (3.8)	0.167	14 (5.2)	14 (4.3)	0.599	22 (12.5)	18 (10.8)	0.620	32 (15.8)	19 (10.0)	0.089	45 (16.6)	25 (12.2)	0.179	26 (13.4)	28 (14.8)	0.691
Rheumatologic disease	3 (1.1)	3 (1.1)	1.000	4 (1.5)	3 (0.9)	0.522	6 (3.4)	3 (1.8)	0.350	5 (2.5)	5 (2.6)	0.916	3 (1.1)	4 (2.0)	0.449	7 (3.6)	7 (3.7)	0.960
Peptic ulcer disease	5 (1.9)	7 (2.7)	0.559	7 (2.6)	4 (1.2)	0.214	2 (1.1)	2 (1.2)	0.958	3 (1.5)	3 (1.6)	0.935	9 (3.3)	4 (2.0)	0.364	11 (5.7)	7 (3.7)	0.363
Mild liver disease	11 (4.2)	5 (1.9)	0.128	2 (0.7)	3 (0.9)	0.815	1 (0.6)	1 (0.6)	0.970	7 (3.4)	3 (1.6)	0.240	8 (3.0)	6 (2.9)	0.987	7 (3.6)	11 (5.8)	0.207
Diabetes without chronic complications	22 (8.3)	26 (9.8)	0.545	23 (8.6)	32 (9.9)	0.599	17 (9.7)	15 (9.0)	0.829	16 (7.9)	17 (8.9)	0.704	27 (10.0)	24 (11.7)	0.542	23 (11.9)	13 (6.9)	0.095
Diabetes with chronic complications	14 (5.3)	18 (6.8)	0.466	14 (5.2)	20 (6.2)	0.629	7 (4.0)	8 (4.8)	0.713	9 (4.4)	16 (8.4)	0.106	26 (9.6)	12 (5.9)	0.136	15 (7.7)	14 (7.4)	0.905
Hemiplegia or paraplegia	2 (0.8)	3 (1.1)	0.653	1 (0.4)	0 (0.0)	0.270	0 (0.0)	0 (0.0)	n/a	3 (1.5)	2 (1.1)	0.707	4 (1.5)	3 (1.5)	0.991	0 (0.0)	1 (0.5)	0.310
Renal disease	4 (1.5)	2 (0.8)	0.412	8 (3.0)	8 (2.5)	0.694	0 (0.0)	4 (2.4)	0.039	12 (5.9)	4 (2.1)	0.056	10 (3.7)	8 (3.9)	0.904	11 (5.7)	12 (6.3)	0.789
Any malignancy, including leukemia and lymphoma	68 (25.8)	73 (27.7)	0.623	116 (43.4)	165 (50.9)	0.070	94 (53.4)	101 (60.5)	0.186	85 (41.9)	86 (45.3)	0.498	97 (35.8)	88 (42.9)	0.114	78 (40.2)	93 (49.2)	0.077

(Continued)

	Hospital A			Hospital B			Hospital C			Hospital D			Hospital E			Hospital F		
Characteristic	**Pre-ERAS N = 264**	**Post-ERAS N = 264**	**P-value**	**Pre-ERAS N = 267**	**Post-ERAS N = 324**	**P-value**	**Pre-ERAS N = 176**	**Post-ERAS N = 167**	**P-value**	**Pre-ERAS N = 203**	**Post-ERAS N = 190**	**P-value**	**Pre-ERAS N = 271**	**Post-ERAS N = 205**	**P-value**	**Pre-ERAS N = 194**	**Post-ERAS N = 189**	**P-value**
Moderate or severe liver disease	0 (0.0)	3 (1.1)	0.082	1 (0.4)	0 (0.0)	0.270	0 (0.0)	0 (0.0)	n/a	0 (0.0)	2 (1.1)	0.143	3 (1.1)	1 (0.5)	0.464	1 (0.5)	1 (0.5)	0.985
Metastatic solid tumor	107 (40.5)	114 (43.2)	0.537	61 (22.8)	61 (18.8)	0.230	30 (17.0)	23 (13.8)	0.402	47 (23.2)	54 (28.4)	0.232	67 (24.7)	39 (19.0)	0.139	25 (12.9)	25 (13.2)	0.921
AIDS/ HIV	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a	0 (0.0)	1 (0.5)	0.25	0 (0.0)	0 (0.0)	n/a

Values are displayed as n(%) unless specified otherwise

Table 6 Patient characteristics pre and post ERAS implementation by hospital, for patients with diabetes

	Hospital A			Hospital B			Hospital C			Hospital D			Hospital E			Hospital F		
Characteristic	**Pre-ERAS N = 36**	**Post-ERAS N = 44**	**P-value**	**Pre-ERAS N = 37**	**Post-ERAS N = 52**	**P-value**	**Pre-ERAS N = 24**	**Post-ERAS N = 23**	**P-value**	**Pre-ERAS N = 25**	**Post-ERAS N = 33**	**P-value**	**Pre-ERAS N = 53**	**Post-ERAS N = 36**	**P-value**	**Pre-ERAS N = 38**	**Post-ERAS N = 27**	**P-value**
Age, mean (SD)	66.6 (9.7)	65.2 (10.5)	0.53	68.8 (10.9)	65.9 (9.7)	0.19	66.1 (12.1)	68.6 (8.8)	0.42	65.5 (11.7)	68.1 (7.3)	0.30	68.4 (10.2)	65.6 (9.2)	0.20	63.4 (13.6)	63.3 (13.3)	0.99
Male	22 (61.1)	32 (72.7)	0.27	21 (56.8)	37 (71.2)	0.16	16 (66.7)	15 (65.2)	0.91	13 (52.0)	21 (63.6)	0.37	36 (67.9)	20 (55.6)	0.23	26 (68.4)	17 (63.0)	0.64
Rural residence	3 (8.3)	7 (15.9)	0.30	7 (18.9)	4 (7.7)	0.11	6 (25.0)	3 (13.0)	0.29	3 (12.0)	3 (9.1)	0.71	10 (18.9)	5 (13.9)	0.53	8 (21.1)	5 (18.5)	0.80
Procedure type			0.07			0.68			0.11			0.41			0.67			0.28
Colon	17 (47.2)	29 (65.9)		20 (54.1)	24 (46.2)		12 (50.0)	15 (65.2)		10 (40.0)	19 (57.6)		28 (52.8)	18 (50.0)		20 (52.6)	10 (37.0)	
Rectal	12 (33.3)	13 (29.5)		13 (35.1)	23 (44.2)		8 (33.3)	8 (34.8)		11 (44.0)	10 (30.3)		12 (22.6)	11 (30.6)		11 (28.9)	13 (48.1)	
Revision	7 (19.4)	2 (4.5)		4 (10.8)	5 (9.6)		4 (16.7)	0 (0.0)		4 (16.0)	4 (12.1)		13 (24.5)	7 (19.4)		7 (18.4)	4 (14.8)	
Surgical approach			0.60			0.41			0.18			0.83			0.54			0.39
Laparoscopic	8 (22.2)	12 (27.3)		16 (43.2)	27 (51.9)		10 (41.7)	14 (60.9)		9 (36.0)	11 (33.3)		21 (39.6)	12 (33.3)		1 (2.6)	0 (0.0)	

(Continued)

Characteristic	Hospital A			Hospital B			Hospital C			Hospital D			Hospital E			Hospital F		
	Pre-ERAS N = 36	Post-ERAS N = 44	P-value	Pre-ERAS N = 37	Post-ERAS N = 52	P-value	Pre-ERAS N = 24	Post-ERAS N = 23	P-value	Pre-ERAS N = 25	Post-ERAS N = 33	P-value	Pre-ERAS N = 53	Post-ERAS N = 36	P-value	Pre-ERAS N = 38	Post-ERAS N = 27	P-value
Open	28 (77.8)	32 (72.7)		21 (56.8)	25 (48.1)		14 (58.3)	9 (39.1)		16 (64.0)	22 (66.7)		32 (60.4)	24 (66.7)		37 (97.4)	27 (100.0)	
Charlson comorbidity	5.2 (2.6)	5.1 (2.7)	0.87	4.6 (2.4)	4.2 (2.2)	0.39	3.5 (1.8)	4.1 (2.3)	0.36	4.1 (2.3)	4.8 (2.3)	0.20	5.3 (2.9)	4.0 (2.6)	0.03	4.3 (2.3)	4.2 (1.8)	0.86
Myocardial infarction	5 (13.9)	1 (2.3)	0.05	2 (5.4)	2 (3.8)	0.72	0 (0.0)	3 (13.0)	0.06	1 (4.0)	4 (12.1)	0.27	6 (11.3)	2 (5.6)	0.35	6 (15.8)	3 (11.1)	0.59
Congestive heart failure	4 (11.1)	0 (0.0)	0.02	5 (13.5)	2 (3.8)	0.09	1 (4.2)	2 (8.7)	0.52	2 (8.0)	2 (6.1)	0.77	4 (7.5)	0 (0.0)	0.09	4 (10.5)	2 (7.4)	0.66
Peripheral vascular disease	0 (0.0)	1 (2.3)	0.36	0 (0.0)	2 (3.8)	0.22	1 (4.2)	0 (0.0)	0.32	2 (8.0)	0 (0.0)	0.09	1 (1.9)	0 (0.0)	0.40	4 (10.5)	1 (3.7)	0.30
Cerebrovascular disease	1 (2.8)	1 (2.3)	0.88	4 (10.8)	4 (7.7)	0.61	0 (0.0)	1 (4.3)	0.30	2 (8.0)	2 (6.1)	0.773	1 (1.9)	2 (5.6)	0.34	1 (2.6)	2 (7.4)	0.36
Dementia	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a	1 (4.2)	1 (4.3)	0.97	0 (0.0)	0 (0.0)	n/a	2 (3.8)	1 (2.8)	0.79	1 (2.6)	1 (3.7)	0.80
Chronic pulmonary	3 (8.3)	5 (11.4)	0.65	3 (8.1)	2 (3.8)	0.39	8 (33.3)	5 (21.7)	0.37	7 (28.0)	4 (12.1)	0.12	13 (24.5)	5 (13.9)	0.22	8 (21.1)	7 (25.9)	0.64

(Continued)

	Hospital A			Hospital B			Hospital C			Hospital D			Hospital E			Hospital F		
Characte-ristic	Pre-ERAS N = 36	Post-ERAS N = 44	P-value	Pre-ERAS N = 37	Post-ERAS N = 52	P-value	Pre-ERAS N = 24	Post-ERAS N = 23	P-value	Pre-ERAS N = 25	Post-ERAS N = 33	P-value	Pre-ERAS N = 53	Post-ERAS N = 36	P-value	Pre-ERAS N = 38	Post-ERAS N = 27	P-value
Rheumatologic disease	0 (0.0)	1 (2.3)	0.36	0 (0.0)	1 (1.9)	0.39	0 (0.0)	0 (0.0)	n/a	0 (0.0)	1 (3.0)	0.38	0 (0.0)	0 (0.0)	n/a	1 (2.6)	1 (3.7)	0.80
Peptic ulcer disease	2 (5.6)	2 (4.5)	0.83	1 (2.7)	0 (0.0)	0.23	0 (0.0)	1 (4.3)	0.30	1 (4.0)	1 (3.0)	0.84	4 (7.5)	2 (5.6)	0.71	2 (5.3)	2 (7.4)	0.72
Mild liver disease	3 (8.3)	1 (2.3)	0.21	0 (0.0)	1 (1.9)	0.39	1 (4.2)	0 (0.0)	0.32	1 (4.0)	1 (3.0)	0.84	1 (1.9)	3 (8.3)	0.15	1 (2.6)	2 (7.4)	0.36
Diabetes without chronic	22 (61.1)	26 (59.1)	0.85	23 (62.2)	32 (61.5)	0.95	17 (70.8)	15 (65.2)	0.68	16 (64.0)	17 (51.5)	0.34	27 (50.9)	24 (66.7)	0.14	23 (60.5)	13 (48.1)	0.32
Diabetes with chronic complications	14 (38.9)	18 (40.9)	0.85	14 (37.8)	20 (38.5)	0.95	7 (29.2)	8 (34.8)	0.68	9 (36.0)	16 (48.5)	0.34	26 (49.1)	12 (33.3)	0.14	15 (39.5)	14 (51.9)	0.32
Hemiplegia or paraplegia	1 (2.8)	0 (0.0)	0.26	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a	1 (4.0)	1 (3.0)	0.84	0 (0.0)	2 (5.6)	0.08	0 (0.0)	0 (0.0)	n/a
Renal disease	0 (0.0)	2 (4.5)	0.19	2 (5.4)	2 (3.8)	0.72	0 (0.0)	1 (4.3)	0.30	1 (4.0)	0 (0.0)	0.24	3 (5.7)	1 (2.8)	0.51	5 (13.2)	3 (11.1)	0.80
Any malignancy, including	16 (44.4)	17 (38.6)	0.60	21 (56.8)	29 (55.8)	0.92	15 (62.5)	15 (65.2)	0.84	15 (60.0)	17 (51.5)	0.52	26 (49.1)	20 (55.6)	0.54	23 (60.5)	17 (63.0)	0.84
Moderate or severe liver disease	0 (0.0)	1 (2.3)	0.36	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a	1 (1.9)	0 (0.0)	0.40	1 (2.6)	0 (0.0)	0.39
Metastatic solid tumor	14 (38.9)	18 (40.9)	0.85	10 (27.0)	12 (23.1)	0.67	2 (8.3)	3 (13.0)	0.60	3 (12.0)	10 (30.3)	0.09	18 (34.0)	6 (16.7)	0.07	4 (10.5)	2 (7.4)	0.66
AIDS/HIV	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a

Values are displayed as n(%) unless specified otherwise

Table 7 Patient outcomes pre and post ERAS implementation for all patients and the diabetes subgroup

	All Patients				Diabetes Subgroup			
Outcome	**Pre-ERAS N = 1375**	**Post-ERAS N = 1339**	**P-value**	**Adjusted* change (95% CI)**	**Pre-ERAS N = 213**	**Post-ERAS N = 215**	**P-value**	**Adjusted* change (95% CI)**
30 day death/readmission, n(%)	186 (13.5)	191 (14.3)	0.579	OR = 1.12 (0.89 to 1.40)	31 (14.6)	37 (17.2)	0.452	OR = 1.36 (0.79 to 2.34)
30 day death/ED visit, n(%)	413 (30.0)	364 (27.2)	0.100	OR = 0.93 (0.78 to 1.10)	70 (32.9)	68 (31.6)	0.785	OR = 1.02 (0.67 to 1.56)
30 day death/readmission/ED visit, n(%)	421 (30.6)	372 (27.8)	0.104	OR = 0.93 (0.78 to 1.10)	72 (33.8)	69 (32.1)	0.707	OR = 1.00 (0.66 to 1.53)
Total length of stay (days), mean (SD)	10.8 (16.8)	9.4 (17.4)	0.032	Diff = -1.15 (-2.44 to 0.13)	13.4 (19.5)	12.0 (17.0)	0.424	Diff = -0.84 (-4.23 to 2.55)
Acute length of stay (days), mean (SD)	9.5 (11.6)	8.5 (9.8)	0.011	Diff = -0.84 (-1.64 to -0.04)	11.6 (15.3)	10.7 (13.6)	0.529	Diff = -0.63 (-3.35 to 2.09)
Any index hosp. complication, n(%)	496 (36.1)	520 (38.8)	0.137	OR = 1.22 (1.03 to 1.43)	77 (36.2)	90 (41.9)	0.226	OR = 1.49 (0.98 to 2.27)
Gastrointestinal	283 (20.6)	327 (24.4)	0.017		33 (15.5)	50 (23.3)	0.042	
Wounds	138 (10.0)	141 (10.5)	0.672		16 (7.5)	22 (10.2)	0.322	
Infections	154 (11.2)	155 (11.6)	0.758		28 (13.1)	35 (16.3)	0.360	
Renal and Endocrine	72 (5.2)	61 (4.6)	0.412		19 (8.9)	23 (10.7)	0.537	
Cardiovascular disorders	120 (8.7)	116 (8.7)	0.953		34 (16.0)	31 (14.4)	0.656	
Pulmonary	34 (2.5)	41 (3.1)	0.349		9 (4.2)	13 (6.0)	0.394	
Neurological	21 (1.5)	32 (2.4)	0.105		5 (2.3)	10 (4.7)	0.195	

ED Emergency Department; *SD* standard Deviation

*OR = Odds ratio adjusted for age, sex, Charlson score, procedure type, surgical approach and hospital

*Diff = Difference in means adjusted for age, sex, Charlson score, procedure type, surgical approach and hospital

Table 8 Interrupted time series analysis for all patients using 2-month periods

	Intercept Pre-ERAS		Slope Pre-ERAS		Level change Post-ERAS		Change in slope Post-ERAS	
Outcome	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value
Death/readmission, %	11.49 (1.03)	<.0001	0.53 (0.26)	0.080	2.50 (1.30)	0.090	-1.31 (0.37)	0.008
Death/ED visit, %	26.37 (1.85)	<.0001	0.98 (0.47)	0.072	-2.86 (2.34)	0.256	-1.53 (0.67)	0.053
Death/readmission/ED visit, %	26.68 (1.77)	<.0001	1.07 (0.45)	0.047	-2.95 (2.24)	0.224	-1.63 (0.64)	0.035
Total length of stay, mean	10.86 (1.14)	<.0001	-0.04 (0.29)	0.903	-1.22 (1.44)	0.421	0.05 (0.41)	0.908
Acute length of stay, mean	9.63 (0.82)	<.0001	-0.05 (0.21)	0.831	-1.17 (1.04)	0.295	0.15 (0.30)	0.626
Any complication, %	36.04 (2.56)	<.0001	-0.01 (0.66)	0.983	-1.75 (3.24)	0.604	1.38 (0.93)	0.175

ED Emergency Department; *SE* Standard Error

Table 9 Interrupted time series analysis for all patients with diabetes using 2-month periods

	Intercept - Pre-ERAS		Slope - Pre-ERAS		Level change - Post-ERAS		Change in slope - Post-ERAS	
Outcome	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value
Death/readmission, %	13.39 (3.95)	0.010	0.44 (1.01)	0.678	-0.06 (5.01)	0.991	-0.21 (1.44)	0.888
Death/ED visit, %	29.86 (5.20)	0.000	0.78 (1.33)	0.576	-11.05 (6.58)	0.132	1.39 (1.89)	0.482
Death/readmission/ED visit, %	30.11 (4.47)	0.000	0.99 (1.15)	0.414	-11.88 (5.66)	0.069	1.11 (1.62)	0.514
Total length of stay, mean	9.57 (2.79)	0.009	1.12 (0.72)	0.155	-4.11 (3.53)	0.278	-1.27 (1.01)	0.245
Acute length of stay, mean	11.83 (2.67)	0.002	-0.11 (0.69)	0.881	-2.05 (3.37)	0.560	0.45 (0.97)	0.657
Any complication, %	36.08 (9.10)	0.004	-0.06 (2.34)	0.979	-2.30 (11.53)	0.847	2.08 (3.31)	0.547

ED Emergency Department; *SE* Standard Error

Table 10 Breakdown of gastrointestinal complications using ICD-10 codes

ICD-10 Code Description of Gastrointestinal Complications	All Patients		Diabetes Subgroup	
	Pre-ERAS N = 1375	Post-ERAS N = 1339	Pre-ERAS N = 213	Post-ERAS N = 215
Duodenal ulcer, acute with haemorrhage	1 (0.1)	0 (0.0)	1 (0.5)	0 (0.0)
Acute vascular disorders of intestine	4 (0.3)	9 (0.7)	0 (0.0)	4 (1.9)
Paralytic ileus	2 (0.1)	1 (0.1)	1 (0.5)	0 (0.0)
Intestinal adhesions [bands] with obstruction	15 (1.1)	9 (0.7)	0 (0.0)	1 (0.5)
Other and unspecified intestinal obstruction	41 (3.0)	44 (3.3)	5 (2.3)	3 (1.4)
Ileus, unspecified	57 (4.1)	76 (5.7)	9 (4.2)	19 (8.8)
Perforation of intestine (nontraumatic)	4 (0.3)	7 (0.5)	0 (0.0)	2 (0.9)
Other specified diseases of intestine (small)(large)	3 (0.2)	4 (0.3)	0 (0.0)	1 (0.5)
Peritoneal adhesions	92 (6.7)	131 (9.8)	12 (5.6)	22 (10.2)
Acute pancreatitis, unspecified	3 (0.2)	1 (0.1)	2 (0.9)	0 (0.0)
Postoperative intestinal obstruction	109 (7.9)	137 (10.2)	17 (8.0)	24 (11.2)
Malfunction of colostomy stoma, not elsewhere classified	9 (0.7)	2 (0.1)	2 (0.9)	1 (0.5)
Enterostomy malfunction, not elsewhere classified	12 (0.9)	13 (1.0)	1 (0.5)	4 (1.9)
Other postprocedural disorders of digestive system, not elsewhere classified	4 (0.3)	3 (0.2)	1 (0.5)	0 (0.0)
Melaena	4 (0.3)	2 (0.1)	2 (0.9)	0 (0.0)
Haemorrhage and haematoma complicating a procedure, not elsewhere classified	35 (2.5)	41 (3.1)	6 (2.8)	7 (3.3)

Table 11 Sensitivity Analysis: Patient outcomes pre and post ERAS implementation for all patients excluding revision procedures

Outcome	Pre-ERAS N = 1102	Post-ERAS N = 1217	P-value	Adjusted change (95% CI)
30 day death/readmission, n(%)	151 (13.7)	178 (14.6)	0.524	OR = 1.16 (0.91 to 1.47)
30 day death/ED visit, n(%)	332 (30.1)	325 (26.7)	0.068	OR = 0.91 (0.75 to 1.09)
30 day death/readmission/ED visit, n(%)	339 (30.8)	333 (27.4)	0.072	OR = 0.91 (0.76 to 1.10)
Total length of stay (days), mean (SD)	11.3 (17.5)	9.3 (17.3)	0.006	Diff = -1.58 (-2.99 to -0.18)
Acute length of stay (days), mean (SD)	9.9 (12.3)	8.4 (9.3)	0.000	Diff = -1.25 (-2.11 to -0.39)
Any index hosp. complication, n(%)	422 (38.3)	467 (38.4)	0.969	OR = 1.12 (0.94 to 1.34)
Gastrointestinal	243 (22.1)	284 (23.3)	0.461	
Wounds	120 (10.9)	123 (10.1)	0.539	
Infections	135 (12.3)	142 (11.7)	0.666	
Renal and Endocrine	58 (5.3)	55 (4.5)	0.406	
Cardiovascular disorders	103 (9.3)	110 (9.0)	0.798	
Pulmonary	31 (2.8)	39 (3.2)	0.582	
Neurological	19 (1.7)	28 (2.3)	0.325	

ED Emergency Department; *SD* standard Deviation

*OR = Odds ratio adjusted for age, sex, Charlson score, procedure type, surgical approach and hospital

*Diff = Difference in means adjusted for age, sex, Charlson score, procedure type, surgical approach and hospital

Table 12 Comparison of patients POST-ERAS by whether or not they were identified by the Alberta Health Services ERAS Team as having received ERAS services

Characteristic	No N = 225	Yes N = 1114	P-value
Age, mean (SD)	60.5 (13.7)	60.7 (14.8)	0.832
Male	126 (56.0)	622 (55.8)	0.964
Rural residence	32 (14.2)	118 (10.6)	0.115
Hospital			<.0001
A	76 (33.8)	188 (16.9)	
B	21 (9.3)	303 (27.2)	
C	11 (4.9)	156 (14.0)	
D	24 (10.7)	166 (14.9)	
E	71 (31.6)	134 (12.0)	
F	22 (9.8)	167 (15.0)	
Procedure type			<.0001
Colon	157 (69.8)	582 (52.2)	
Rectal	39 (17.3)	439 (39.4)	
Revision	29 (12.9)	93 (8.3)	
Surgical approach			<.0001
Laparoscopic	59 (26.2)	488 (43.8)	
Open	166 (73.8)	626 (56.2)	
Charlson comorbidity score, mean (SD)	3.8 (2.9)	2.7 (2.3)	<.0001
Myocardial infarction	13 (5.8)	37 (3.3)	0.076
Congestive heart failure	4 (1.8)	25 (2.2)	0.661
Peripheral vascular disease	6 (2.7)	17 (1.5)	0.230
Cerebrovascular disease	10 (4.4)	24 (2.2)	0.046
Dementia	4 (1.8)	10 (0.9)	0.237
Chronic pulmonary disease	27 (12.0)	87 (7.8)	0.040
Rheumatologic disease	4 (1.8)	21 (1.9)	0.914
Peptic ulcer disease	7 (3.1)	20 (1.8)	0.200
Mild liver disease	9 (4.0)	20 (1.8)	0.038
Diabetes without chronic complications	19 (8.4)	108 (9.7)	0.559
Diabetes with chronic complications	21 (9.3)	67 (6.0)	0.067
Hemiplegia or paraplegia	3 (1.3)	6 (0.5)	0.183
Renal disease	15 (6.7)	23 (2.1)	0.000
Any malignancy, including leukemia and lymphoma	70 (31.1)	536 (48.1)	<.0001
Moderate or severe liver disease	1 (0.4)	6 (0.5)	0.858
Metastatic solid tumor	87 (38.7)	229 (20.6)	<.0001
AIDS/HIV	1 (0.4)	0 (0.0)	0.026
Outcomes:			
In-hospital mortality, n(%)	13 (5.8)	0 (0.0)	<.0001
30 day death, including in-hospital, n(%)	16 (7.1)	4 (0.4)	<.0001
30 day death/readmission, n(%)	52 (23.1)	139 (12.5)	<.0001
30 day death/ED visit, n(%)	78 (34.7)	286 (25.7)	0.006
30 day death/readmission/ED visit, n(%)	80 (35.6)	292 (26.2)	0.004
Total length of stay (days), mean (SD)	11.7 (12.7)	8.9 (18.1)	0.026
Acute length of stay (days), mean (SD)	11.0 (11.4)	8.0 (9.4)	<.0001
Any index hosp. complication, n(%)	124 (55.1)	396 (35.5)	<.0001

Values are displayed as n(%) unless specified otherwise
ERAS Enhanced Recovery After Surgery; *SD* Standard Deviation; *AIDS* Acquired Immune Deficiency Syndrome; *HIV* Human Immunodeficiency Virus; ED Emergency Department; SE Standard Error

Table 13 Sensitivity Analysis: Patient characteristics pre and post ERAS implementation for all patients, excluding POST patients who were not part of the ERAS program

Characteristic	Pre-ERAS N = 1375	Post-ERAS N = 1114	P-value
Age, mean (SD)	59.7 (15.0)	60.7 (14.8)	0.086
Male	738 (53.7)	622 (55.8)	0.281
Rural residence	158 (11.5)	118 (10.6)	0.478
Hospital			<.0001
A	264 (19.2)	188 (16.9)	
B	267 (19.4)	303 (27.2)	
C	176 (12.8)	156 (14.0)	
D	203 (14.8)	166 (14.9)	
E	271 (19.7)	134 (12.0)	
F	194 (14.1)	167 (15.0)	
Procedure type			<.0001
Colon	645 (46.9)	582 (52.2)	
Rectal	457 (33.2)	439 (39.4)	
Revision	273 (19.9)	93 (8.3)	
Surgical approach			<.0001
Laparoscopic	396 (28.8)	488 (43.8)	
Open	979 (71.2)	626 (56.2)	
Charlson comorbidity score, mean (SD)	2.9 (2.6)	2.7 (2.3)	0.085
Myocardial infarction	68 (4.9)	37 (3.3)	0.045
Congestive heart failure	44 (3.2)	25 (2.2)	0.149
Peripheral vascular disease	32 (2.3)	17 (1.5)	0.153
Cerebrovascular disease	36 (2.6)	24 (2.2)	0.453
Dementia	12 (0.9)	10 (0.9)	0.947
Chronic pulmonary disease	156 (11.3)	87 (7.8)	0.003
Rheumatologic disease	28 (2.0)	21 (1.9)	0.787
Peptic ulcer disease	37 (2.7)	20 (1.8)	0.138
Mild liver disease	36 (2.6)	20 (1.8)	0.169
Diabetes without chronic complications	128 (9.3)	108 (9.7)	0.744
Diabetes with chronic complications	85 (6.2)	67 (6.0)	0.862
Hemiplegia or paraplegia	10 (0.7)	6 (0.5)	0.558
Renal disease	45 (3.3)	23 (2.1)	0.066
Any malignancy, including leukemia and lymphoma	538 (39.1)	536 (48.1)	<.0001
Moderate or severe liver disease	5 (0.4)	6 (0.5)	0.513
Metastatic solid tumor	337 (24.5)	229 (20.6)	0.019
AIDS/HIV	0 (0.0)	0 (0.0)	n/a

Values are displayed as n(%) unless specified otherwise
ERAS Enhanced Recovery After Surgery; *SD* Standard Deviation; *AIDS* Acquired Immune Deficiency Syndrome; *HIV* Human Immunodeficiency Virus

Table 14 Sensitivity Analysis: Patient outcomes pre and post ERAS implementation, excluding POST patients who were not part of the ERAS program

Outcome	Pre-ERAS N = 1375	Post-ERAS N = 1114	P-value	Adjusted* change (95% CI)
30 day death/readmission, n(%)	186 (13.5)	139 (12.5)	0.440	OR = 0.97 (0.76 to 1.24)
30 day death/ED visit, n(%)	413 (30.0)	286 (25.7)	0.016	OR = 0.86 (0.72 to 1.04)
30 day death/readmission/ED visit, n(%)	421 (30.6)	292 (26.2)	0.016	OR = 0.87 (0.72 to 1.04)
Total length of stay (days), mean (SD)	10.8 (16.8)	8.9 (18.1)	0.007	Diff = -1.43 (-2.83 to -0.04)
Acute length of stay (days), mean (SD)	9.5 (11.6)	8.0 (9.4)	0.000	Diff = -1.23 (-2.08 to -0.39)
Any index hosp. complication, n(%)	496 (36.1)	396 (35.5)	0.786	OR = 1.10 (0.92 to 1.31)
Gastrointestinal	283 (20.6)	252 (22.6)	0.218	
Wounds	138 (10.0)	99 (8.9)	0.331	
Infections	154 (11.2)	110 (9.9)	0.286	
Renal and Endocrine	72 (5.2)	42 (3.8)	0.082	
Cardiovascular disorders	120 (8.7)	79 (7.1)	0.135	
Pulmonary	34 (2.5)	25 (2.2)	0.709	
Neurological	21 (1.5)	23 (2.1)	0.312	

ED Emergency Department; *SD* standard Deviation

*OR = Odds ratio adjusted for age, sex, Charlson score, procedure type, surgical approach and hospital

*Diff = Difference in means adjusted for age, sex, Charlson score, procedure type, surgical approach and hospital

Table 15 Sensitivity Analysis: Interrupted time series analysis excluding POST patients who were not part of the ERAS program

	Intercept Pre-ERAS		Slope Pre-ERAS		Level change Post-ERAS		Change in slope Post-ERAS	
Outcome	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value
Death/readmission, %	11.49 (1.18)	<.0001	0.53 (0.30)	0.120	0.19 (1.50)	0.903	-1.24 (0.43)	0.020
Death/ED visit, %	26.37 (2.23)	<.0001	0.98 (0.57)	0.124	-3.88 (2.82)	0.207	-1.78 (0.81)	0.059
Death/readmission/ED, %	26.68 (2.17)	<.0001	1.07 (0.56)	0.092	-4.06 (2.74)	0.177	-1.87 (0.79)	0.045
Total length of stay, mean	10.86 (1.28)	<.0001	-0.04 (0.33)	0.914	-0.89 (1.62)	0.597	-0.19 (0.46)	0.699
Acute length of stay, mean	9.63 (0.86)	<.0001	-0.05 (0.22)	0.838	-1.04 (1.09)	0.370	-0.04 (0.31)	0.904
Any complication, %	36.04 (2.60)	<.0001	-0.01 (0.67)	0.983	-3.27 (3.30)	0.350	0.91 (0.94)	0.367

Table 16 Sensitivity Analysis: Patient characteristics pre and post ERAS implementation for all patients excluding revision procedures

Characteristic	Pre-ERAS N = 1102	Post-ERAS N = 1217	P-value
Age, mean (SD)	60.6 (14.8)	61.5 (14.3)	0.144
Male	576 (52.3)	669 (55.0)	0.192
Rural residence	128 (11.6)	136 (11.2)	0.739
Hospital			0.010
A	206 (18.7)	235 (19.3)	
B	213 (19.3)	301 (24.7)	
C	147 (13.3)	161 (13.2)	
D	164 (14.9)	172 (14.1)	
E	217 (19.7)	184 (15.1)	
F	155 (14.1)	164 (13.5)	
Procedure type			0.282
Colon	645 (58.5)	739 (60.7)	
Rectal	457 (41.5)	478 (39.3)	
Surgical approach			<.0001
Laparoscopic	378 (34.3)	536 (44.0)	
Open	724 (65.7)	681 (56.0)	
Charlson comorbidity score, mean (SD)	3.0 (2.6)	3.0 (2.4)	0.653
Myocardial infarction	49 (4.4)	47 (3.9)	0.480
Congestive heart failure	36 (3.3)	29 (2.4)	0.198
Peripheral vascular disease	21 (1.9)	17 (1.4)	0.335
Cerebrovascular disease	29 (2.6)	33 (2.7)	0.905
Dementia	11 (1.0)	13 (1.1)	0.868
Chronic pulmonary disease	126 (11.4)	101 (8.3)	0.011
Rheumatologic disease	19 (1.7)	22 (1.8)	0.879
Peptic ulcer disease	30 (2.7)	26 (2.1)	0.359
Mild liver disease	28 (2.5)	25 (2.1)	0.434
Diabetes without chronic complications	108 (9.8)	116 (9.5)	0.827
Diabetes with chronic complications	66 (6.0)	77 (6.3)	0.736
Hemiplegia or paraplegia	8 (0.7)	7 (0.6)	0.651
Renal disease	34 (3.1)	31 (2.5)	0.433
Any malignancy, including leukemia and lymphoma	465 (42.2)	582 (47.8)	0.007
Moderate or severe liver disease	4 (0.4)	6 (0.5)	0.633
Metastatic solid tumor	288 (26.1)	298 (24.5)	0.362
AIDS/HIV	0 (0.0)	1 (0.1)	0.341
Values are displayed as n(%) unless specified otherwise			

Table 17 Sensitivity Analysis: Interrupted time series analysis for all patients excluding revision procedures

	Intercept Pre-ERAS		Slope Pre-ERAS		Level change Post-ERAS		Change in slope Post-ERAS	
Outcome	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value
Death/readmission, %	11.74 (0.83)	<.0001	0.51 (0.21)	0.044	3.69 (1.05)	0.008	-1.55 (0.30)	0.001
Death/ED visit, %	27.75 (2.58)	<.0001	0.58 (0.66)	0.408	-3.03 (3.27)	0.382	-0.92 (0.94)	0.356
Death/readmission/ED, %	28.25 (2.51)	<.0001	0.62 (0.64)	0.363	-2.99 (3.18)	0.375	-0.99 (0.91)	0.311
Total length of stay, mean	11.57 (1.57)	<.0001	-0.08 (0.40)	0.849	-1.69 (1.99)	0.421	0.07 (0.57)	0.904
Acute length of stay, mean	10.40 (1.12)	<.0001	-0.13 (0.29)	0.652	-1.40 (1.42)	0.353	0.20 (0.41)	0.638
Any complication, %	40.75 (3.79)	<.0001	-0.72 (0.97)	0.480	-3.28 (4.80)	0.514	2.24 (1.38)	0.142

ED Emergency Department; *SE* Standard Error

Table 18 Sensitivity Analysis: Patient characteristics pre and post ERAS implementation for all patients and the diabetes subgroup excluding revision procedures *and* POST patients who were not part of the ERAS program

	All Patients			Diabetes Subgroup		
Characteristic	**Pre-ERAS N = 1102**	**Post-ERAS N = 1021**	**P-value**	**Pre-ERAS N = 174**	**Post-ERAS N = 159**	**P-value**
Age, mean (SD)	60.6 (14.8)	61.5 (14.4)	0.134	67.4 (10.9)	66.8 (9.1)	0.566
Male	576 (52.3)	563 (55.1)	0.185	102 (58.6)	106 (66.7)	0.130
Rural residence	128 (11.6)	109 (10.7)	0.492	29 (16.7)	16 (10.1)	0.078
Hospital			<.0001			0.007
A	206 (18.7)	170 (16.7)		29 (16.7)	32 (20.1)	
B	213 (19.3)	281 (27.5)		33 (19.0)	45 (28.3)	
C	147 (13.3)	150 (14.7)		20 (11.5)	20 (12.6)	
D	164 (14.9)	150 (14.7)		21 (12.1)	27 (17.0)	
E	217 (19.7)	124 (12.1)		40 (23.0)	15 (9.4)	
F	155 (14.1)	146 (14.3)		31 (17.8)	20 (12.6)	
Procedure type			0.477			0.171
Colon	645 (58.5)	582 (57.0)		107 (61.5)	86 (54.1)	
Rectal	457 (41.5)	439 (43.0)		67 (38.5)	73 (45.9)	
Surgical approach			<.0001			0.443
Laparoscopic	378 (34.3)	479 (46.9)		64 (36.8)	65 (40.9)	
Open	724 (65.7)	542 (53.1)		110 (63.2)	94 (59.1)	
Charlson comorbidity score, mean (SD)	3.0 (2.6)	2.8 (2.3)	0.029	4.6 (2.4)	4.4 (2.2)	0.348
Myocardial infarction	49 (4.4)	35 (3.4)	0.229	13 (7.5)	10 (6.3)	0.671
Congestive heart failure	36 (3.3)	25 (2.4)	0.260	17 (9.8)	8 (5.0)	0.101
Peripheral vascular disease	21 (1.9)	13 (1.3)	0.246	5 (2.9)	3 (1.9)	0.557
Cerebrovascular disease	29 (2.6)	24 (2.4)	0.679	7 (4.0)	10 (6.3)	0.348
Dementia	11 (1.0)	10 (1.0)	0.965	4 (2.3)	3 (1.9)	0.794
Chronic pulmonary disease	126 (11.4)	80 (7.8)	0.005	31 (17.8)	19 (11.9)	0.134
Rheumatologic disease	19 (1.7)	19 (1.9)	0.812	1 (0.6)	4 (2.5)	0.146
Peptic ulcer disease	30 (2.7)	20 (2.0)	0.247	8 (4.6)	5 (3.1)	0.494
Mild liver disease	28 (2.5)	17 (1.7)	0.162	5 (2.9)	5 (3.1)	0.885
Diabetes without chronic complications	108 (9.8)	100 (9.8)	0.996	108 (62.1)	100 (62.9)	0.877
Diabetes with chronic complications	66 (6.0)	59 (5.8)	0.837	66 (37.9)	59 (37.1)	0.877
Hemiplegia or paraplegia	8 (0.7)	4 (0.4)	0.305	1 (0.6)	2 (1.3)	0.510
Renal disease	34 (3.1)	22 (2.2)	0.181	8 (4.6)	4 (2.5)	0.309
Any malignancy, including leukemia and lymphoma	465 (42.2)	518 (50.7)	<.0001	100 (57.5)	95 (59.7)	0.674
Moderate or severe liver disease	4 (0.4)	5 (0.5)	0.653	2 (1.1)	1 (0.6)	0.616
Metastatic solid tumor	288 (26.1)	216 (21.2)	0.007	41 (23.6)	34 (21.4)	0.634
AIDS/HIV	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a

Values are displayed as n(%) unless specified otherwise
ERAS Enhanced Recovery After Surgery; *SD* Standard Deviation; *AIDS* Acquired Immune Deficiency Syndrome; *HIV* Human Immunodeficiency Virus

Table 19 Sensitivity Analysis: Patient outcomes pre and post ERAS implementation, excluding revision procedures *and* POST patients who were not part of the ERAS program

	All Patients				Diabetes Subgroup			
Outcome	**Pre-ERAS N = 1102**	**Post-ERAS N = 1021**	**P-value**	**Adjusted* change (95% CI)**	**Pre-ERAS N = 174**	**Post-ERAS N = 159**	**P-value**	**Adjusted* change (95% CI)**
30 day death/readmission, n(%)	151 (13.7)	131 (12.8)	0.554	OR = 1.01 (0.78 to 1.31)	26 (14.9)	20 (12.6)	0.532	OR = 0.82 (0.43 to 1.59)
30 day death/ED visit, n(%)	332 (30.1)	256 (25.1)	0.009	OR = 0.84 (0.69 to 1.03)	56 (32.2)	41 (25.8)	0.199	OR = 0.74 (0.45 to 1.23)
30 day death/readmission/ED visit, n(%)	339 (30.8)	262 (25.7)	0.009	OR = 0.85 (0.70 to 1.03)	58 (33.3)	42 (26.4)	0.169	OR = 0.73 (0.44 to 1.21)
Total length of stay (days), mean (SD)	11.3 (17.5)	8.9 (18.2)	0.002	Diff = -1.75 (-3.27 to -0.24)	14.1 (21.1)	11.2 (17.5)	0.176	Diff = -1.90 (-6.04 to 2.23)
Acute length of stay (days), mean (SD)	9.9 (12.3)	7.9 (9.1)	<.0001	Diff = -1.50 (-2.42 to -0.58)	12.0 (16.5)	9.7 (13.0)	0.160	Diff = -2.06 (-5.27 to 1.16)
Any index hosp. complication, n(%)	422 (38.3)	360 (35.3)	0.148	OR = 1.03 (0.86 to 1.24)	63 (36.2)	59 (37.1)	0.865	OR = 1.34 (0.82 to 2.19)
Gastrointestinal	243 (22.1)	224 (21.9)	0.951		24 (13.8)	32 (20.1)	0.123	
Wounds	120 (10.9)	89 (8.7)	0.093		15 (8.6)	13 (8.2)	0.884	
Infections	135 (12.3)	102 (10.0)	0.099		24 (13.8)	21 (13.2)	0.876	
Renal and Endocrine	58 (5.3)	37 (3.6)	0.068		14 (8.0)	12 (7.5)	0.865	
Cardiovascular disorders	103 (9.3)	75 (7.3)	0.097		29 (16.7)	19 (11.9)	0.221	
Pulmonary	31 (2.8)	24 (2.4)	0.503		8 (4.6)	7 (4.4)	0.932	
Neurological	19 (1.7)	21 (2.1)	0.573		4 (2.3)	8 (5.0)	0.181	

ED Emergency Department; *SD* standard Deviation

*OR = Odds ratio adjusted for age, sex, Charlson score, procedure type, surgical approach and hospital

*Diff = Difference in means adjusted for age, sex, Charlson score, procedure type, surgical approach and hospital

Table 20 Sensitivity Analysis: Interrupted time series analysis for all patients excluding revision procedures *and* POST patients who were not part of the ERAS program

	Intercept Pre-ERAS		Slope Pre-ERAS		Level change Post-ERAS		Change in slope Post-ERAS	
Outcome	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value
Death/readmission, %	11.74 (1.18)	<.0001	0.51 (0.30)	0.133	0.97 (1.50)	0.535	-1.37 (0.43)	0.013
Death/ED visit, %	27.75 (3.03)	<.0001	0.58 (0.78)	0.479	-5.13 (3.84)	0.219	-0.91 (1.10)	0.434
Death/readmission/ED, %	28.25 (2.95)	<.0001	0.62 (0.76)	0.436	-5.19 (3.74)	0.203	-0.97 (1.07)	0.392
Total length of stay, mean	11.57 (1.66)	<.0001	-0.08 (0.43)	0.857	-1.47 (2.11)	0.505	-0.11 (0.60)	0.860
Acute length of stay, mean	10.40 (1.14)	<.0001	-0.13 (0.29)	0.657	-1.37 (1.44)	0.371	0.06 (0.41)	0.884
Any complication, %	40.75 (3.67)	<.0001	-0.72 (0.94)	0.466	-4.95 (4.64)	0.318	1.84 (1.33)	0.205

ED Emergency Department; *SE* Standard Error

Table 21 Sensitivity Analysis: Interrupted time series analysis for patients with diabetes excluding revision procedures *and* POST patients who were not part of the ERAS program.

	Intercept Pre-ERAS		Slope Pre-ERAS		Level change Post-ERAS		Change in slope Post-ERAS	
Outcome	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value
Death/readmission, %	16.96 (6.48)	0.031	-0.49 (1.66)	0.775	-0.38 (8.20)	0.964	0.00 (2.35)	0.999
Death/ED visit, %	31.49 (8.77)	0.007	0.00 (2.25)	1.000	-15.89 (11.11)	0.191	2.65 (3.19)	0.429
Death/readmission/ED, %	31.76 (8.28)	0.005	0.26 (2.13)	0.907	-16.81 (10.49)	0.148	2.30 (3.01)	0.466
Total length of stay, mean	10.05 (3.37)	0.018	1.14 (0.86)	0.223	-3.11 (4.27)	0.487	-1.89 (1.22)	0.160
Acute length of stay, mean	12.54 (2.80)	0.002	-0.19 (0.72)	0.803	-1.47 (3.54)	0.689	0.06 (1.02)	0.957
Any complication, %	39.88 (10.06)	0.004	-1.17 (2.58)	0.663	-3.07 (12.74)	0.816	3.07 (3.65)	0.425

Figure 2 Flow chart

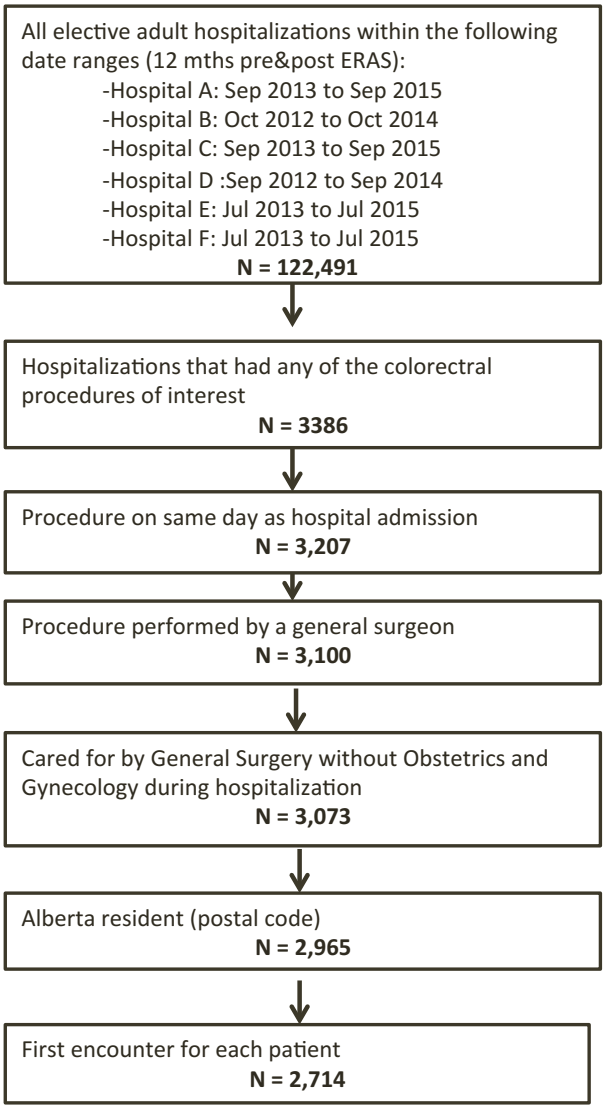


Figure 3 Acute LOS in all patients, ITS analysis

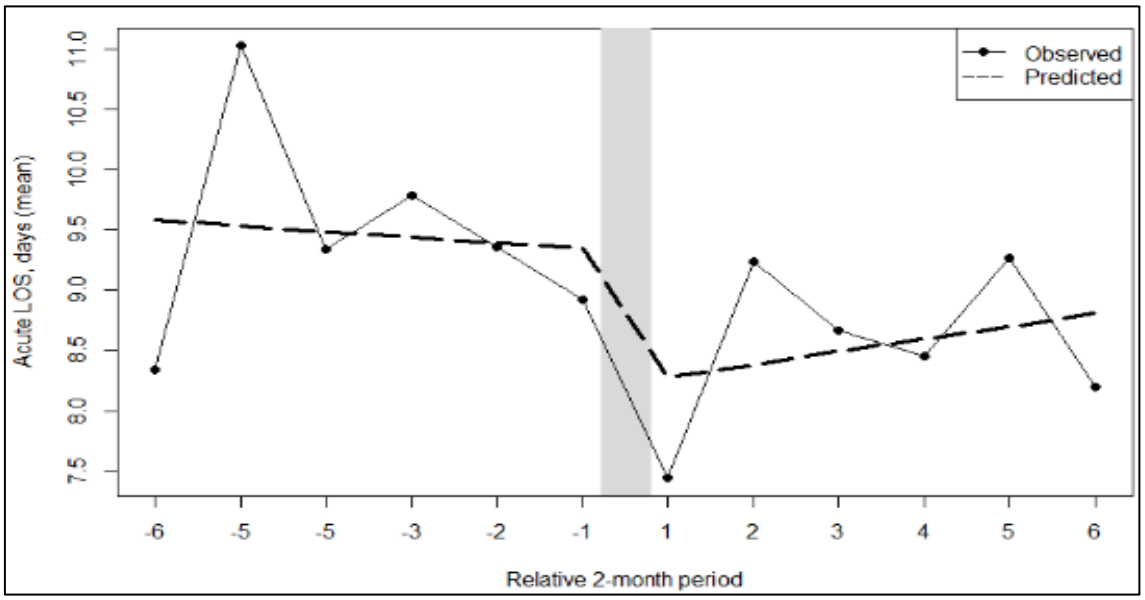


Figure 4 Total LOS in all patients, ITS analysis

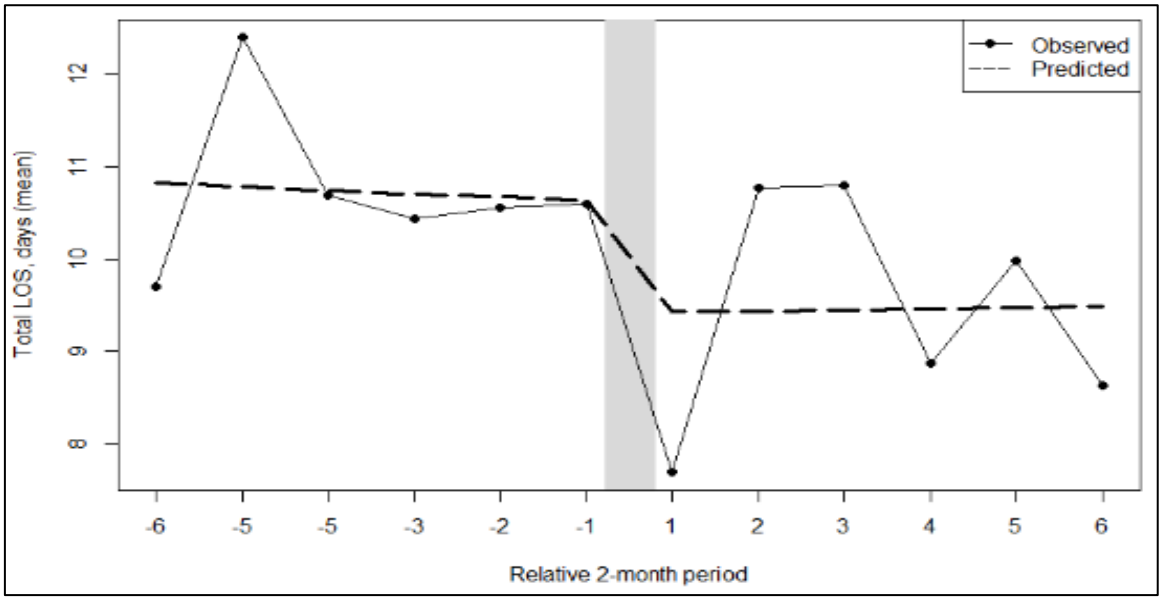


Figure 5 Acute LOS in the diabetes subgroup, ITS analysis

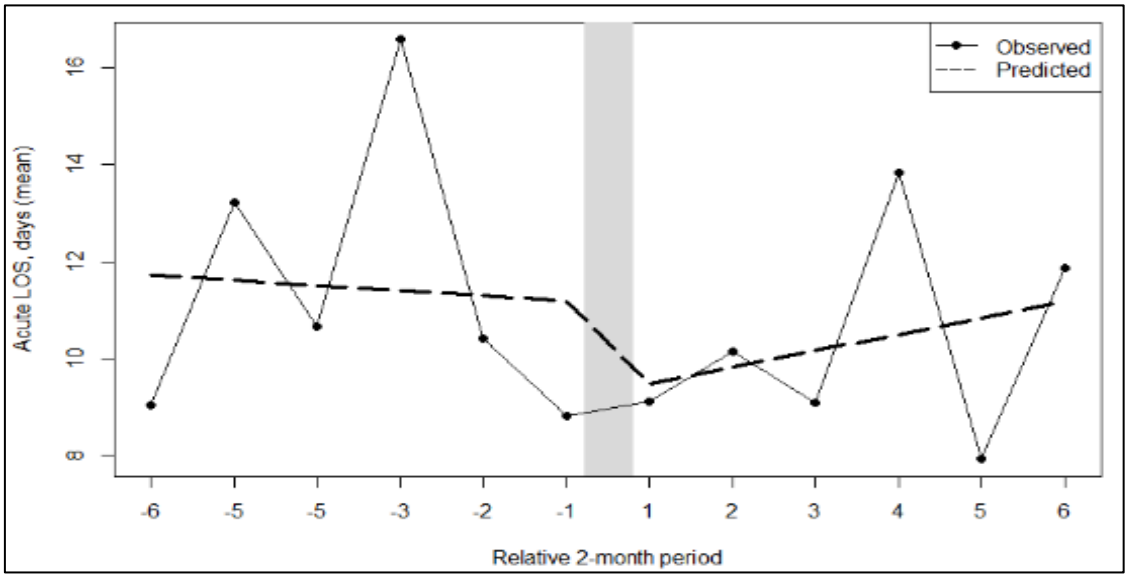


Figure 6 Total LOS in the diabetes subgroup, ITS analysis

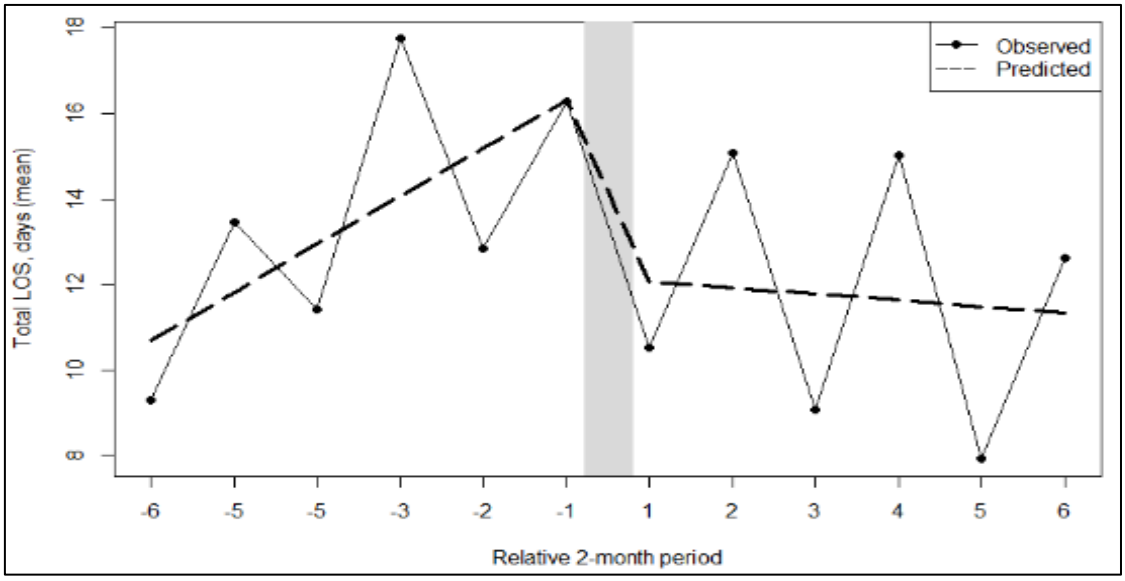


Figure 7 30-day death/readmission rates in all patients, ITS analysis

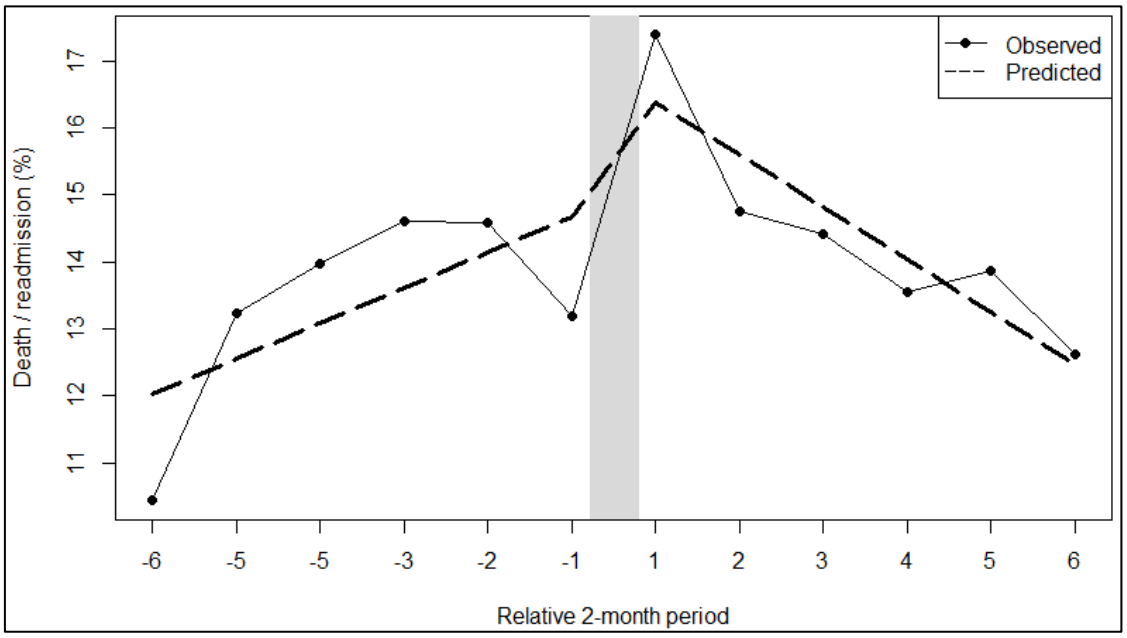


Figure 8 30-day death/ED visit in all patients, ITS analysis

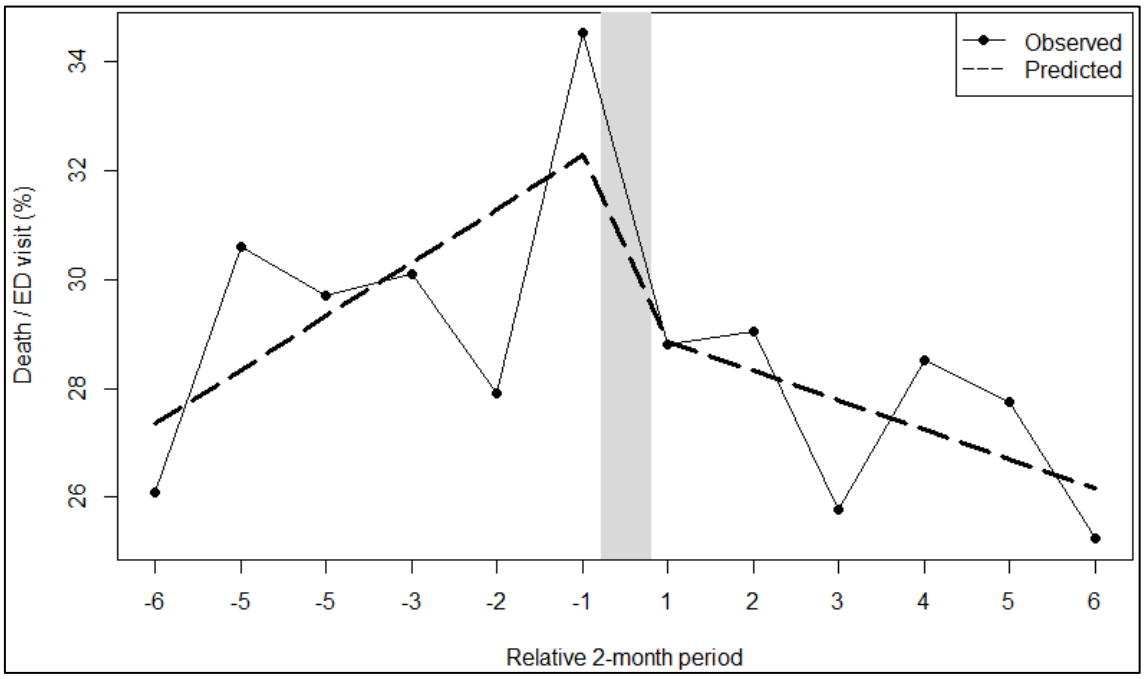


Figure 9 30-day death/readmission/ED visit in all patients, ITS analysis

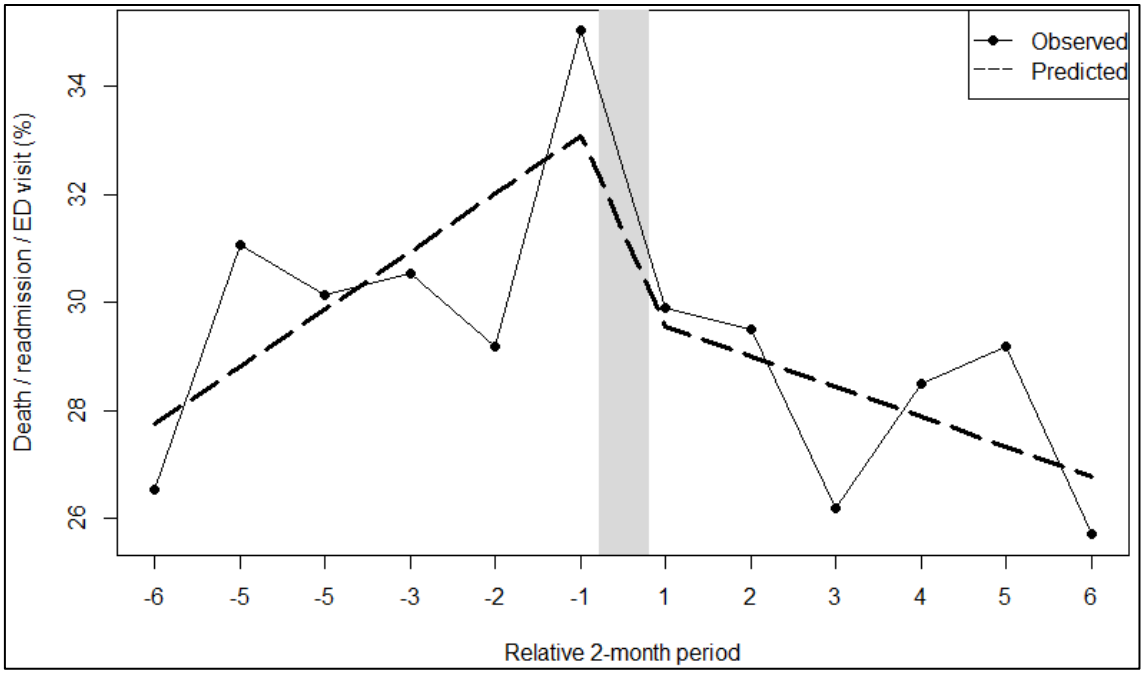


Figure 10 30-day death/readmission rates in the Diabetes subgroup, ITS analysis

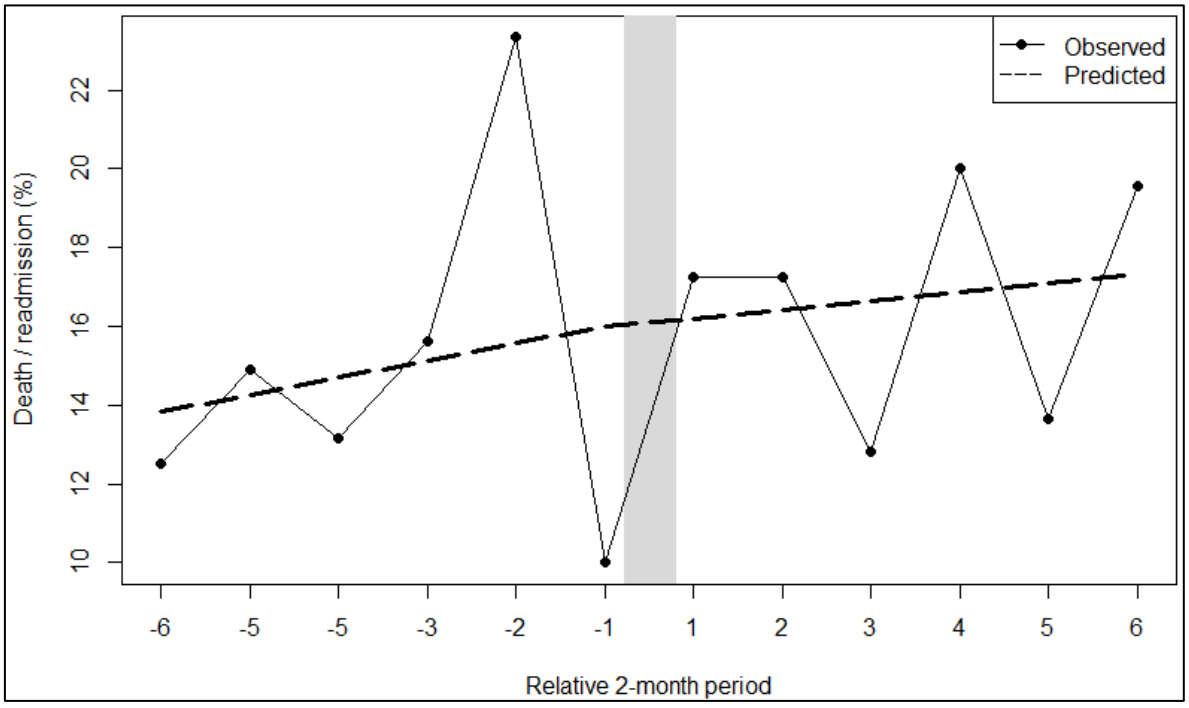


Figure 11 30-day death/readmission/ED visit in the Diabetes subgroup, ITS analysis

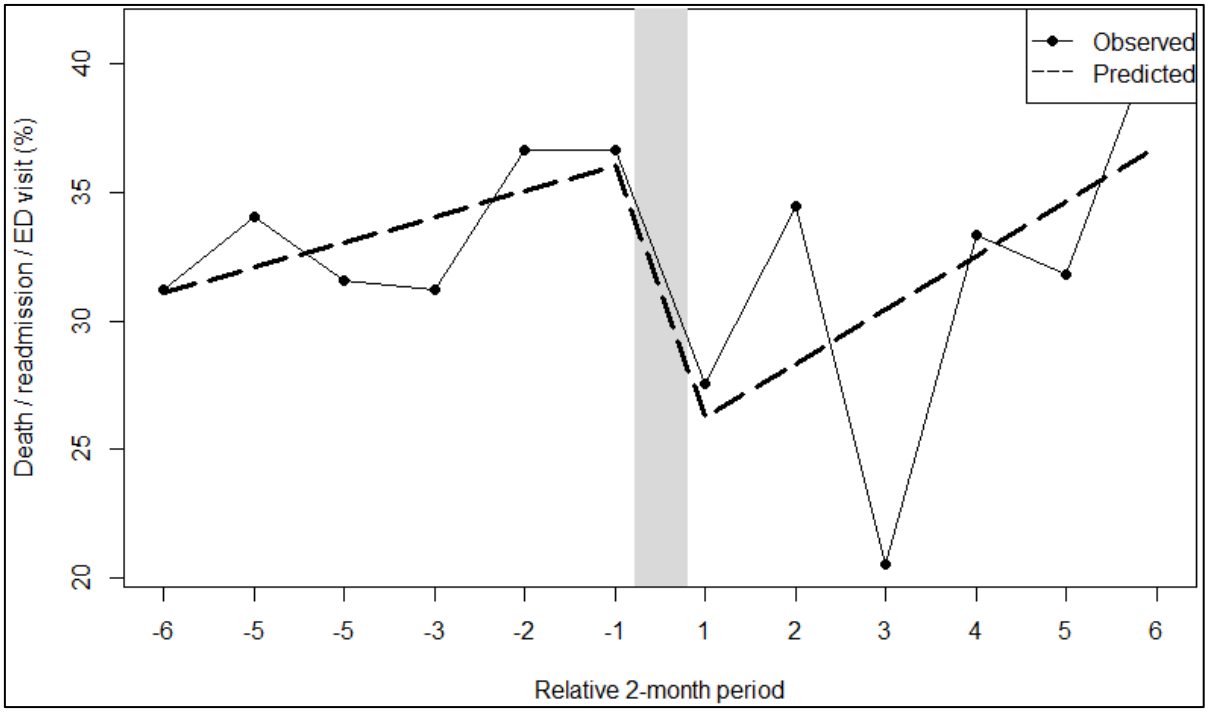


Figure 12 30-day death/ED visit in the Diabetes subgroup, ITS analysis

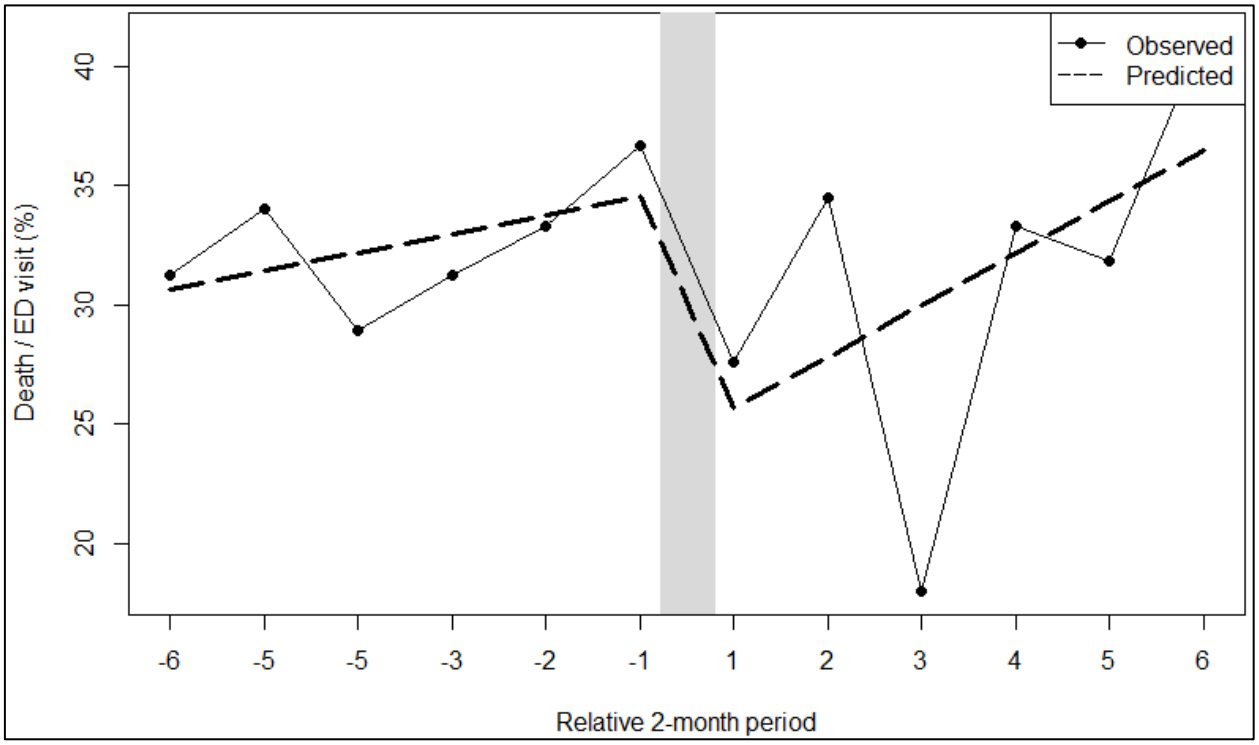


Figure 13 Complications in all patients, ITS analysis

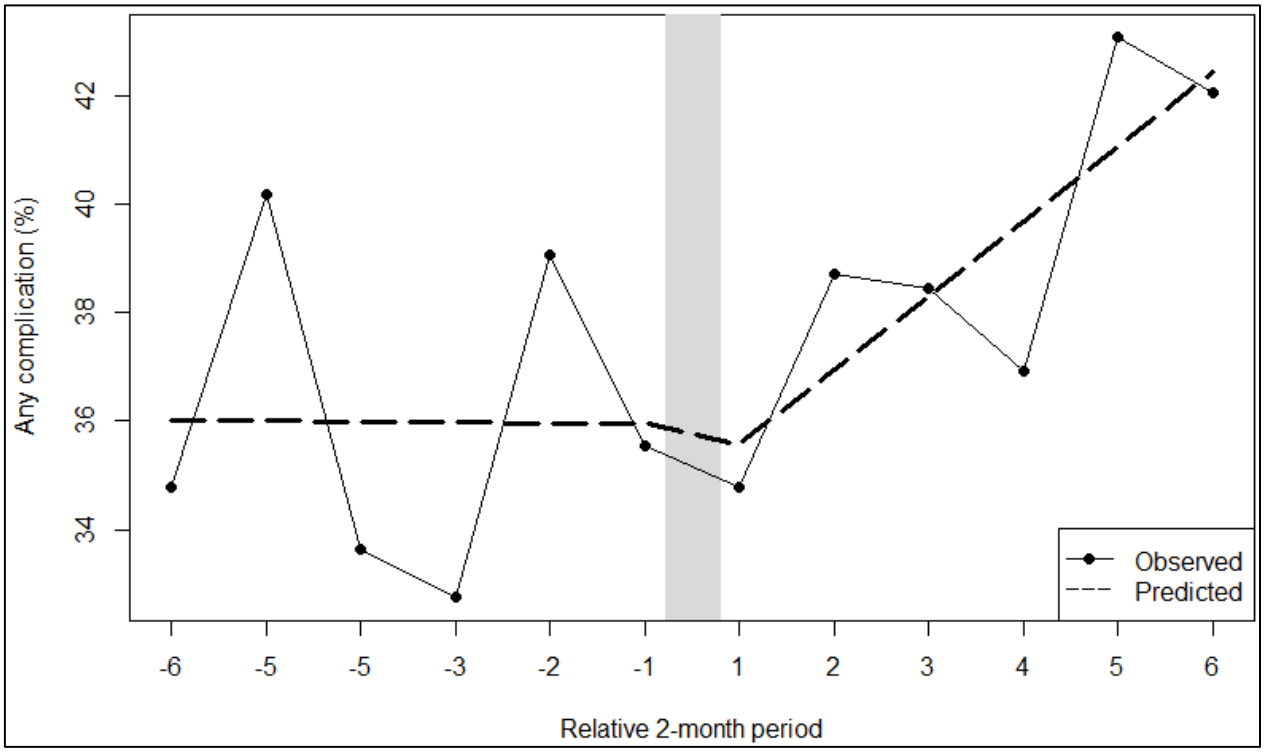


Figure 14 Complications in the Diabetes subgroup, ITS analysis

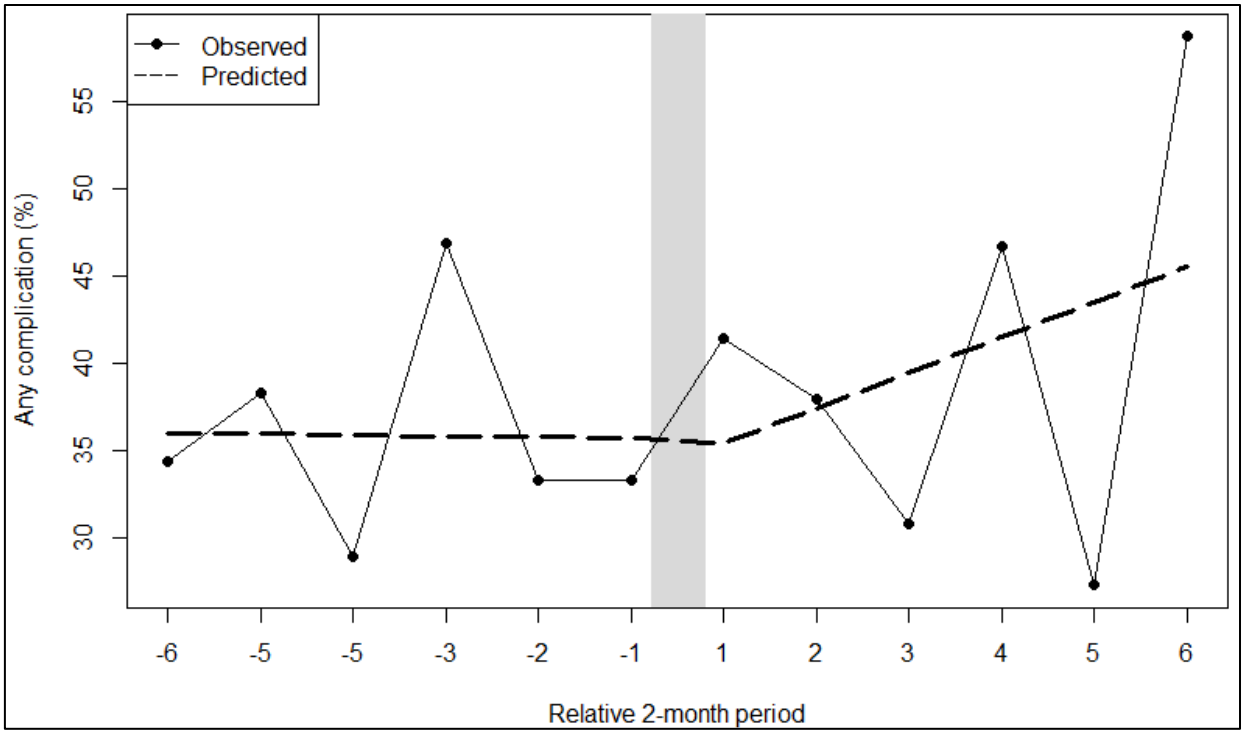


Figure 15 Sensitivity analysis: 30-day death/readmission rates in all patients, ITS analysis

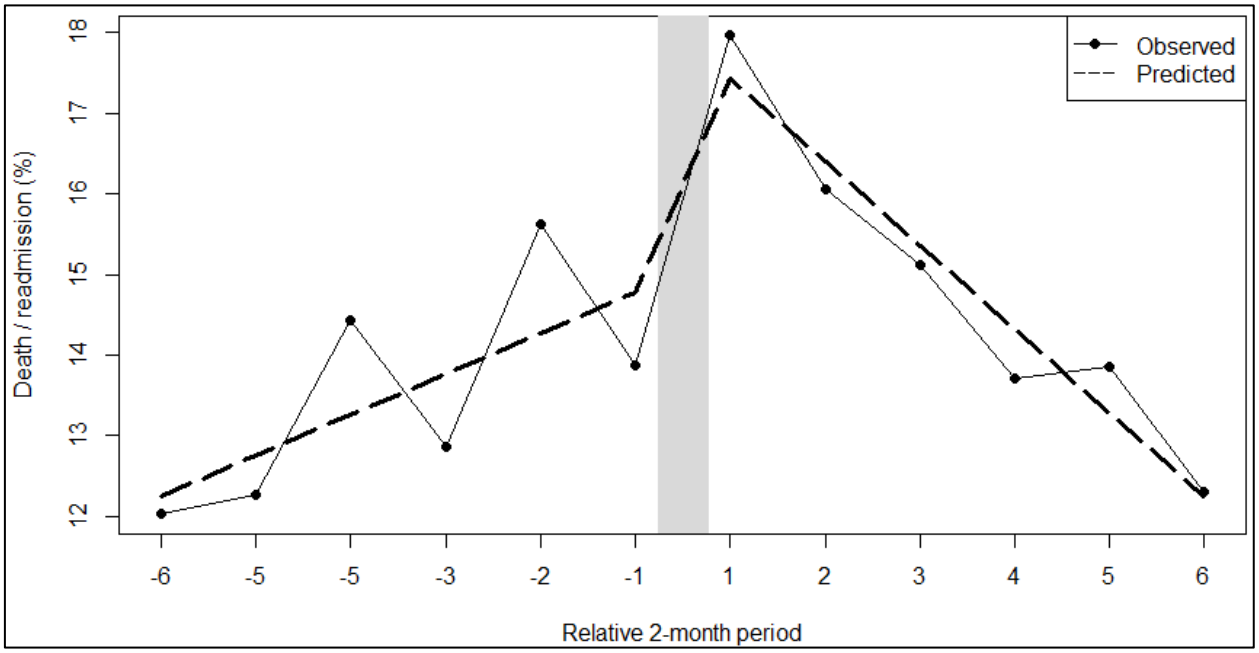


Figure 16 Sensitivity analysis: Acute LOS in all patients excluding revision procedures *and* POST patients who were not part of the ERAS program, ITS analysis

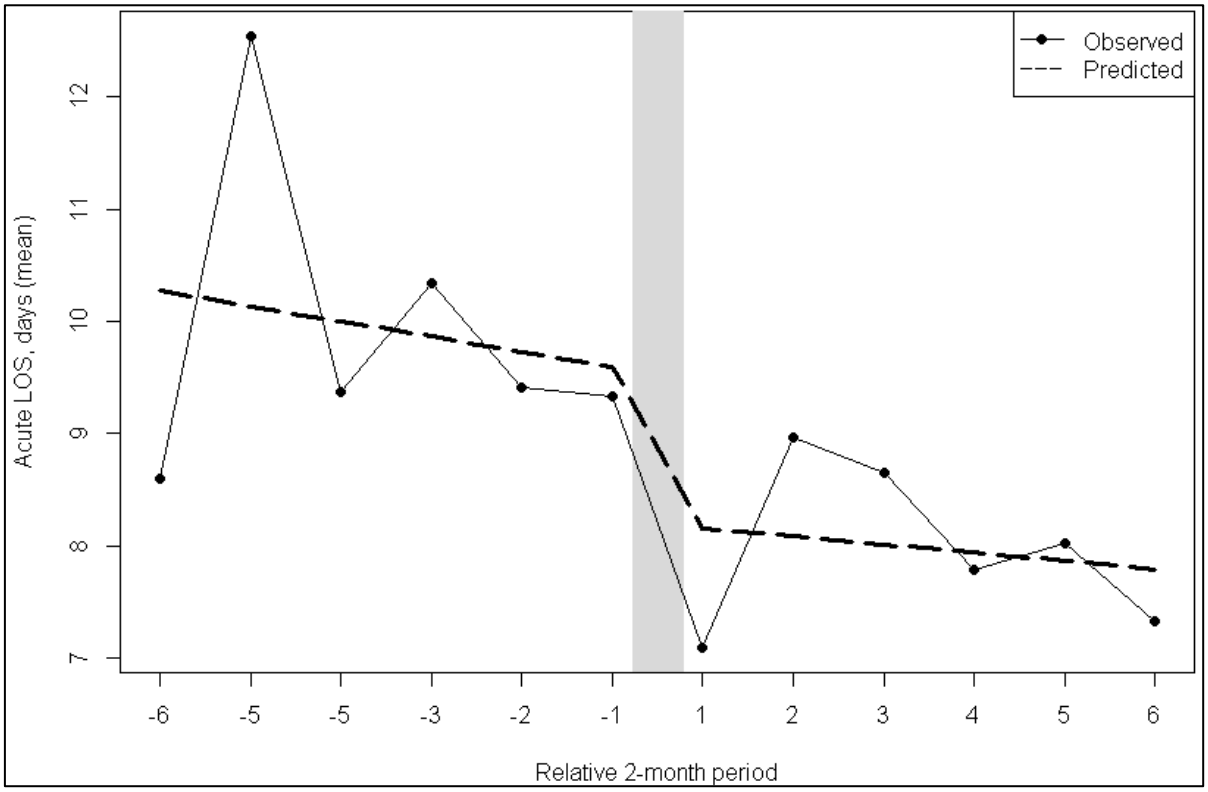


Figure 17 Sensitivity analysis: postoperative complications in all patients excluding revision procedures *and* POST patients who were not part of the ERAS program, ITS analysis

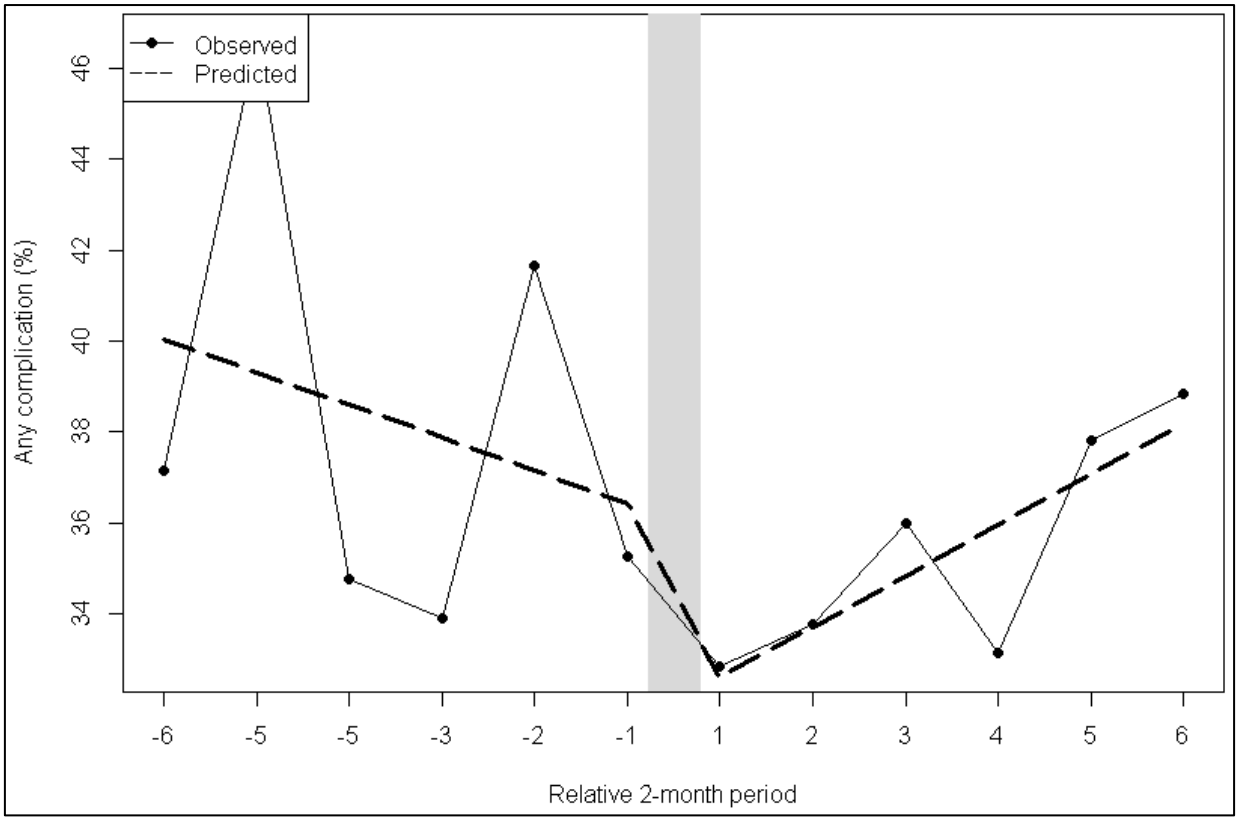


Figure 18 Sensitivity analysis: 30-day death/readmission rates in all patients excluding revision procedures *and* POST patients who were not part of the ERAS program, ITS analysis

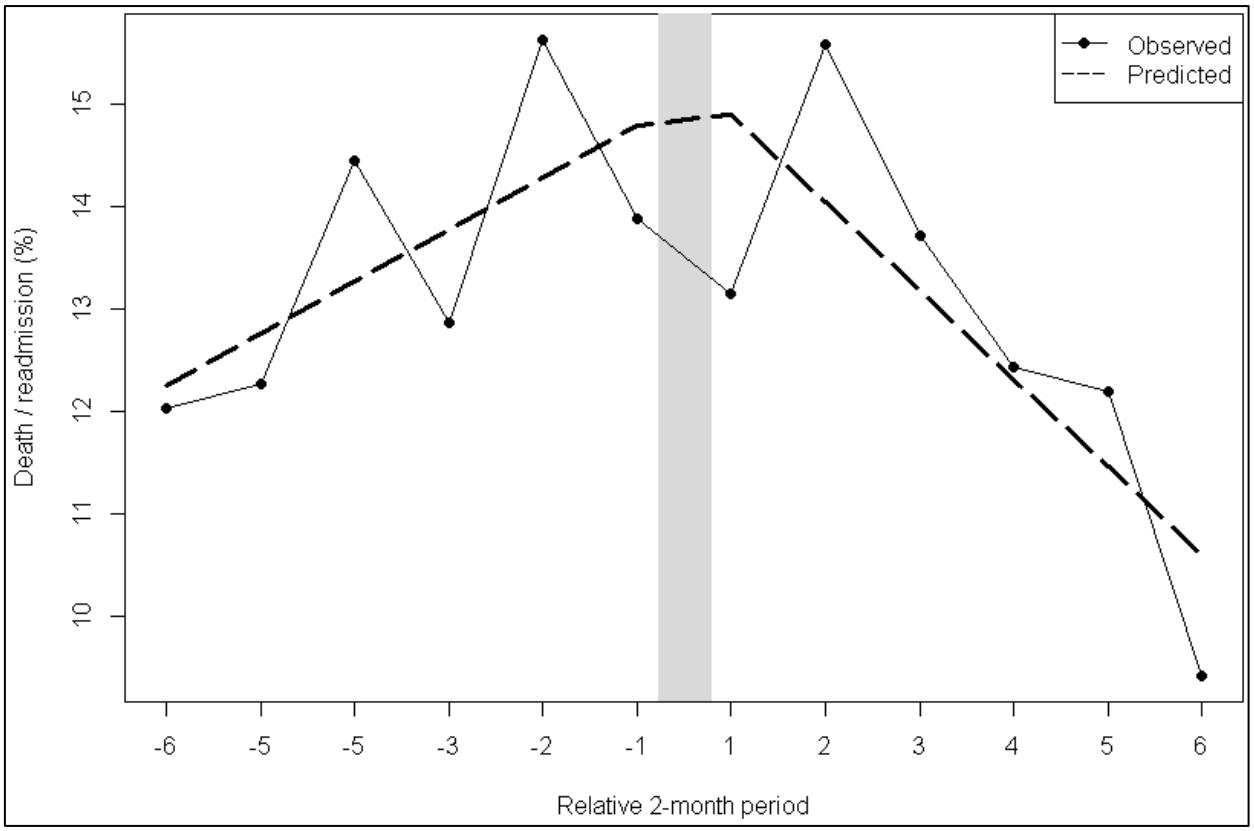


Figure 19 Sensitivity analysis: 30-day death/ED visits in all patients excluding revision procedures *and* POST patients who were not part of the ERAS program, ITS analysis

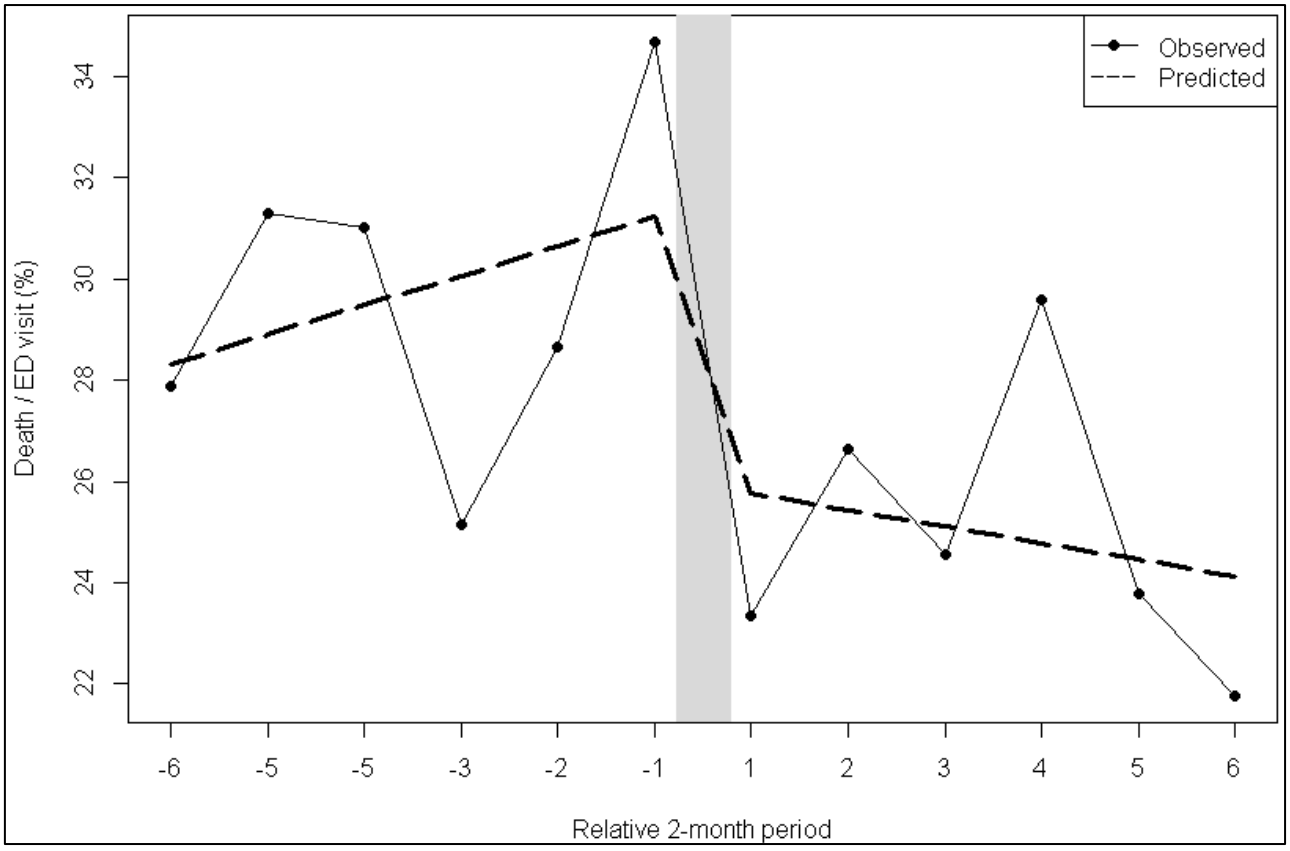


Figure 20 Sensitivity analysis: 30-day death/readmission/ED visits in all patients excluding revision procedures *and* POST patients who were not part of the ERAS program, ITS analysis

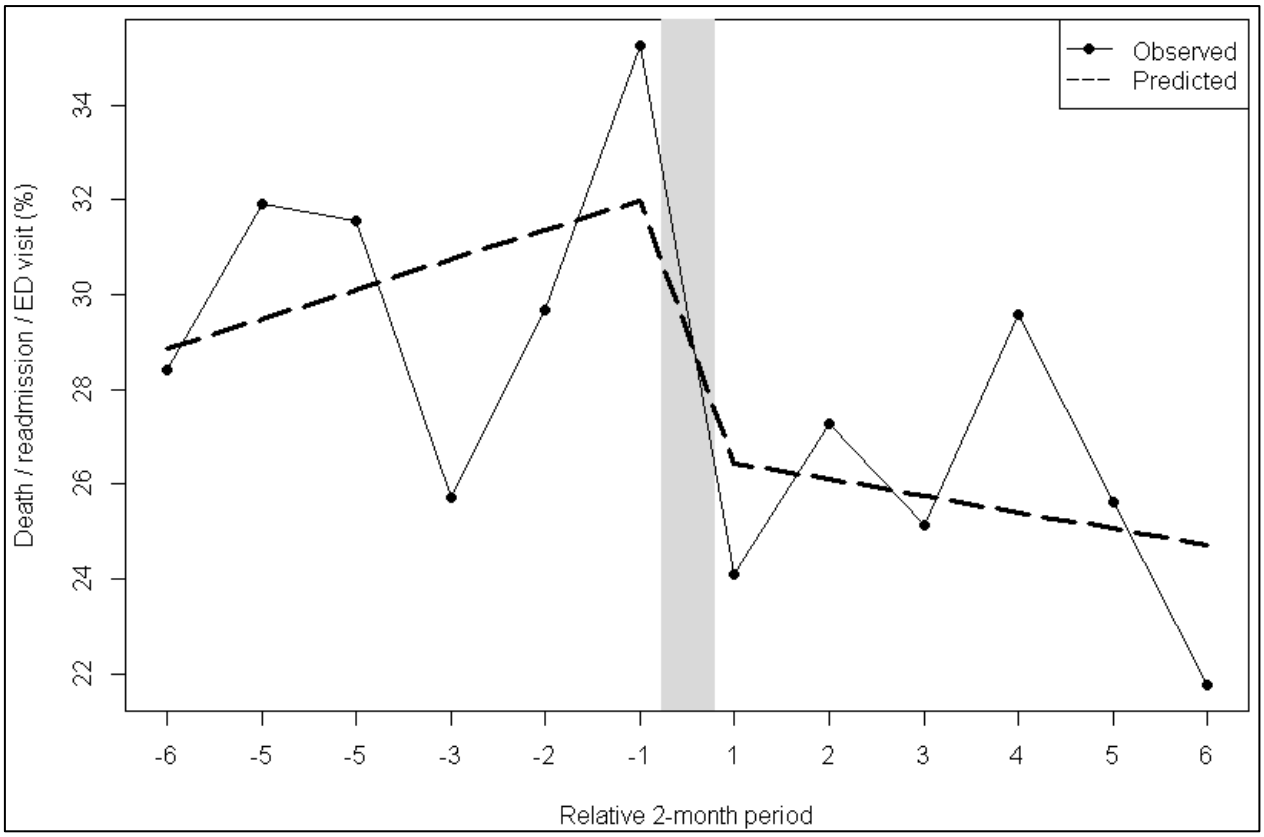


Figure 21 Sensitivity analysis: Acute LOS in the diabetes subgroup excluding revision procedures *and* POST patients who were not part of the ERAS program, ITS analysis

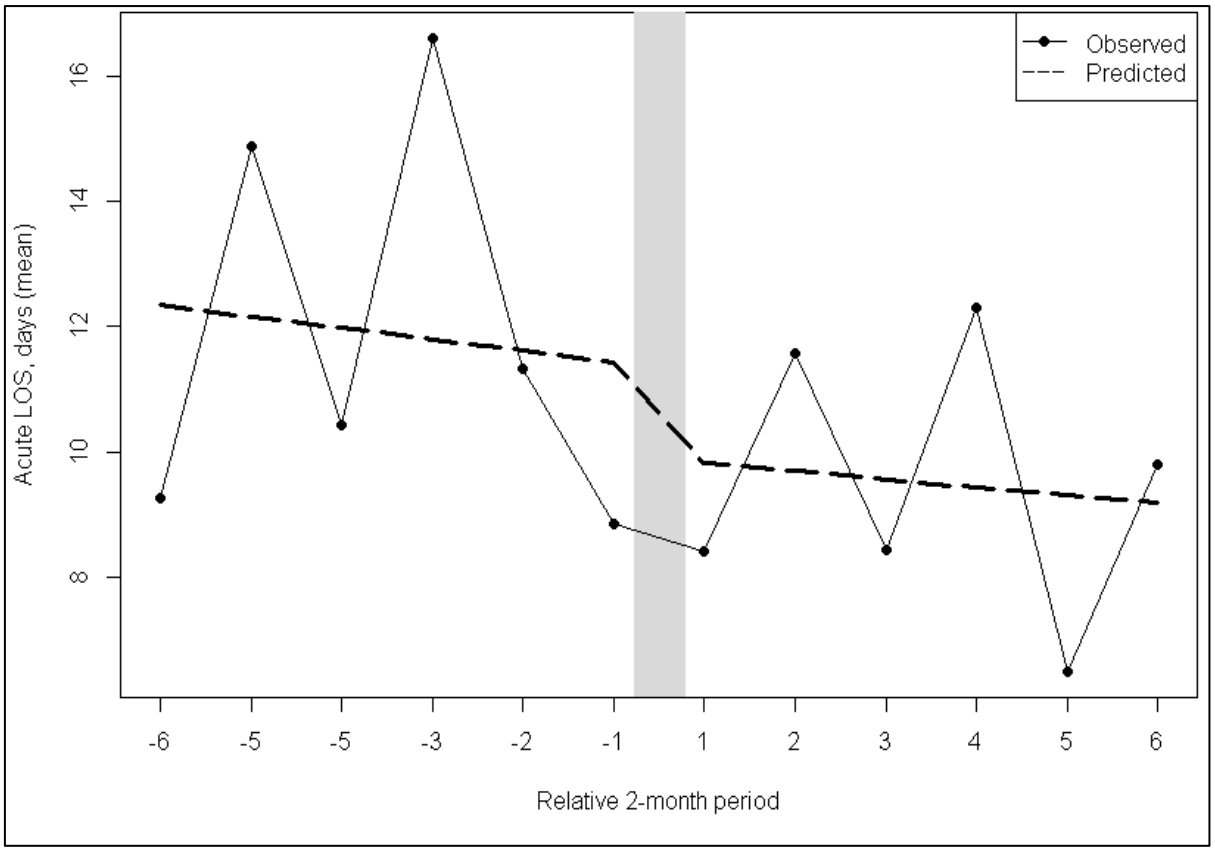


Figure 22 Sensitivity analysis: postoperative complications in the diabetes subgroup excluding revision procedures *and* POST patients who were not part of the ERAS program, ITS analysis

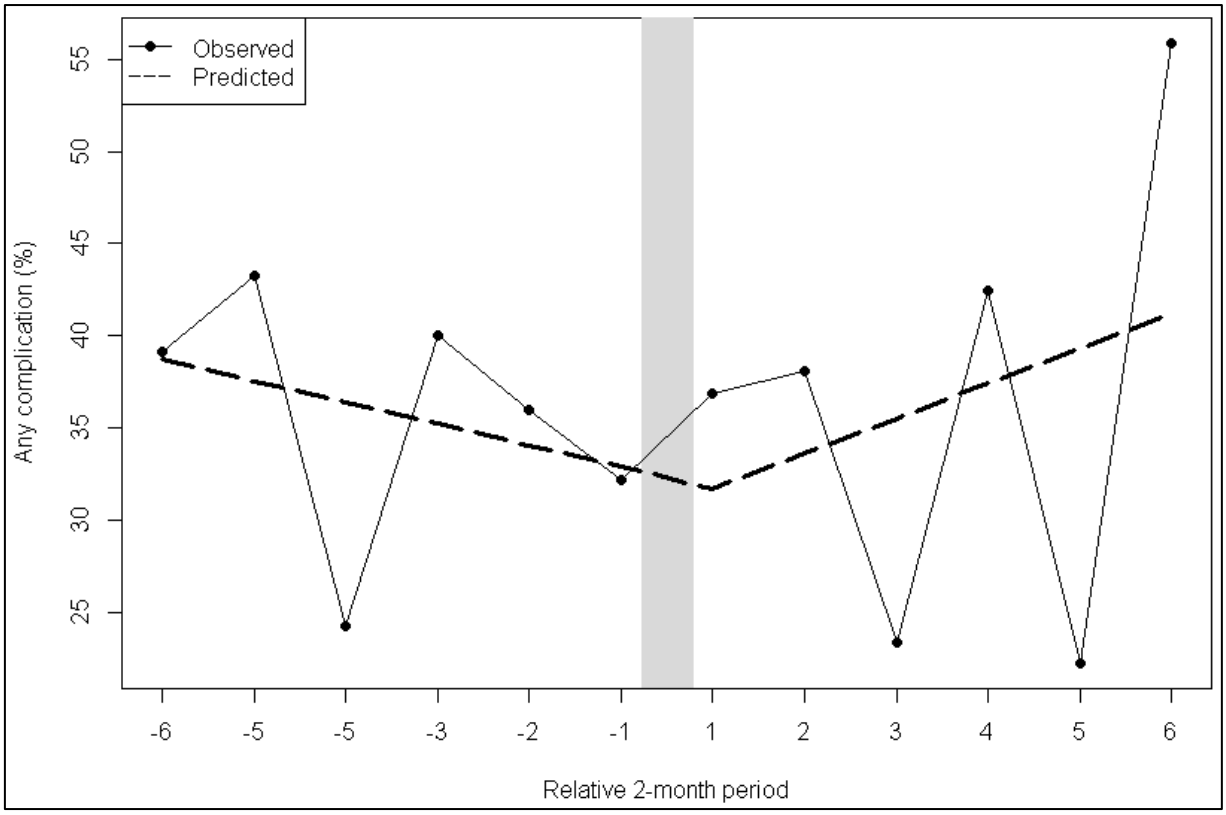


Figure 23 Sensitivity analysis: 30-day death/readmission in the diabetes subgroup excluding revision procedures *and* POST patients who were not part of the ERAS program, ITS analysis

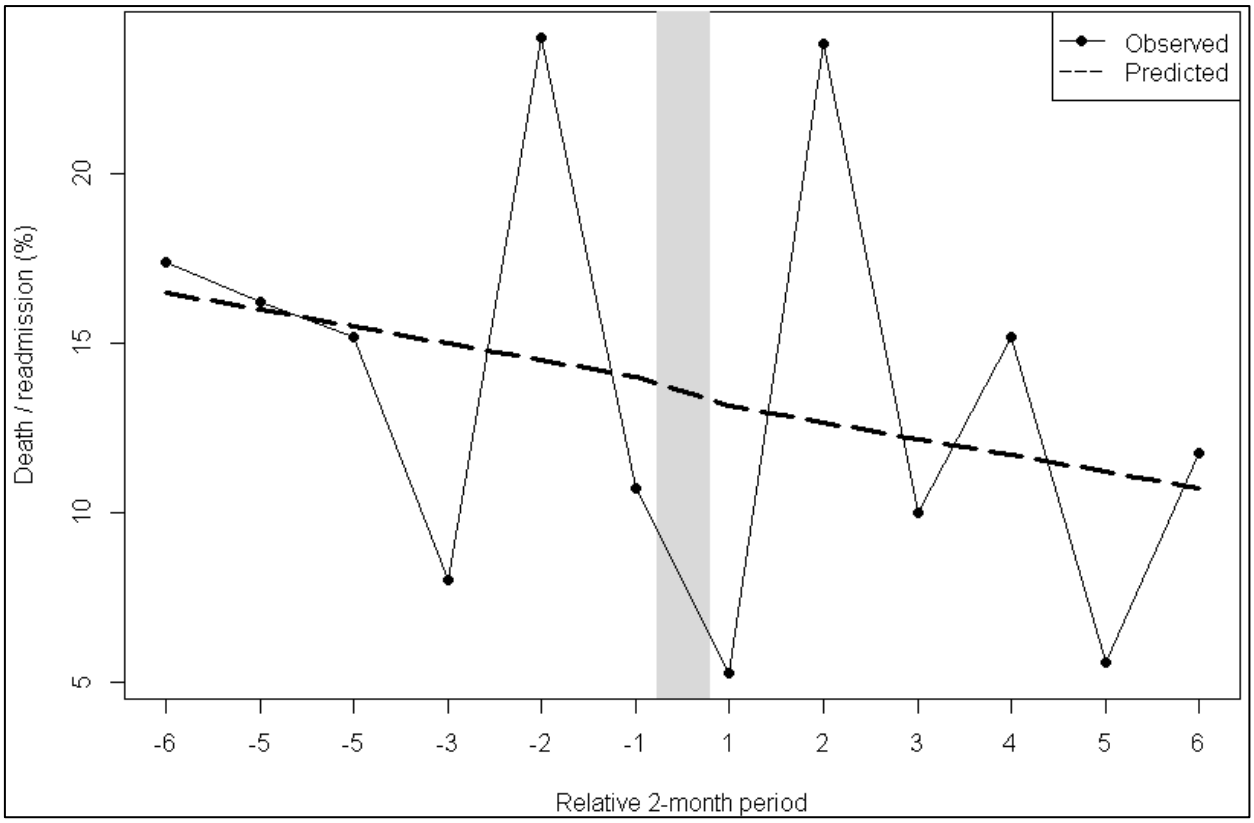


Figure 24 Sensitivity analysis: 30-day death/ED visits in the diabetes subgroup excluding revision procedures *and* POST patients who were not part of the ERAS program, ITS analysis

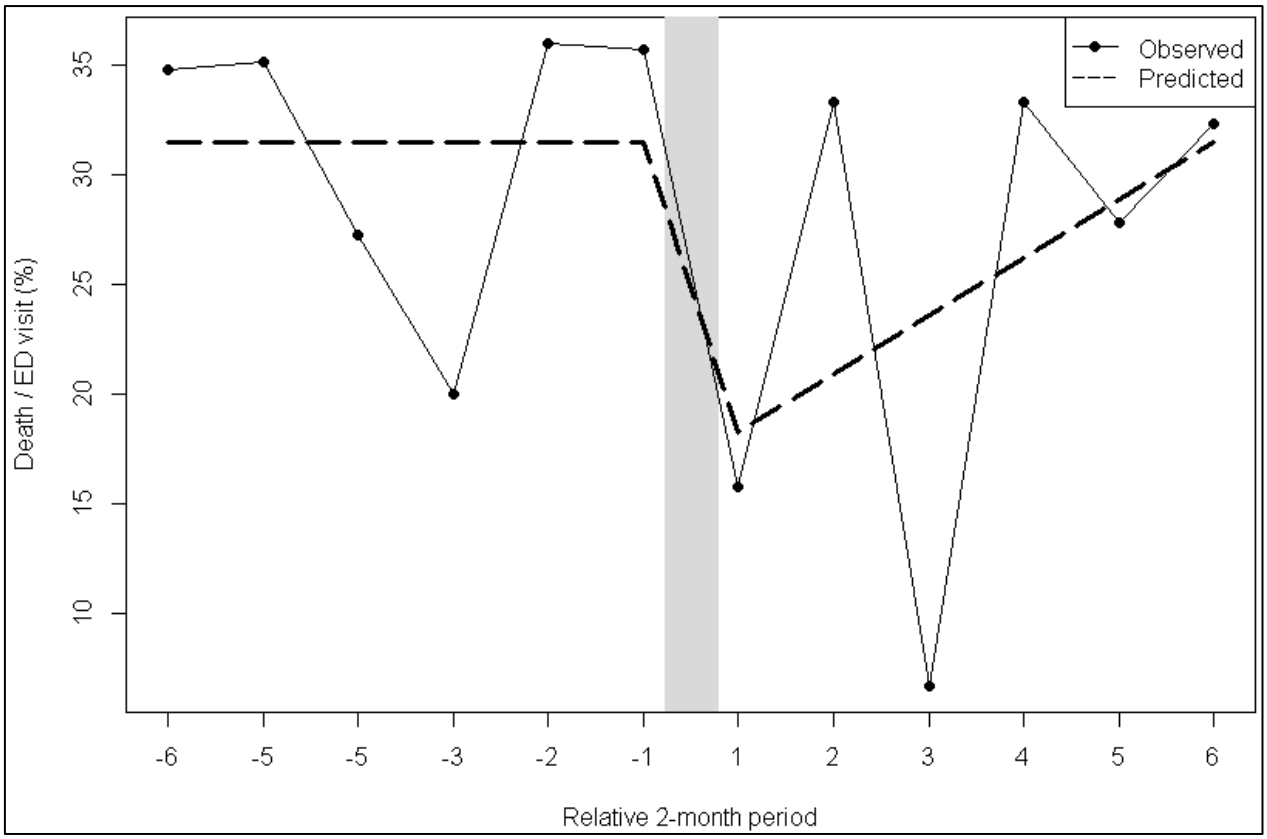
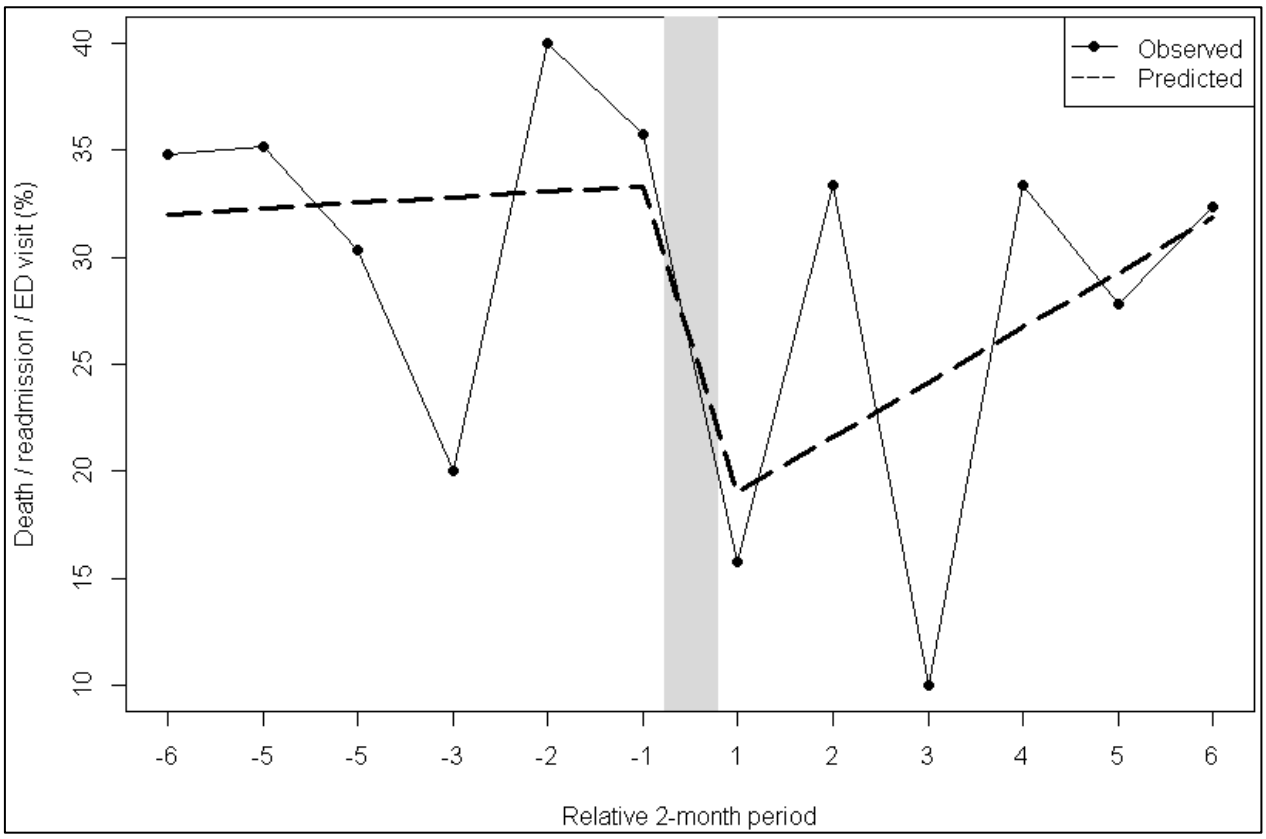


Figure 25 Sensitivity analysis: 30-day death/readmission/ED visits in the diabetes subgroup excluding revision procedures *and* POST patients who were not part of the ERAS program, ITS analysis



Bibliography

1. Fearon KCH, Ljungqvist O, Von Meyenfeldt M, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr Edinb Scotl*. 2005;24(3):466-477.

2. ERAS Compliance Group. The Impact of Enhanced Recovery Protocol Compliance on Elective Colorectal Cancer Resection: Results From an International Registry. *Ann Surg*. 2015;261(6):1153-1159.

3. Nygren J, Thacker J, Carli F, et al. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *Clin Nutr*. 2012;31(6):801-816.

4. Gustafsson U o., Scott M j., Schwenk W, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *Clin Nutr*. 2012;31(6):783-800.

5. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced Recovery Program in Colorectal Surgery: A Meta-analysis of Randomized Controlled Trials. *World J Surg*. 2014;38(6):1531-1541.

6. Wind J, Polle SW, Fung Kon Jin PHP, et al. Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg*. 2006;93(7):800-809.

7. Walter CJ, Collin J, Dumville JC, Drew PJ, Monson JR. Enhanced recovery in colorectal resections: a systematic review and meta-analysis. *Colorectal Dis Off J Assoc Coloproctology G B Irel*. 2009;11(4):344-353.

8. Gouvas N, Tan E, Windsor A, Xynos E, Tekkis PP. Fast-track vs standard care in colorectal surgery: a meta-analysis update. *Int J Colorectal Dis*. 2009;24(10):1119-1131.

9. Gustafsson UO, Hausel J, Thorell A, et al. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. *Arch Surg Chic Ill 1960*. 2011;146(5):571-577.

10. Albalawi Z, Laffin M, Gramlich L, Senior P, McAlister FA. Enhanced Recovery After Surgery (ERAS(®)) in Individuals with Diabetes: A Systematic Review. *World J Surg*. March 2017. [Epub ahead of print]

11. Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. *BMJ*. 2015;350:h2750.

12. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139.

13. Quan H, Li B, Saunders LD, et al. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. *Health Serv Res*. 2008;43(4):1424-1441.

14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.

15. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676-682.

16. Aarts MJ, Lemmens VEPP, Louwman MWJ, Kunst AE, Coebergh JWW. Socioeconomic status and changing inequalities in colorectal cancer? A review of the associations with risk, treatment and outcome. *Eur J Cancer Oxf Engl 1990*. 2010;46(15):2681-2695.

17. Ma C, Crespin M, Proulx M-C, et al. Postoperative complications following colectomy for ulcerative colitis: A validation study. *BMC Gastroenterol*. 2012;12:39.

18. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213.

19. Rosenthal R, Hoffmann H, Clavien P-A, Bucher HC, Dell-Kuster S. Definition and Classification of Intraoperative Complications (CLASSIC): Delphi Study and Pilot Evaluation. *World J Surg*. 2015;39(7):1663-1671.

20. McAlister FA, Bakal JA, Majumdar SR, et al. Safely and effectively reducing inpatient length of stay: a controlled study of the General Internal Medicine Care Transformation Initiative. *BMJ Qual Saf*. 2014;23(6):446-456.

21. Varadhan KK, Neal KR, Dejong CHC, Fearon KCH, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. *Clin Nutr Edinb Scotl*. 2010;29(4):434-440.

22. Spanjersberg WR, van Sambeeck JDP, Bremers A, Rosman C, van Laarhoven CJHM. Systematic review and meta-analysis for laparoscopic versus open colon surgery with or without an ERAS programme. *Surg Endosc*. 2015;29(12):3443-3453.

23. Lv L, Shao Y-F, Zhou Y. The enhanced recovery after surgery (ERAS) pathway for patients undergoing colorectal surgery: an update of meta-analysis of randomized controlled trials. *Int J Colorectal Dis*. 2012;27(12):1549-1554.

24. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. *JAMA Surg*. 2017;152(3):292-298.

25. Ljungqvist O. Jonathan E. Rhoads lecture 2011: Insulin resistance and enhanced recovery after surgery. *JPEN J Parenter Enteral Nutr*. 2012;36(4):389-398.

26. Gillissen F, Hoff C, Maessen JMC, et al. Structured synchronous implementation of an enhanced recovery program in elective colonic surgery in 33 hospitals in The Netherlands. *World J Surg*. 2013;37(5):1082-1093.

27. Nelson G, Kiyang LN, Crumley ET, et al. Implementation of Enhanced Recovery After Surgery (ERAS) Across a Provincial Healthcare System: The ERAS Alberta Colorectal Surgery Experience. *World J Surg*. 2016;40(5):1092-1103.

28. Gotlib Conn L, McKenzie M, Pearsall EA, McLeod RS. Successful implementation of an enhanced recovery after surgery programme for elective colorectal surgery: a process evaluation of champions' experiences. *Implement Sci IS*. 2015;10:99.

29. Adamina M, Kehlet H, Tomlinson GA, Senagore AJ, Delaney CP. Enhanced recovery pathways optimize health outcomes and resource utilization: a meta-analysis of randomized controlled trials in colorectal surgery. *Surgery*. 2011;149(6):830-840.

30. Luther A, Panteleimonitis S, Kang P, Evans J. Tu1759 Diabetic Patients Take Longer to Recover Than Non-Diabetics Within an Enhanced Recovery Programme. Gastroenterology. 2012 May 1;142(5):S-1092

31. Jørgensen CC, Madsbad S, Kehlet H, Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group. Postoperative morbidity and mortality in type-2 diabetics after fast-track primary total hip and knee arthroplasty. *Anesth Analg*. 2015;120(1):230-238.

32. Chapuis PH, Bokey L, Keshava A, et al. Risk factors for prolonged ileus after resection of colorectal cancer: an observational study of 2400 consecutive patients. *Ann Surg*. 2013;257(5):909-915.

33. Schnüriger B, Barmparas G, Branco BC, Lustenberger T, Inaba K, Demetriades D. Prevention of postoperative peritoneal adhesions: a review of the literature. *Am J Surg*. 2011;201(1):111-121.

34. Okabayashi K, Ashrafian H, Zacharakis E, et al. Adhesions after abdominal surgery: a systematic review of the incidence, distribution and severity. *Surg Today*. 2014;44(3):405-420.

35. Ramsay CR, Matowe L, Grilli R, Grimshaw JM, Thomas RE. Interrupted time series designs in health technology assessment: lessons from two systematic reviews of behavior change strategies. *Int J Technol Assess Health Care*. 2003;19(4):613-623.

36. Zhang F, Wagner AK, Ross-Degnan D. Simulation-based power calculation for designing interrupted time series analyses of health policy interventions. *J Clin Epidemiol*. 2011;64(11):1252-1261.

37. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol*. 2017;46(1):348-355.

Appendix 1 ICD-10 codes used to define index hospitalization complications (17)

Category	Complications	ICD-10
Gastrointestinal	Small bowel obstruction, Anastomotic stricture (include peritoneal adhesions), Pouch leak Pouch failure, Bowel perforation, Ileus, Ischaemic bowel, GI bleeding (also include other hemorrhage and hemorrhagic conditions), Ileostomy / colostomy complication or malfunction, Digestive organ disorders (include acute hepatic failure and acute pancreatitis), Other GI complications (include pneumatosis)	K22.8, K25.0, K25.2, K25.4, K25.6, K26.0, K26.1, K26.2, K26.4, K26.5, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K55.0, K55.9, K56.0, K56.5, K56.6, K56.7, K62.5, K63.1, K63.8, K66.0, K65.5, K65.6, K72.0, K72.9 ,K85, K91.3, K91.4, K91.8, K91.9, K92, T79.2, T81.0, T88.8
Wounds	Fistula, Hematoma/seroma, Wound dehiscence and Delayed wound healing, Iatrogenic injuries (include foreign body accidentally left during procedure) and pressure ulcer.	K60.3, K60.4, K60.5, K63.2, K82.9, K83.2, L89, N36.0, N82.4, T81.2, T81.3, T81.5, T81.8, 1.OT.52.DA, 1.OT.56.DA, 1.OT.70.LA ,1.OW.80, 2.OT.70.LA
Infections	Sepsis and bacteremia, Abscess, Wound infection, Urinary tract infection, Pneumonia and empyema, Other infections (include peritonitis, bacterial, skin and subcutaneous tissue infection).	A40, A41, A49, B95, B96, J10.0, J11.0, J12, J13, J14, J15, J16, J17, J18, J69.0, J85, J86, K61, K63.0, K65, L03, L04, N10, N12, N15.1, N15.9, N30.0, N30.9, N39.0, R78.8, T79.3, T80.2, T81.4, T81.6, T82.7, T83.6, T85.7
Renal and Endocrine	Acute renal failure, Fluid and electrolyte disorders (include hypokalemia), Severe endocrine disorders (include adrenal disorders, hypoglycemic coma), Retention of urine (include atony of bladder), Other urinary complication (include urinary obstruction)	E15, E272, E86, E87, N13.9, N17, N19, N31.2 ,N99.0, N99.9, R33
Cardiovascular disorders	Thrombosis/embolism, Myocardial infarction, Cardiac arrest, Hypotension or shock, Cardiac arrhythmias (exclude tachycardia), Heart failure, Other Cardiovascular complication (include atherosclerotic heart disease, angina)	I21, I26, I46, I48, I49, I50, I74, I80, I81, I82, I95.0, I95.2, I95.9, I97.8, I97.9, R57, T79.0, T80.0, T80.1, T81.1, T81.7, T88.2
Pulmonary	Acute respiratory failure, Hypoxia, Pleural effusion and pulmonary edema, Pneumothorax and atelectasis, Other pulmonary complications (include asthma, extubation failure, difficulty breathing)	J80, J81, J90, J91, J93, J95.5, J95.8, J95.9, J96.0, J96.9, J98.1, R09
Neurological disorders	Cerebrovascular disease, Neurological disorders (psychoses/delirium/seizure), Disorders /complications of nervous system (include neuropathies)	F05, F13, F15, F19, G45, G46, G81, G82, G83, G93.1, G93.6, G97.0, G97.1, G97.8, G97.9, I63, I65

4 Chapter 4: Discussion and Conclusion

Individuals with diabetes are a high-risk surgical population, and despite advances in perioperative care with the introduction of the ERAS® program over a decade ago, it is unknown whether postoperative outcomes (LOS, complications and 30-day outcomes) are altered by enrollment in an ERAS® program compared to conventional care in individuals with diabetes. The first aim of this thesis was to evaluate the impact of ERAS® on individuals with diabetes undergoing elective surgery by systematically evaluating the state of the evidence, and the second aim was to analyze the "real-life" cohort that underwent ERAS® implementation for elective colorectal surgery in those *with* and *without* diabetes in the province of Alberta -where ERAS® was implemented at the main surgical sites.

The systematic review presented in chapter 2 did not identify any robust study meeting the EPOC criteria examining the impact of ERAS® program on individuals with diabetes. Reasons for excluding this population from ERAS® could be related to unsubstantiated concerns of aspiration secondary to gastric paresis from carbohydrate loading preoperatively -one of the ERAS® protocol components-, and hyperglycemia.(142) The presence of multiple comorbidities in this population, and the well-recognized higher postoperative risk for complications might have put them at a disadvantage of being included in outcome trials, along with the challenges of perioperative glycemic control, which if not optimally managed in a trial would have a direct negative effect on postoperative outcomes, resulting in masking any potential

impact of ERAS®.(7,8) The wide spread use of uncontrolled before-after observational studies in the ERAS® literature has also contributed to the lack of *robust* study designs in this area.

The second focus of this thesis was to address this knowledge gap by analyzing the cohort that underwent ERAS® implementation for elective colorectal surgery at the six main surgical sites in the province of Alberta, under a single health care system. An interrupted time series (ITS) analysis was conducted on the diabetes subgroup as well as the whole cohort (patients with and without diabetes) to allow contextual understanding and interpretation of the results, this is presented in chapter 3. The diabetes subgroup did not demonstrate any changes in postoperative outcomes (LOS, postoperative complications, 30-day outcomes). On the other hand, a significant reduction in postoperative LOS in the whole cohort was observed, however the ITS analysis confirmed that there was no level change meaning that the observed reduction in LOS was due to underlying secular trends and not attributable to the ERAS® program. The negative findings of this analysis (i.e. the absence of a measurable effect attributed to ERAS®) are contrary to multiple observational studies demonstrating the effectiveness of ERAS® program in colorectal surgery patients, and RCTs evaluating other fast track and heterogeneous enhanced recovery programs.

The absence of a measurable benefit in our study relating to ERAS® could be related to low adherence to the ERAS® program, inadequate power, intrinsic factors relating to surgical care in Alberta, or due to the absence of a significant measurable benefit. Although adherence was not directly evaluated in our study, a recognized limitation, a recent analysis by Gramlich et al of the same Alberta cohort analyzed up to 2015 –overlapping with our study's post ERAS® period- demonstrated an increase in

adherence in ERAS® program from 39% pre-ERAS® to 60% post-ERAS® with similar findings across all six sites.(9) Optimal ERAS® outcomes have been consistently reported when adherence is > 70%,(10,11) and so repeating this analysis as the sites mature and adherence improves might yield different results. It is also important to consider the possibility that previous studies in the literature reporting on postoperative outcomes in colorectal surgery and ERAS® might have been biased overestimates due to inherent limitations of the study designs used (i.e. uncontrolled before-after studies). Our study therefore might have been underpowered to detect a smaller magnitude of effect of ERAS®, and including additional data points pre- and post-ERAS® by extending the data collection to 24 months instead of 12 months would improve the power to detect a smaller difference, if one was present. This was considered at the stage of protocol development, however due to the staggered implementation dates and delayed availability of the provincial mortality data, only 12 months were available to be included pre- and post-ERAS® to ensure consistent data collection at all the sites, and minimize bias.

Important intrinsic factors to consider are surgical care practices pre-ERAS® -not possible to ascertain via administrative databases- which might have already included components of the ERAS® program contributing to the lack of a level change on the ITS analysis -particularly given the staggered implementation dates and availability of evidence supporting individual components of the ERAS® pathway over the past decade which might have already been incorporated into surgeons' practices. Length of stay might have already been on the decline due to increased use of laparoscopic approach, early detection and management of colorectal cancer with development of the Alberta

Rectal Cancer Clinical Pathway, or extra homecare nursing capacity which was observed on medicine wards in Alberta recently.(11–14)

Nevertheless, the question that arises is whether the results are truly negative in the Alberta cohort, and whether this stands true for the ERAS® program in colorectal surgery. With the lack of RCTs evaluating the ERAS® program, the previously observed outcomes from other fast track and enhanced recovery programs extrapolated to support ERAS® might not be accrued in routine clinical practice, hence the importance of evaluating the evidence base for any intervention or program, and prospectively evaluating any changes in care delivery models at a system level. Examining the ERAS® program evaluated in our study might suggest gaps in the current program with the absence of core elements that have been shown to have a significant impact on postoperative outcomes such as: consistent use of laparoscopic surgery, stringent glycemic control in individuals with and without diabetes, as well as structured prehabilitation. Whether these components would have an independent effect would need to be evaluated in an RCT.

A large body of evidence supports the beneficial effect of laparoscopic surgery in reducing the surgical stress and inflammatory response and promoting rapid recovery in colorectal cancer surgery.(15–20) One of the early studies to evaluate laparoscopic surgery within a fast track program was the multicenter LAFA-Study; in a 2x2 factorial design trial, 427 subjects were randomly assigned to one of four groups: laparoscopy/fast track, open/fast track, laparoscopy/standard care, and open/standard care. The results revealed that the optimal treatment combination for colorectal surgery within a fast track program was the laparoscopic approach with a median LOS of 5 days (IQR 4-7, $p<0.001$), and overall postoperative morbidity 34%; $p=0.2$ with readmission rates at 6%,

p=0.97.(21) A subsequent systematic review by Spanjersberg et al evaluating whether laparoscopy and ERAS carry additional synergistic effects in colorectal surgery analyzed 3 RCTs and 6 controlled clinical trials (CCTs) and found an effect on LOS with the combination of both (median LOS -2.34 [-3.77, -0.91], Z=3.20, p= 0.001), but not postoperative morbidity. Of note, laparoscopy had an impact independent of ERAS on postoperative morbidity (OR 0.42 [0.26, 0.66], Z=3.73, p=0.006), however ERAS did not have a significant impact independent of laparoscopy (OR 0.97 [0.62, 1.53], Z=0.11, p=0.91).(22) A recent observational study evaluating the surgical approach (laparoscopy, laparoscopy converted to open surgery, and open surgery) within an ERAS program demonstrated a significantly higher 5-year survival rate in colorectal cancer surgery patients with the laparoscopy approach (survival rate=78%) compared to both the converted group (survival rate=68%), and open surgery group (survival rate=70%) p<0.007.(17,19) Therefore, incorporating routine laparoscopic surgery within ERAS® is likely to improve outcomes.

Hyperglycemia is associated with increased risk of postoperative morbidity and mortality including surgical site infections (SSI), acute coronary syndrome, and sepsis.(8,23–26) The prevalence of postoperative hyperglycemia (glucose >10 mmol/l) in individuals without known diabetes in a large multicenter cohort of colorectal surgery patients was 14%, and among those with known diabetes 68%.(27) Despite the recognized prevalence and impact of this metabolic derangement, detection and management of hyperglycemia is often overlooked in surgical patients.(8) Hence, glycemic management is essential for an ERAS® program.

Prehabilitation is an evolving concept in surgical care. A relationship between physical fitness preoperatively, and postoperative outcomes has been demonstrated and is

supported by a large body of evidence in cardio-pulmonary and non cardio-pulmonary surgery.(28–32) Objective measures of cardiorespiratory reserve such as cardiopulmonary exercise testing (CPET) have been shown to be a good predictor of postoperative morbidity and mortality.(33–35) A trial assessing the value of prehabilitation in patients undergoing colorectal surgery within an ERAS program is underway and study completion is expected soon.(36) This may be another missing link in the continuum of surgical care that impacts postoperative outcomes.

To date, no comparable study to the robust multicenter ITS analysis presented here is available evaluating the ERAS® program in colorectal surgery. Although a recent publication from 20 hospitals in Kaiser Permanente Northern California included a contemporaneous surgical comparator group in an ITS analysis of an ERAS program for colorectal surgery, perusal of their supplementary tables raises questions about whether the comparators really were an appropriate choice. For example, they were almost a decade younger than the ERAS patients, less than 10% had lower GI surgery (3/4 had gastrectomy, nephrectomy, or hernia repairs), and their LOS (2.2 days vs. 5.1 days) and complication rates (6.9% vs. 18.1%) were already substantially lower than LOS for colorectal surgery patients–meaning that the size of any potential improvements for the comparator patients was markedly restricted. Furthermore, that study was at high risk for bias with the absence of standardized and validated complications data for their cohorts, and inconsistency in acquisition of this data.(37) The other large-scale observational studies demonstrating benefit of the ERAS® program on postoperative outcomes are uncontrolled pre- post- studies; well recognized to have inherent limitations and to overestimate intervention effects.(11,37–39) Although RCTs exist for fast-track and enhance recovery pathways in colorectal surgery -differing form the ERAS® program

evaluated in our study- they are not thought to be appropriate comparators given the heterogeneous pathways utilized and the moderate to high risk of bias most of these small trials were at risk of.(40,41)

For the diabetes subgroup, reasons for the absence of a significant difference in any of the postoperative outcomes are unclear and warrant further investigation. The lack of a measurable effect of ERAS® on postoperative outcomes could be explained by similar factors to the whole cohort such as low adherence, under powering of the study, intrinsic factors relating to surgical care in Alberta, or due to the absence of a significant measurable benefit. Additional unique variables to consider in this population are underlying insulin resistance, which is innate to the pathophysiology of type 2 diabetes. The goal of the ERAS® program is to reduce perioperative stress and insulin resistance through its various components, however fasting in individuals with diabetes - contrary to carbohydrate loading preoperatively as recommended by ERAS®- would be expected to reduce insulin resistance and the risk of hyperglycemia which in turn would be expected to have a positive impact on postoperative outcomes.(42) This raises the concern that preoperative carbohydrate loading might have resulted in hyperglycemia and initiated a series of inflammatory cascades predisposing to surgical site infections and increased morbidity postoperatively. On the other hand, in a small study by Schricker and colleagues, protein catabolism after colorectal surgery was found to be increased in patients with type 2 diabetes compared to those without diabetes, as reflected by an increased oxidative protein loss(43). Metabolic benefits were observed in RCTs in individuals without diabetes where carbohydrate loading was shown to preserve skeletal muscle mass postoperatively(44,45) and improve nitrogen economy.(46) It is unclear if having patients with diabetes in a well-fed state (i.e. carbohydrate loaded preoperatively)

with concurrent optimal glycemic control would attenuate depletion of muscle mass after surgery and improve mobilization and early discharge postoperatively(45) – there is clearly a need for a randomized trial to answer this question.

The non-significant increase in postoperative complications observed in the diabetes group post-ERAS® which was related to higher gastrointestinal complications was unexpected given that these particular complications have been shown to occur less frequently with early post surgery nutrition, removal of gastric tubes, less use of opioids and early mobility – all key components of the ERAS® program. This raises the question of whether hyperglycemia was managed properly perioperatively for these patients. The extent to which hyperglycemia had an impact on postoperative outcomes needs to be investigated further in an RCT (which we have initiated in Alberta).

4.2 Implications and Future Directions

The lack of identified studies on the impact of ERAS® in the diabetes subgroup draws attention to the need for robust study designs to evaluate outcomes in this surgical population. In addition to RCTs, Non-randomized Controlled Trials (NRCTs), Controlled Before-After (CBA) studies, and ITS studies are the designs of choice when evaluating the effects of health system interventions. To ensure rigorous evaluation of future ERAS® program implementations in individuals with diabetes, we recommend including one of the previous robust study designs at the time of implementation instead of the current practice of conducting uncontrolled pre- post-ERAS studies. Further work is required to address the gap in perioperative care in this group, and analyzing the diabetes subgroup within ERAS® databases will help guide the design of RCTs utilizing diabetes-specific protocols; taking into account the higher preoperative risk, the need for

surgical prehabilitation, perioperative glycemic control, and adopting routine use of laparoscopy. A pilot RCT is already underway in Alberta to address carbohydrate loading within ERAS® program in individuals with diabetes to help inform clinical decisions in this area.

The same robust study designs outlined above are also needed to *reevaluate* the impact of ERAS® on patients (without diabetes) undergoing colorectal surgery to determine whether the negative results observed in our study are replicated in other ERAS® cohorts, or whether these findings are specific to Alberta's surgical population, with an assumed lower adherence to the program in the first year of implementation. This would be best pioneered by the ERAS® Society to provide guidance and methodological support for analyzing their central database with data linkage to local administrative databases. Repeating our ITS analysis in a couple of years, as ERAS® programs in Alberta mature and with more data points for added study power, would aid in determining whether the results are different with wider implementation and adherence to ERAS.

4.3 Conclusion

In conclusion, despite advances in perioperative care and the introduction of multidisciplinary pathways in the early 1990s, individuals with diabetes remain at a higher risk for postoperative complications. A gap exists in the field of diabetes and postoperative outcomes within ERAS®, this thesis confirmed this gap through systematic evaluation of the evidence, and contributed by analyzing the first real-life diabetes cohort using an ITS analysis on individuals undergoing elective colorectal surgery in Alberta.

The lack of effect observed in those with diabetes, and the unexpected findings of lack of an important effect attributed to ERAS® in a mixed cohort without diabetes from our study raises questions about the effectiveness of ERAS® for this patient group and highlights the need to evaluate the program implementation intrinsically (by utilizing audit data to determine barriers) and extrinsically (by *rigorously* analyzing other centers' data) to evaluate whether these findings are reproduced, or whether they are unique to Alberta's early post implementation period, or other extrinsic factors. Priorities for future research include rigorously evaluating modified multimodal pathways for individuals with diabetes with emphasis on structured prehabilitation, standardized glycemic control perioperatively, and consistent utilization of laparoscopic approach.

Bibliography

1. Gustafsson UO, Nygren J, Thorell A, Soop M, Hellström PM, Ljungqvist O, et al. Pre-operative carbohydrate loading may be used in type 2 diabetes patients. Acta Anaesthesiol Scand. 2008 Aug;52(7):946–51.

2. Kashyap P, Farrugia G. Diabetic gastroparesis: what we have learned and had to unlearn in the past 5 years. Gut. 2010 Dec;59(12):1716–26.

3. Dhatariya K, Levy N, Kilvert A, Watson B, Cousins D, Flanagan D, et al. NHS Diabetes guideline for the perioperative management of the adult patient with diabetes. Diabet Med J Br Diabet Assoc. 2012 Apr;29(4):420–33.

4. Farrukh A, Higgins K, Singh B, Gregory R. Can pre-operative carbohydrate loading be used in diabetic patients undergoing colorectal surgery? Br J Diabetes. 2014 Sep 12;14(3):102–4.

5. Hill LT, Miller MGA. Carbohydrate loading in the preoperative setting. South Afr Med J Suid-Afr Tydskr Vir Geneeskd. 2015 Mar;105(3):173–4.

6. Laffin MR, Li S, Brisebois R, Senior PA, Wang H. The Use of a Pre-operative Carbohydrate Drink in Patients with Diabetes Mellitus: A Prospective, Non-inferiority, Cohort Study. World J Surg. 2017 Dec 27;

7. Umpierrez GE, Smiley D, Jacobs S, Peng L, Temponi A, Mulligan P, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). Diabetes Care. 2011 Feb;34(2):256–61.

8. Kwon S, Thompson R, Dellinger P, Yanez D, Farrohki E, Flum D. Importance of perioperative glycemic control in general surgery: a report from the Surgical Care and Outcomes Assessment Program. Ann Surg. 2013 Jan;257(1):8–14.

9. Gramlich LM, Sheppard CE, Wasylak T, Gilmour LE, Ljungqvist O, Basualdo-Hammond C, et al. Implementation of Enhanced Recovery After Surgery: a strategy to transform surgical care across a health system. Implement Sci IS. 2017 May 19;12(1):67.

10. Li L, Jin J, Min S, Liu D, Liu L. Compliance with the enhanced recovery after surgery protocol and prognosis after colorectal cancer surgery: A prospective cohort study. Oncotarget. 2017 Aug 8;8(32):53531–41.

11. Aarts M-A, Rotstein OD, Pearsall EA, Victor JC, Okrainec A, McKenzie M, et al. Postoperative ERAS Interventions Have the Greatest Impact on Optimal Recovery:

Experience With Implementation of ERAS Across Multiple Hospitals. Ann Surg. 2018 Jan 4;

12. McAlister FA, Bakal JA, Majumdar SR, Dean S, Padwal RS, Kassam N, et al. Safely and effectively reducing inpatient length of stay: a controlled study of the General Internal Medicine Care Transformation Initiative. BMJ Qual Saf. 2014 Jun;23(6):446–56.

13. Services AH. Cancer SCN [Internet]. Alberta Health Services. [cited 2018 Mar 16]. Available from: https://www.albertahealthservices.ca/scns/Page7677.aspx

14. Simpson JC, Moonesinghe SR, Grocott MPW, Kuper M, McMeeking A, Oliver CM, et al. Enhanced recovery from surgery in the UK: an audit of the enhanced recovery partnership programme 2009-2012. Br J Anaesth. 2015 Oct;115(4):560–8.

15. Fleshman J, Sargent DJ, Green E, Anvari M, Stryker SJ, Beart RW, et al. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. Ann Surg. 2007 Oct;246(4):655–62; discussion 662-664.

16. Kennedy RH, Francis EA, Wharton R, Blazeby JM, Quirke P, West NP, et al. Multicenter randomized controlled trial of conventional versus laparoscopic surgery for colorectal cancer within an enhanced recovery programme: EnROL. J Clin Oncol Off J Am Soc Clin Oncol. 2014 Jun 10;32(17):1804–11.

17. Zhao J, Sun J, Huang X, Gao P, Chen X, Song Y, et al. Meta-analysis of the laparoscopic versus open colorectal surgery within fast track surgery. Int J Colorectal Dis. 2016 Mar;31(3):613–22.

18. Pache B, Hübner M, Jurt J, Demartines N, Grass F. Minimally invasive surgery and enhanced recovery after surgery: The ideal combination? J Surg Oncol. 2017 Oct;116(5):613–6.

19. Curtis NJ, Taylor M, Fraser L, Salib E, Noble E, Hipkiss R, et al. Can the combination of laparoscopy and enhanced recovery improve long-term survival after elective colorectal cancer surgery? Int J Colorectal Dis. 2018 Feb;33(2):231–4.

20. Salem JF, Gummadi S, Marks JH. Minimally Invasive Surgical Approaches to Colon Cancer. Surg Oncol Clin N Am. 2018 Apr;27(2):303–18.

21. Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). Ann Surg. 2011 Dec;254(6):868–75.

22. Spanjersberg WR, van Sambeeck JDP, Bremers A, Rosman C, van Laarhoven CJHM. Systematic review and meta-analysis for laparoscopic versus open colon surgery with or without an ERAS programme. Surg Endosc. 2015 Dec;29(12):3443–53.

23. Ata A, Lee J, Bestle SL, Desemone J, Stain SC. Postoperative hyperglycemia and surgical site infection in general surgery patients. Arch Surg Chic Ill 1960. 2010 Sep;145(9):858–64.

24. King JT, Goulet JL, Perkal MF, Rosenthal RA. Glycemic control and infections in patients with diabetes undergoing noncardiac surgery. Ann Surg. 2011 Jan;253(1):158–65.

25. Jackson RS, Amdur RL, White JC, Macsata RA. Hyperglycemia is associated with increased risk of morbidity and mortality after colectomy for cancer. J Am Coll Surg. 2012 Jan;214(1):68–80.

26. Martin ET, Kaye KS, Knott C, Nguyen H, Santarossa M, Evans R, et al. Diabetes and Risk of Surgical Site Infection: A Systematic Review and Meta-analysis. Infect Control Hosp Epidemiol. 2016 Jan;37(1):88–99.

27. Mohan S, Kaoutzanis C, Welch KB, Vandewarker JF, Winter S, Krapohl G, et al. Postoperative hyperglycemia and adverse outcomes in patients undergoing colorectal surgery: results from the Michigan surgical quality collaborative database. Int J Colorectal Dis. 2015 Nov;30(11):1515–23.

28. Hoogeboom TJ, Dronkers JJ, Hulzebos EHJ, van Meeteren NLU. Merits of exercise therapy before and after major surgery. Curr Opin Anaesthesiol. 2014 Apr;27(2):161–6.

29. Levett DZH, Grocott MPW. Cardiopulmonary exercise testing, prehabilitation, and Enhanced Recovery After Surgery (ERAS). Can J Anaesth J Can Anesth. 2015 Feb;62(2):131–42.

30. Moran J, Wilson F, Guinan E, McCormick P, Hussey J, Moriarty J. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. Br J Anaesth. 2016 Feb;116(2):177–91.

31. West MA, Asher R, Browning M, Minto G, Swart M, Richardson K, et al. Validation of preoperative cardiopulmonary exercise testing-derived variables to predict in-hospital morbidity after major colorectal surgery. Br J Surg. 2016 May;103(6):744–52.

32. Heldens AFJM, Bongers BC, Lenssen AF, Stassen LPS, Buhre WF, van Meeteren NLU. The association between performance parameters of physical fitness and postoperative outcomes in patients undergoing colorectal surgery: An evaluation of care

data. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2017 Nov;43(11):2084–92.

33. Snowden CP, Prentis JM, Anderson HL, Roberts DR, Randles D, Renton M, et al. Submaximal cardiopulmonary exercise testing predicts complications and hospital length of stay in patients undergoing major elective surgery. Ann Surg. 2010 Mar;251(3):535–41.

34. Wilson RJT, Davies S, Yates D, Redman J, Stone M. Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. Br J Anaesth. 2010 Sep;105(3):297–303.

35. Lee CHA, Kong JC, Ismail H, Riedel B, Heriot A. Systematic Review and Meta-analysis of Objective Assessment of Physical Fitness in Patients Undergoing Colorectal Cancer Surgery. Dis Colon Rectum. 2018 Mar;61(3):400–9.

36. Merki-Künzli C, Kerstan-Huber M, Switalla D, Gisi D, Raptis DA, Greco N, et al. Assessing the Value of Prehabilitation in Patients Undergoing Colorectal Surgery According to the Enhanced Recovery After Surgery (ERAS) Pathway for the Improvement of Postoperative Outcomes: Protocol for a Randomized Controlled Trial. JMIR Res Protoc. 2017 Oct 27;6(10):e199.

37. Liu VX, Rosas E, Hwang J, Cain E, Foss-Durant A, Clopp M, et al. Enhanced Recovery After Surgery Program Implementation in 2 Surgical Populations in an Integrated Health Care Delivery System. JAMA Surg. 2017 Jul 19;152(7):e171032.

38. ERAS Compliance Group. The Impact of Enhanced Recovery Protocol Compliance on Elective Colorectal Cancer Resection: Results From an International Registry. Ann Surg. 2015 Jun;261(6):1153–9.

39. Nelson G, Kiyang LN, Crumley ET, Chuck A, Nguyen T, Faris P, et al. Implementation of Enhanced Recovery After Surgery (ERAS) Across a Provincial Healthcare System: The ERAS Alberta Colorectal Surgery Experience. World J Surg. 2016 May 1;40(5):1092–103.

40. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced Recovery Program in Colorectal Surgery: A Meta-analysis of Randomized Controlled Trials. World J Surg. 2014 Jun 1;38(6):1531–41.

41. Lau CSM, Chamberlain RS. Enhanced Recovery After Surgery Programs Improve Patient Outcomes and Recovery: A Meta-analysis. World J Surg. 2017;41(4):899–913.

42. Thompson RE, Broussard EK, Flum DR, Wisse BE. Perioperative Glycemic Control During Colorectal Surgery. Curr Diab Rep. 2016 Mar;16(3):32.

43. Schricker T, Gougeon R, Eberhart L, Wykes L, Mazza L, Carvalho G, et al. Type 2 diabetes mellitus and the catabolic response to surgery. Anesthesiology. 2005 Feb;102(2):320–6.

44. Henriksen MG, Hessov I, Dela F, Hansen HV, Haraldsted V, Rodt SA. Effects of preoperative oral carbohydrates and peptides on postoperative endocrine response, mobilization, nutrition and muscle function in abdominal surgery. Acta Anaesthesiol Scand. 2003 Feb;47(2):191–9.

45. Yuill KA, Richardson RA, Davidson HIM, Garden OJ, Parks RW. The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively--a randomised clinical trial. Clin Nutr Edinb Scotl. 2005 Feb;24(1):32–7.

46. Crowe PJ, Dennison A, Royle GT. The effect of pre-operative glucose loading on postoperative nitrogen metabolism. Br J Surg. 1984 Aug;71(8):635–7.