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Assessment of Intensive Care Unit Outreach Transition Programs effect on readmissions and mortality among ICU survivors discharged to ward in Calgary – a Time Series Study.

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Assessment of Intensive Care Unit Outreach Transition Programs effect on readmissions and mortality among ICU survivors discharged to ward in Calgary – a Time Series Study.

by

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Abstract

Introduction: Potentially preventable errors and adverse events can occur as a consequence of patient transfer of care between health care providers. Intensive Care Unit transition programs (ICUTP) are a type of Rapid Response System Model, which presents a very simple idea: if a patient shows signs of imminent clinical deterioration, a team of providers is called up to the bedside to immediately assess and treat the patient in order to prevent intensive care unit transfer, cardiac arrest, or death. ICUTP incorporate ICU transition assignments, having a role in facilitating discharge and providing a smooth transition for complex convalescent patients to a general hospital ward. However, when assessing the ICU transition assignments for these teams, there is a substantial lack of available data, essential for assessing their effectiveness. This led us to inquire into the real role of a program in which significant investments have been placed.

Objectives: Primary: To assess if ICU transition programs decrease the risk of ICU readmission when compared to standard care among patients who survive their initial admission to an adult ICU. Secondary: To assess if ICU transition programs decrease the risk of in-hospital mortality when compared to standard care among patients who survive their initial admission to an adult ICU.

Methods: We performed an interrupted time series (ITS) study, a variation of time-series studies classified as quasi-experiments, involving all adults older than 18 years old, who survived their first ICU admission and were discharged to ward between 2002 and 2010 in Calgary, Alberta. The outcomes (ICU readmission and hospital mortality) were measured at every 3 months, before and after the implementation of our ICUTP - the ICU outreach team (ICUOT). Multivariable segmented logistic regression was used to adjust the estimates of

the odds ratio (OR) of each outcome measure before and after the intervention. Data were reported as odds ratios (OR) and proportions with 95% confidence intervals (CI) and were evaluated for multicollinearity and autocorrelation.

Results: At the start of the study 6.0% (95% confidence interval [CI] 4.9% to 7.0%) of the patients of our study population were readmitted to ICU. During the pre-intervention period, we could see a non-significant decrease of 0.02%(-0.02%, 95% CI -0.10% to +0.07%) in the proportion of patients readmitted to ICU per quarter of study. After implementation of the ICUOT, there was a 2.0% significant increase in the proportion of patients readmitted to ICU (+2.0%, 95% CI +0.5% to +3.2%). Subsequently, we saw a non-significant decrease in that proportion (-0.04% per quarter; 95% CI, -0.2% to +0.1%). At the end of the study, the proportion of patients readmitted in the ICU was 6.0% (95% CI, 4.8% to 7.0%). Regarding hospital mortality, 7.0% (95% confidence interval [CI] 6.0% to 9.0%) of the patients of our study population died in the hospital at the start of the study period. In the pre-intervention period, there was a non-significant decrease of 0.01% (-0.01% 95% CI, -0.09% to +0.07%) in the proportion of patients who died in the hospital per quarter. After implementation of the ICUOT, there was an immediate non-significant increase of 1.0% in the proportion of patients dying in the hospital, (+1.0%, 95% CI -0.3% to +2.4%). Subsequently, there was a significant small decrease in that proportion (-0.2% per quarter; 95% CI, -0.3% to -0.05%). At the end of the study, the proportion of in-hospital deaths was 4.0% (95% CI, 3.0% to 5.0%).

Conclusion: This work, based on a robust methodology that uses an interrupted time-series with segmented logistic regression, showed that ICU readmission rates remain the same based on the estimated changes in intercept and slope when comparing pre and post-

intervention periods. There is insufficient evidence of a statistically significant effect of the ICUOT on ICU readmissions. However, it is possible that closer monitoring and faster actions on those ICU survivors who required or did not required ICU readmission have been lead to a small but significant improvement in mortality.

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CHAPTER ONE: INTRODUCTION

Potentially preventable errors and adverse events can occur as a consequence of patient transfer of care between health care providers.[1,2] In this context, the transfer of patients from an intensive care unit (ICU) to a medical or surgical hospital ward is associated with a substantial decrease in their level of monitoring, which could make them susceptible to delays in the diagnosis of any clinical deterioration.[2] Intensive Care Unit transition programs, which incorporate ICU transition assignments might have a role in facilitating discharge and providing a smooth transition for complex convalescent patients to a general hospital ward.

Transition programs have been developed by many hospitals, and come in different forms like rapid response systems (RRS), medical emergency teams (METs) or Intensive Care Unit Outreach teams (ICUOTs). They are usually composed of a combination of a critical care/emergency nurse, a respiratory therapist, and/or an intensive care/emergency physician.[3] Proper assessment of critical care response systems is complex and studies have been performed with inconclusive evidence as to their effectiveness. In addition, when assessing the ICU transition assignments for these teams, there is a substantial lack of available data, essential for assessing their effectiveness. Although we can draw an overall reduction of the pooled risk of ICU readmissions and mortality on recent studies of critical care outreach transition programs, these studies were based on a poor statistical analysis, which weakens the validity of the study findings. Nonetheless, considerable resources have been invested in outreach services worldwide over the last fifteen years.[4] In fact, currently, there is a culture of ICUTP around the world even without a firm evidence of their

effectiveness and cost-effectiveness.[5] This led us to inquire into the real role of a program in which significant investments have been placed.[7,8.]

CHAPTER TWO: BACKGROUND

2.0 The 'quicker and sicker' discharged ICU patient.

Strategies to decrease ICU length of stay (LOS) can improve patient outcomes since prolonged stay in the ICU potentially increases the risk for nosocomial complications like bloodstream and urinary catheter-related infections, pulmonary edema and critical illness polyneuropathy/myopathy.[6] Additionally, patients with prolonged LOS are troublesome for families, increase costs and resource consumption, and reduce the number of beds available for other acutely ill patients requiring ICU.[9,10,11] However, discharge from the ICU is not without risk. When patients requiring high-intensity care are discharged before they can safely fit a lower level of monitoring and a less intensive care environment, they are at risk for both complications and delayed recognition of clinical deterioration.[12] If readmitted to ICU, these patients will have higher risk-adjusted mortality and LOS.[12,13] The average hospital stay for readmitted patients is at least twice as long as for patients discharged from ICU but not readmitted.[13-17]

A systematic review found that up to 42% of readmitted patients have probably been prematurely discharged, 22% of readmissions were potentially preventable, and 11% were potentially anticipated.[12] In addition, hospital death rates are 1.5 to 10 times higher among ICU readmissions.[12,16] Certainly, readmissions to an ICU may reflect opportunity for improved care. Concerns that patients are being discharged "quicker and sicker" from ICU

have been raised and have led some payers and health researchers to propose two possible ways to minimize the risks among these discharged patients. The first way, the developments of ICU-discharge risk scores intending to help determine the optimal time to discharge a patient to ward. Decisions to discharge ICU patients to a general ward are often made with subjective clinical judgment. There may be a need for reliable tools to quantify the risk of discharge, in order to aid with discharge decision-making. Some characteristics that tend to increase the probability of readmissions are transfer from another hospital, age, chronic comorbidities, length of initial ICU stay, and severity of illness at ICU discharge. Recent studies found that sedation, Glasgow Coma Scale score at discharge, and a low serum creatinine and albumin (the latter two possibly reflecting patient malnutrition), are also indicators of high risk for deterioration at ward after discharge.[18]

Scores and risk models intending to identify patients with high probability of complications after ICU discharge have been developed and used. Examples are the SAPS II at ICU admission, SOFA score at ICU discharge, Stability and Workload Index for Transfer (SWIFT) on the day of ICU discharge and The Sabadell score, based on the physician's subjective impression at ICU discharge. In previous studies, they were able to predict post-ICU ward mortality.[13,19-22] However, these tools are usually prediction models created and tested in specific populations, which can limit their external validity and they have not been tested in interventional studies to reduce ICU readmissions and mortality among ICU survivors.[12,15-22] Also, their use is not practical, since they contain too many details and may be lengthy. In addition, they are based on risk analysis and on our best guess. Patients might still be at risk when discharged to ward. The second way to minimize the risks among these discharged patients would be the close follow-up of discharged

patients by a skilled critical care team – the ICU transition program – it would provide a smooth patient transition to a general ward.

2.1 Potential Solutions: The ICU Transition Program

The ICU outreach team is a type of Rapid Response System Model (fig 1). Therefore, it presents a very simple idea: if a patient shows signs of imminent clinical deterioration, a team of providers is called up to the bedside to immediately assess and treat the patient in order to prevent intensive care unit transfer, cardiac arrest, or death. ICUTP incorporate ICU transition assignments, having a role in facilitating discharge and providing a smooth transition for complex convalescent patients to a general hospital ward. ICUTP, like all the Rapid Response System Models, have what is classically called “afferent and efferent limbs”, or the criteria for activating a code that calls the team and the response to that code, respectively. Ward staff will call the team for any of a number of prespecified criteria: heart rate over 140/min or less than 40/min, respiratory rate over 28/min or less than 8/min, systolic blood pressure greater than 180 mmHg or less than 90 mmHg, oxygen saturation less than 90% despite supplementation, acute change in mental status, urine output less than 50 cc over 4 hours and when staff member has significant concern about the patient's condition - are examples of those criteria.

They provide an excellent opportunity to address the risk of preventable errors, anticipate potential readmissions and follow those patients who would have been discharged prematurely. Most clinicians believe that ICUTP are the most solid way to minimize risks among ICU discharged patients.

2.2 Literature Review

A reduction in hospital mortality represents the most comprehensive and important outcome measure for rapid response systems. In fact, the achievement of intermediate endpoints, such as the rates of unexpected cardiac arrests outside ICU or unplanned ICU admission, is of limited benefit, if the patient's final outcome does not change.

Few studies have examined the effect of outreach teams on the risk of ICU readmission and death in ICU survivors discharged to ward. It is potentially attributable to many factors, e.g., these teams provide different follow-ups for patients discharged from the ICU, their composition differs substantially, and finally, the idea of a dedicated ICU transition service is something new within the context of rapid response teams in general. Nonetheless, there are many points that remain unclear regarding the ICU outreach transition programs effect on ICU survivors. Recent meta-analyses of controlled before-and-after studies suggest that ICU transition programs facilitate the high-risk transition of patients from an ICU to a general ward by reducing the risk of ICU readmissions and death.[32,35] However, more robust methodological approaches (i.e., segmented regression analysis of interrupted time series studies) have not been used to assess the effect of ICU transition programs on ICU survivors, until very recently.[36] Also, some questions have arisen. What is the ideal model for the ICU transition programs? They are usually composed of a combination of a critical care/emergency nurse, a respiratory therapist, and/or an intensive care/emergency physician. Is physician inclusion in the team necessary? What are

the mechanisms through which patient outcomes could be improved? What is the effect on the rate of ICU readmissions of establishing goals of care?

To lay the groundwork for this research proposal, we recently conducted a systematic review and meta-analysis of Critical Care Transition Programs and the Risk of Readmission or Death After ICU Discharge[32]. It assessed if critical care transition programs reduce the risk of ICU readmission or death when compared to standard care among patients who survive their incident admission to an adult ICU. Studies had to meet each of the following inclusion criteria: 1) study population primarily included adult patients (<10% of study population was < 18 years of age) admitted to an ICU; 2) intervention cohort exposed to a critical care transition program; 3) control population was not managed with the aid of a critical care transition program; 4) ICU readmission rate reported; and 5) controlled study design (randomized clinical trial, controlled clinical trial, interrupted time-series, cohort, before/after study). Articles that met any one of the following exclusion criteria were not included in the review: 1) pediatric study population (>10% of study population < 18 years of age); 2) no clear description of a critical care transition program; 3) no control population described; 4) ICU readmission rate not reported; 5) article did not report on original research (i.e. narrative review, editorial, letter-to-the editor); and 6) animal study.

A critical care transition program included any rapid response team/system, medical emergency team, critical care outreach team/service, or ICU liaison nurse program that provided routine follow-up to patients recently discharged from ICU. The search strategy included filters for the themes critical illness, outreach programs, readmission/mortality, and controlled study designs using a combination of exploded Medical Subject Heading (MeSH)

terms and text words that were combined with the Boolean operator "OR." The literature review identified 3,590 citations, of which nine studies were included in the systematic review. The studies generally included a mixed medical-surgical population, with a median sample size of 1,516 (470 – 3,001) patients. Most studies occurred in the United Kingdom and Australia/New Zealand. Seven of the nine studies took place in teaching hospitals.[27,29,30]

The critical care transition programs were frequently associated with a hospital's outreach/medical emergency team (MET) that was also responsible for attending to other unstable ward-based patients. A critical care physician was an active member of the transition program in only four studies and considering all nine studies and a respiratory therapist was included in just one program.[24-27] However, three Australian centers utilized an ICU liaison nurse to specifically facilitate the high-risk transition from ICU to the general ward.[26] With respect to the follow-up of patients discharged from ICU, only one of the outreach/MET teams visited patients prior to ICU discharge[28], whereas the three ICU nurse liaison programs routinely visited patients prior to ICU discharge.[27,29,30] Discharged patients were commonly followed for up to 48 hours or until evidence of clinical stability. Eight studies were included in the primary meta-analysis, among which there was no significant heterogeneity (I^2 = 0.0%, p = 0.5). Each study employed a controlled before-and-after design, and all but one[30] took place in a single hospital. The pooled risk ratio estimates demonstrated a reduced risk of ICU readmission (0.87, 95% CI 0.76 – 0.99, p = 0.03) and a trend towards a reduction in hospital mortality (0.84, 95% CI 0.66 – 1.05, p = 0.1) associated with a critical care transition program (Fig.3).[32] While including outreach teams and nurse liaison programs, this review did not find any significant differences in the risk of

ICU readmission for the nurse liaison versus outreach programs in a subgroup analysis. In addition, the presence of a physician also did not significantly affect the risk of readmission to ICU. Although the two most important randomized clinical trials on rapid response teams (in which ICU outreach teams were included) failed to provide consistent results on their effectiveness, their design did not focus on that very high-risk population of ICU survivors. The benefit in terms of mortality rates and ICU readmissions seen in this systematic review of before and after studies, could be possibly explained by the fact that ICU survivors were much higher-risk patients than the average of patients rescued by general rapid response teams.[27-30,32]

The potential benefit of critical care transition programs might be restricted to ICU survivors, who have the greatest risk of experiencing an adverse event among intra-hospital patients.[32] In fact, making sure that outreach teams that encompass a transition program are effective in our health system is our goal. Interrupted time series design is the strongest, quasi-experimental approach for evaluating longitudinal effects of such time-limited interventions. Segmented regression analysis of interrupted time series data allows us to assess, in statistical terms, how much an intervention changed pre-specified outcomes over time and whether factors other than the intervention could explain the change.[38] Although many institutions worldwide have had ICU transition programs over a decade ago, formal longitudinal evaluation of these programs using adequate study designs is lacking. As ICU outreach programs are expensive, and evidence for their effectiveness on mortality is generally lacking, it is important to understand whether these services can improve outcomes. Consequently, the effect of ICU transition programs on ICU readmissions and mortality remains unclear. Based on the currently available literature on ICU outreach teams

with discharge transition programs, further research is required before recommendations concerning their universal implementation can be made. A systematic review of before and after studies was not adequate for an evaluation of the ICU Outreach programs.

As data had been collected from our ICU outreach program since its implementation in the 2002's, it was time to clarify some of these points. Hence, since a natural experiment already existed, we decided to take advantage of an existent change, choosing a robust interrupted time-series with segmented logistic regression to evaluate our program.

2.3 Research Question

A well-built question should include four parts, referred to as PICOD, identifying the population (P), the intervention (I), comparison (C), outcomes (O), and design (D). The PICOD questions for the proposed project is as follows:

1. Patients**:** Adult patients who survive an initial admission to ICU and were discharged to ward in Calgary, in the province of Alberta.
2. Intervention**:** ICU transition program
3. Control: No ICU transition program
4. Outcomes: *Primary* = ICU Readmission during the same hospitalization. *Secondary* = in-hospital death among patients discharged from ICU to a general ward.
5. Design**:** Quasi-experimental study, using Interrupted time-series analysis
6. From the PICOD question, the primary and the secondary research questions are:

Primary: Do ICU transition programs decrease the risk of ICU readmission when compared to standard care among patients who survive their initial admission to an adult ICU?

Secondary: Do ICU transition programs decrease the risk of in-hospital mortality when compared to standard care among patients who survive their initial admission to an adult ICU?

CHAPTER THREE: METHODS

3.0 Study Design

The study design is an interrupted time series (ITS) method, a variation of time-series studies classified as quasi-experiments. The term “interrupted” refers to the points over time when there is a change from the established pattern because of a real-world event, a policy change, or an experimental intervention. Quasi-experimental studies, also known as quasi-experiments, are studies in which the investigators do not have full control over the assignment or the moment of the intervention, although the studies are still conducted as if they were experiments.[33,37] The defining aspects of these studies are an identifiable intervention and the absence of a random allocation. In addition, many of those studies do not have control groups. Time-series studies are the most epidemiologically strong quasi-experiments. In this quasi-experimental design, there is a time-oriented or chronological sequence of observations on a variable of interest.[33,37,39]

In ITS method, multiple measurements of the study outcome are taken before and following the intervention without the use of a separate control group. Also, the repeated measurements will be equally spaced in time (Fig.4). The ITS analysis is a reasonable method for this study, where true randomization of cases and controls is not possible. In addition, it is well suited for retrospective clinical data. ITS detects trends of intervention effects and whether the effect of the intervention occurs immediately, or there is a delay between intervention and effect. Also, we can see if the effect continues to trend over time, stabilizes, or even goes away after a certain time – an advantage of the ITS designs. This

design permits the effect of the intervention to be estimated while taking into account secular trends or cyclic patterns that usually affect the study outcomes.[33,40] These outcome measures could not be obtained with typical pre/post studies or randomized clinical trials.

3.1 ICU Transition Program in Calgary, AB – The ICU Outreach Team (ICUOT)

After a successful pilot project started at Rockview General Hospital in 2004, which led to a reduction of 39.7% in the code blue calls, the Intensive Care Unit Outreach Team (ICUOT) program was fully implemented at three sites in Calgary in 2006 (July 01 at Foothills Medical Center, July 01 at Rockview General Hospital and October 01 at Peter Lougheed Center). The main goal is to assist in the safe transfer of patients from ICU to the ward and also the management of adult patients (other than ICU survivors) and visitors who have been identified as or are at imminent risk of becoming physiologically unstable. The ICUOT responds to Code 66 calls (the specific overhead alarm that activates the ICUOT) in the adult population only. For individuals 17 years of age or less, the appropriate pediatric or neonatal code blue should be activated. The primary response to changes in patient condition is the responsibility of the attending medical team. The attending medical team, including the most responsible physician and the primary care registered nurse/licensed practical nurse or designate, are expected to attend the code 66. In the event that the attending medical team is not available to respond within 15 minutes, and the specified clinical triggers are present, a Code 66 alarm is activated to add to the response of the attending medical team. When a Code 66 is activated for an admitted patient, the attending medical team will urgently attend the patient. The expected time for the ICUOT to respond

to a Code 66 is up to 15 minutes. A Code 66 can be activated by any staff member for any of the following:

- threatened airway
- respiratory rate less than 8, or greater than 30 breaths per minute
- acute change in oxygen saturation to less than 90%, despite oxygen delivery greater than 5 liters per minute
- pulse rate less than 40 or greater than 140 beats per minute
- systolic blood pressure less than 90 mmHg, greater than 200 mmHg, or an acute change in systolic pressure
- sudden decrease in level of consciousness or decrease in Glasgow Coma Scale Score of 2 points or more
- prolonged or repeated seizures
- acute change in urinary output to less than 50 milliliters in four hours
- any time a caregiver has a patient they are seriously worried about

A Code 66 should generally not be activated for a patient receiving palliative care, and for whom the development of physiologic changes represents the natural evolution of the dying process. The inter-professional ICUOT program in Calgary includes:

1. 01 Physician or 01 Nurse practitioners
2. 01 Registered nurse
3. 01 Registered respiratory therapist

One special characteristic of the ICUOT in Calgary is the fact that the team is led by a physician. The ICU Outreach Team Physician works as a member of the Intensive Care Unit (ICU) and collaborates with staff to assist in caring for critically ill patients with multi-system failure. The physician responds to all Outreach (Code 66) calls and assists in Code Blue response as required. It is expected that the ICU Outreach Physician speaks with the ICU Attending Physician at the end of every shift either in person or by telephone. It is also expected that the ICU Outreach Physician participates in ongoing continuing medical education. In addition, the ICU Outreach Physician assists in caring for critically ill patients both in and outside the ICU as designated by the ICU Attending Physician at each site.

3.2 Population, Exposure and Outcome variables, Data Source

The population of this study is all adults older than 18 years old, who survived their first ICU admission and were discharged to the ward between 2002 and 2010 in Calgary, Alberta (Fig.2). ICU is defined as a distinct hospital specialty care unit staffed by specialized healthcare professionals where immediate and continuous life-sustaining treatment (e.g. mechanical ventilation) is provided to hospitalized patients suffering from life-threatening conditions (e.g. septic shock).[34] A hospital ward is defined as any inpatient hospital unit that does not provide immediate and continuous life-sustaining treatment (e.g. medical ward, etc.). ICU discharge is defined as a transition of care that involves transfer of accountability and responsibility for patient care from the ICU to a hospital ward. The exposure variable is the presence of an ICU transition program, which facilitates the transfer of care and provides follow-up to patients discharged from ICU to ward, in the intervention group. The outcome measures are ICU readmission and hospital mortality. A repeat admission to ICU

following discharge during the same hospitalization was categorized into early (< 48 hours after discharge) and late (≥ 48 hours) readmissions.[34]

All quantitative measures (including potential confounders) were obtained from clinical databases derived from the *e*Critical - *TRACER Reports,* which routinely captures demographic, diagnostic, clinical, physiologic and outcome data for all ICU admissions to the participating Calgary ICUs. Hence, using the database *TRACER Reports*, data were collected from Rockyview General Hospital ICU, Peter Lougheed Centre ICU, Foothills Medical Centre (FMC) ICU and FMC Cardiovascular ICU Calgary.

To design interrupted time series studies, it is necessary to know how many time points and how many observations at each time point are needed to obtain stable estimates of intervention effects. The outcomes (ICU readmission and hospital mortality) were measured at every 3 months, from 2002 to 2010. Using an ITS analysis, it allows us to detect trends of intervention effects (if they exist) and to detect whether the effects of the ICU transition program implementation occurred immediately, or whether there was a delay between its execution and the resultant effects.[38,39] In addition, it is possible to see if the effects continued to trend over time, stabilized, or even went away after a certain time.

3.3 Analysis

Statistical analyses were conducted using Stata 14 (Stata Corp, College Station, TX – USA). Histograms and Box-plots were used for inspecting the distribution of continuous variables. Normally distributed variables were reported as means ± standard deviations (SD) and non-normal variables as medians with inter-quartile ranges (IQR). Differences in means were assessed with Student's t-test, and differences in proportions among

quantitative and categorical data were assessed using z-test and Chi^2 test, respectively. The data collected before and following the intervention demonstrated comparable severity of illness, chronic comorbidities, performance indicators, and the population of the study also had comparable exposure to quality improvement co-interventions before and after the implementation of the intervention.

To date, no satisfactory method exists to calculate the power and necessary sample size for interrupted time series studies. Additionally, segmented logistic regression was used to adjust the estimates of the odds ratio (OR) of each outcome measure before and after the intervention. The estimates of the proportions were also obtained from the estimates of the ORs. The following variables have been defined “a priori” to be part of the multivariable model: age, gender, severity of illness (APACHE II score), chronic comorbidities scale score (Charlson Index), admission classification type, ICU discharge time and day, ICU bed capacity/patient flow. Data were reported as odds ratios (OR) and proportions with 95% confidence intervals (CI). Also, data were evaluated for multicollinearity and autocorrelation, which will be discussed further. We used logistic regression including all the covariates above and their interaction terms containing two, three and four variables, in addition to time variables needed in segmented regression. The way we built the segmented regression, which is the core of our ITS study will be described further.

Model calibration and fit were assessed by using the Specification error test, also known as Linktest in STATA. The Stata command Linktest is used to detect a specification error and it is done after the logit or logistic command. If the model is properly specified, there are no additional predictors that are statistically significant except by chance. After the regression command (logit or logistic), linktest uses the linear predicted value (_hat) and

linear predicted value squared (_hatsq) as the predictors to rebuild the model. The variable _hat should be a statistically significant predictor since it is the predicted value from the model. It will happen unless the model is completely misspecified. Otherwise, if the model is properly specified, variable _hatsq does not have predictive power except by chance. So, _hatsq should be non-significant, for a well specified model. Therefore, if _hatsq is significant, then the linktest is significant. This usually means that either we have omitted relevant variable(s) or our link function is not correctly specified.[41,42,43]

We have also used the Hosmer and Lemeshow's goodness-of-fit test. The Hosmer-Lemeshow goodness-of-fit statistic is computed as the Pearson chi-square from the contingency table of observed frequencies and expected frequencies. The idea behind the Hosmer and Lemeshow's goodness-of-fit test is that the predicted frequency and observed frequency should match closely and that the more closely they match, the better the fit. A non-significant test reveals our model properly fits the data.[44] All the statistical significance tests were two-tailed test with a *p*-value <0.05 required for statistical significance.

3.3.1 Segmented Logistic Regression in Interrupted Time-Series

The segmented regression analysis of interrupted time series is a statistical tool that permits us to evaluate, in statistical terms, how much an intervention changed an outcome of interest, immediately and over time. This analysis can show us if the change in an outcome happened immediately or with delay, transiently or for long periods and whether factors other than the intervention could explain or be the reason for the observed change.[33,38,40]

Segmented regression analysis is the best method for statistically modeling the

interrupted time series data and requires data on continuous or counted outcome measures, summarized at regular, equally spaced intervals.[33] Segments in a time series are described as sequences of measures, which have been split into two or more portions at change points. Change points are specific points in time where the observations or measurements of the time series would show a change from an established pattern because of a real-world event, a policy change, or an experimental intervention. The beginning and end of each segment are determined by the beginning and end of the intervention, and there may be some pre-specified lag time to allow the intervention to start working effectively.

There are two parameters that give the meaning of each segment of a time series: level and trend. The level is the value of the series at the beginning of a given time interval or segment (i.e. the y-intercept for the first segment and the value immediately following each change point at successive additional segments). The trend is the rate of change of a measure or simply - the slope of a segment. In segmented regression analysis, each segment of the series shows both a level and a trend. The analysis consists of the evaluation of the changes in level and the trend that follow an intervention. A change in level, (e.g. a jump or drop in the outcome after the intervention) is equivalent to a sudden intervention effect. A change in trend is seen as an increase or decrease in the slope of the segment after the intervention as compared with the previous segment before the intervention. A change in trend represents a gradual change in the value of the outcome in the segment. Interpretation of the results is very straightforward in ITS.

A great strength of ITS studies is the intuitive graphical presentation of the results, and a visual inspection of the series over time is the first step when analyzing time series data, since it approximately gives us a picture of the answers we are looking for.[33] However,

although that graphical presentation frequently can show changes in level and or in trend of the outcome, we cannot easily see whether changes in level and trend could be the result of chance alone or the factors other than intervention.

Chance and control for confounders are strictly necessary when segmented regression analysis is conduct. In segmented regression analysis, we build statistical models to estimate level and trend in the pre-intervention segment and changes in level and trend after the intervention (fig 4). In order to conduct a segmented regression analysis, it is necessary to have at least 12 data points before and after the intervention.[33,38] With a minimum total of 24 equally spaced points of measurement, we are able to assess for seasonal variations.[38] A minimum of 100 observations per time point is also required to achieve an acceptable level of variability of the estimate. It is important to note that our study meets all those requirements.

Segmented regression models commonly fit a least squares regression line to each segment of the independent variable, time, and thus assume a linear relationship between time and the outcome within each segment. However, dealing with a binary outcome, like mortality, and then using a logistic distribution, we need to make an algebraic conversion to arrive at our usual linear regression equation. It is perfectly possible, since a logistic regression is a type of generalized linear model, with the model being linear to the parameters (i.e. $Y = \beta_0 + \beta_1 X + e$). Therefore, logistic regression uses a linear combination of the dependent variable (outcome) with the parameters (β_0 and β_1) to predict the outcomes.

Recall the logistic model: the outcome or dependent variable is in fact, the probability or the odds or the ratio of odds for that event to occur given the presence of the intervention

or not, along with the rate of change of this proportions over time:

$Y = p\ (x)$ which is read as the probability of the outcome for a given value of x, and *logit* $(p\ (x)) = log\ \{p\ (x) / 1- p(x)\} = \beta_0 + \beta_1 + e$.

It is important to note that in classic simple linear regression, ordinary least squares are used to estimate the parameters (also called coefficients). In logistic regression the coefficients will be estimated using maximum likelihood estimation. The maximum likelihood estimate of a parameter is that value that maximizes the probability of the observed data. It estimates β_0 and β_1 by those values of β_0_hat and β_1_hat that maximize the probability of the observed data under the logistic regression model**.** Consequently, we have the following linear equation as the basic model of our segmented logistic regression:

$$Y_t = \beta_0 + \beta_1 * time_t + \beta_2 * intervention_t + \beta_3 * time\ after\ intervention + e_t \quad \text{(Fig.4)}$$

$\boldsymbol{Y_t}$ = is the estimate of the log of the odds of the outcome (i.e. ICU readmission)

- this odds of ICU readmission is conditional on the ICUOT program – if present or not

$\boldsymbol{\beta_0}$ = an estimate of the log odds of ICU readmission at time zero and no ICUOT program.

$\boldsymbol{\beta_1}$ **=** estimates the difference between the log of the odds of ICU readmission for each one-unit increase in the variable time (i.e. one quarter) in the period before the implementation of the program. It is the expected change in log odds of ICU readmission for a one-unit increase in the time variable. In other words, β_1 estimates the log of the odds ratio of ICU admission between each quarter before the implementation of the ICUOT.

time = continuous variable (in quarters).

$\boldsymbol{\beta_2}$ **=** similarly to β_1, estimates the odds ratio of ICU admission, but in this case, just in the quarter immediately after the intervention.

$\boldsymbol{intervention_t}$ **= indicator for time t occurring before** (intervention = 0) **or after**

(intervention = 1) the Code 66, which starts at quarter 20 in the series;

$\boldsymbol{\beta_3}$ = estimates the expected change in log odds of ICU readmission for a one-unit increase in the time (i.e. one quarter) in the period after the implementation of the program. In other words, β_3 estimates the log of the odds ratio of ICU admission between each quarter after the implementation of the ICUOT.

time after intervention = continuous variable, the number of quarters after the intervention at time t , coded "0" before the code 66 and "time –19" after the code 66 implementation.

$\boldsymbol{\beta_1 + \beta_3}$ is the post-intervention slope.

Therefore, pre-intervention becomes *Outcome = constant + β1time*. Post-intervention becomes *Outcome= constant* + β_1*time* + β_2*intervention* + β_3*time after intervention* = *(constant* + β_2*)* + *(*β_1 + β_3*) time*. Here, time and time after intervention are the same variable, considering post-intervention period. Therefore, the difference between the pre and post-intervention constants (intercept) is β_2 and the difference between slopes is β_3.The error term $\boldsymbol{e_t}$ at time t represents the random variability not explained by the model.[33] The covariates and their interaction terms for multivariate analysis are then added to this model.

After removing non-significant interaction terms and assessing for confounding we obtained the following final models:

For ICU admission (categorical outcome)

logit icu_readmit_hosp stdy post_66 ta4_66 Charlson_index CAP CI2, where *logit* stands for the logistic regression command in STATA, *icu_readmit_hosp,* stands for the outcome (ICU readmission), *stdy, post_66 and ta_66*, stand for time variables expressing time respectively for the pre–intervention period, moment of the intervention, and for the after-intervention periods (continuous variables). *Charlson_index* refers to the

index Charlson of comorbidities (continuous variable), *CAP* – the interaction term for the variables Charlson_index and Apache II score *(APACHE_greaterEqual_25, a categorical variable)* and finally, CI2 – the quadratic term of the variable Charlson_index.

For In-hospital mortality (categorical outcome)

logit inhosp_death_dad stdy post_66 ta4_66 Age Gender Charlson_index APACHE_greaterEqual_25 CAP ACAP CI2, where *logit* stands for the logistic regression command in STATA, *inhosp_death_dad* stands for the outcome (In-hospital mortality), *stdy, post_66 and ta_66*, stand for time variables as described above, *Age* in years, *Gender. Charlson_index* refers to the index Charlson of comorbidities and *APACHE_greaterEqual_25* refers to the Apache II score greater or equal 25. *CAP* – the interaction term for the variables Charlson_index and Apache II score and *ACAP* stands for the interaction term between Age, *Charlson_index and APACHE_greaterEqual_25*. *CI2* – the quadratic term of the variable Charlson_index.

3.3.2 Autocorrelation

Studies using time-series data can have some limitations. The traditional statistical analysis assumes independence. Time-series data are not independent. Each measure is from the same source and data will show a unique pattern based on process over time. Past events affect the current events and current events will affect the future outcomes. This dependence of data is called autocorrelation and threatens the internal validity of a time series study. So, the autocorrelation is a measure of the extent to which data collected close together in time are correlated with each other. The standard errors of the regression coefficients will be smaller than they should be and hence the statistical tests of these

parameters will be misleading; they will suggest that the estimates of the parameters are more precise than they really are. [33,38]

A stochastic process generates Time-Series. Frequently, the mean or variance of many time series increases over time. This is a property of time series data called non-stationarity and this often results in a violation of the assumption of no serial correlation when using a generalized linear model.[33,38,40] The stationary process implies that the mean and variance do not change over time and it was checked using Phillips-Perron, and Augmented Dickey-Fuller tests in this study. Therefore, these tests show us if the series have a trend, also called a unit root. If so, in order to build a model, we have to de-trend the series. If the tests are significant, they reject the null hypothesis of a unit root and conclude that the series is stationary, and our model is proper.[33,40]

White noise refers to the fact that a variable does not have autocorrelation. In Stata use the wntestq (white noise Q test or the Portmanteau test for white noise) to check for autocorrelation. The null is that there is no serial correlation, but just white noise or random error accounting for the variability in the series.[45]

Also, changes in the outcome variable due to normal developmental processes can occur, a phenomenon known as “maturation’. This means that contemporaneous quality improvement initiatives or programs – as competing interventions - can occur at exactly the same time, acting as confounders

CHAPTER FOUR: RESULTS

4.0 Study Population

From January 1, 2002, to December 31, 2010, 27571 patients age ≥ 18, excluding inter-ICU transfers, were admitted in 3 medical-surgical ICUs and 1 Post Cardiac Surgery ICU for the first time in their each hospital admission in 3 hospitals in Calgary, Alberta. From that group, 19137 ICU survivor patients were transferred to the ward, constituting our study population (Fig. 2). The mean age was 59 years, 34% were female, 30% had a medical reason for ICU admission, the median Charlson Index was 1 point (IQR 0-2), and the mean APACHE II score was 16 with a SD of 6.7. During their stay in the ICU, 2.2% of these patients underwent continuous renal replacement therapy (CRRT) and the median duration of mechanical ventilation in our study was 2 days (IQR 2-4). Also, the median length of stay in ICU was 2 days (IQR 1-6). Patient characteristics were similar in both the pre-intervention (n=10,562) and the post-intervention (n=8,575) periods (Table 1). Below, we described the results of regression models (crude and multivariable) applied for the specific pre and post-intervention periods – that is, not using segmented regression time-variables, but just using the explanatory and response variables showed in table 1 and 2.

4.1 Crude Pre and Post-Intervention Analysis of Outcomes

Regarding ICU readmission, we saw statistically significant differences comparing the crude proportions of patients readmitted to ICU before and after the intervention. Before the implementation of the ICUOT, 5.5% of the patients in our study population were readmitted to ICU and 6.6% was the same proportion after the implementation of the ICUOT with a *p-value* = 0.0026. In addition, 1.5% of patients were readmitted to ICU within 48 hours after

being transferred to the ward during the pre-intervention period, compared to 1.8% of patients, during the post-intervention period, $p = 0.08$ (table 2).

The crude in-hospital mortality was 6.5% in the pre-ICUOT period and 5.7% in the post-ICUOT period with a *p-value* < 0.001 (table 2).

4.2 Adjusted Pre and Post -Intervention Analysis of Outcomes

ICU readmission in the pre-intervention period of study.

When adjusting for covariates of clinical importance like comorbidities (Charlson Index), length of stay in ICU, severity of the disease (APACHE II), medical category for ICU admission, continuous renal replacement, and age, the multivariable analysis with logistic regression showed the following coefficient and results in the pre-intervention period: the proportion of patients readmitted to ICU was 5.5%. Holding other covariates at a fixed value, for each one-unit increase in age we expect to see about 34% increase in the odds of being readmitted to ICU (OR 1.34 - 95%CI 1.22 to 1.61). In the same way, for each one-unit increase in Charlson Index, is expected 17% increase in the odds of coming back to ICU (OR 1.17 – 95%CI 1.13 to 1.21). Similarly, the odds of being readmitted to ICU is 97.5% higher for patients who underwent CRRT comparing with those with no CRRT (OR 1.97 – 95%CI 1.31 to 2.97). For each day that patients stay in ICU (ICU LOS) it was expected 4% increase in the odds of ICU readmission (OR 1.04 – 95%CI 1.03 to 1.05). Finally, having a APACHE II ≥25 and a medical admission category respectively decrease 22%(OR 0.78 – 95%CI 0.64 to 0.94) and increase 38% (OR 1.38 – 95%CI 1.15 to 1.65) the odds of being readmitted.

ICU readmission in the post-intervention period of study.

During the post-intervention period the adjusted multivariable model shows:

- the proportion of patients readmitted to ICU was 6.6%.
- age – its influence on increase in the odds of being readmitted to ICU was not statistically significant.
- Charlson Index - for each one-unit increase in Charlson Index, is expected 18% (OR 1.18 – 95%CI 1.13 to 1.22) increase in the odds of coming back to ICU.
- CRRT – the odds of being readmitted to ICU is 55.4% (OR 1.55 – 95%CI 1.03 to 2.32) higher for patients who underwent CRRT comparing with those with no CRRT.
- ICU LOS - For each day that patients stay in ICU it was expected 2.7% (OR 1.027 – 95%CI 1.02 to 1.03) increase in the odds of ICU readmission.
- APACHE II ≥ 25 – 44.3% (OR 1.45 – 95%CI 1.19 to 1.74) increase in the odds of being readmitted.
- Medical category of admission - its influence on increase in the odds of being readmitted to ICU was not statistically significant.

In-hospital mortality in the pre-intervention period of study.

Proportion of in-hospital deaths was 6.5%. Holding other covariates at a fixed value, the odds of dying in the hospital was 20% lower for male comparing to female patients (OR 0.80 – 95%CI 0.67 to 0.94) . For each one-unit increase in age, we expected to see about 178% increase in the odds of dying in hospital (OR 2.78 – 95%CI 2.33 to 3.33). In the same way, for each one-unit increase in Charlson Index, was expected 26% increase in the odds of in-hospital death (OR 1.26 – 95%CI 1.22 to 1.30). Similarly, the odds of dying in hospital was 78% higher for patients who underwent CRRT comparing with those with no CRRT

(OR 1.78 – 95%CI 1.20 to 2.64). For each day that patients stayed in ICU (ICU LOS) it was expected 3.8% increase in the odds of in-hospital death (OR 1.03 - 95%IC 1.03 to 1.04). Finally, if patients had a medical admission category, it increased 216% the odds of dying in the hospital in the pre-intervention period when comparing it with patients with a non-medical category of admission, in the same period (OR 3.16 - 95%CI 2.67 to 3.74). Having an APACHE II score ≥25 did not increase the odds of dying in hospital in a statistical point of view.

In-hospital mortality in the post-intervention period of study.

The multivariable analysis showed the following in the post-intervention period:

- Proportion of in-hospital deaths was 5.7%.
- Age - for each one-unit increase in age we expect to see about 173% increase in the odds of dying in the hospital (OR 2.73 - 95%CI 2.23 to 3.35).
- Charlson Index - for each one-unit increase in Charlson Index, it is expected 28% increase in the odds of dying in the hospital (OR 1.28 – 95%CI 1.23 to 1.33).
- Similarly, the odds of dying in hospital is 125% higher for patients who underwent CRRT comparing with those with no CRRT (OR 2.25 – 95%CI 1.53 to 3.30). For each day that patients stay in ICU (ICU LOS) it was expect 3.8% increase in the odds of in-hospital death (OR 1.03 – 95%CI 1.02 to 1.04).
- Finally, having a medical admission category increases 168% the odds of dying in the hospital (OR 2.68 – 95%CI 2.20 to 3.26). Also, having an APACHE II score ≥25 does not increase the odds of dying in hospital in a statistical point of view.

Following, in addition to the ORs, we also used the concept of marginal effects to

show the change in probability when the predictor or independent variable increases by one unit. So, the marginal effect tells you by how many units the probability of the outcome changes if the explanatory variable changes by one unit and is calculated after running a logistic regression of the independent variables on the dependent variable.

4.3 Crude Interrupted Time-Series of ICU Readmission and In-Hospital Mortality

ICU Readmission (Fig.5). When modeling Crude Time-Series Segmented Regression, 6.0% (95% CI 4.9% to 7.0%) of the patients of our study population were readmitted to ICU at the start of the study period.

During the pre-intervention period, we could see a decrease in the odds of ICU readmission of 0.7% per quarter, which represented a non-significant decrease of 0.04%(-0.04% 95% CI -0.13% to +0.05%) in the proportion of patients readmitted to ICU per quarter of study. After implementation of the ICUOT program, there was an immediate significant increase of 50% in the odds of being readmitted to ICU, which means a 2.3% significant increase in the proportion of patients readmitted to ICU (+2.3%, 95% CI 0.9% to +3.7%). Subsequently, we saw a decrease in the odds of ICU readmission of 0.7% per quarter, which in fact, represented a non-significant decrease in the proportion of patients readmitted to ICU in the post-intervention study period (-0.04% per quarter; 95% CI, -0.2% to +0.1%). At the end of the study, the proportion of patients readmitted in the ICU was 6.0% (95% CI, 5.2% to 7.0%) (Table 3).

In-Hospital Mortality (Fig.6). Our Crude Time-Series Segmented Regression shows that 7% (95% confidence interval [CI] 6.0% to 9.0%) of the patients of our study population died in the hospital at the start of the study period. In the pre-intervention period, there was

a decrease in the odds of in-hospital mortality of 0.8% per quarter, which represented a non-significant decrease of 0.04%(-0.04% 95% CI -0.12% to +0.04%) in the proportion of patients who died in the hospital per quarter of study. After implementation of the ICUOT program, there was an immediate significant increase of 30% in the odds of in-hospital mortality, which means a 1.5% significant increase in the proportion of patients dying in the hospital (+1.5%, 95% CI 0.2% to +3.0%). Subsequently, there was a decrease in the odds of in-hospital mortality of 3.4% per quarter, which in fact, represented a significant decrease in the proportion of patients who died in the hospital in this post-intervention study period (-0.2% per quarter; 95% CI, -0.3% to -0.05%). At the end of the study, the proportion of in-hospital deaths was 4.0% (95% CI, 3.0% to 5.0%) (Table 3).

4.4 Adjusted Interrupted Time-Series of ICU Readmission and In-Hospital Mortality

ICU Readmission (Fig.7). The multivariable analysis was based on an adjusted interrupted time-series segmented regression using covariates clinically relevant for the outcomes. In the final model the included covariates were the APACHE II ≥ 25 and the Charlson index. One interaction term with APACHE II and Charlson index and a quadratic term with the Charlson index were required in order to obtain a good fit for the model. When admission categories were included in the complete model, the effects were hold only for cardiac surgery admission. However the inclusion of that variable in the final model made it unfit for the data. Hosmer - Lemeshow's and the linktest just showed goodness-of-fit when the admission category variables were removed from what we considered the best and final model.

At the start of the study 6.0% (95% confidence interval [CI] 4.9% to 7.0%) of the

patients of our study population were readmitted to ICU. During the pre-intervention period, we could see a decrease in the log odds of ICU readmission of 0.3% per quarter, which represented a non-significant decrease of 0.02%(-0.02% 95% CI -0.10% to +0.07%) in the proportion of patients readmitted to ICU per quarter of study. After implementation of the ICUOT program, there was an immediate significant increase of 40% in the odds of being readmitted to ICU, which means a 2.0% significant increase in the proportion of patients readmitted to ICU (+2.0%, 95% CI +0.5% to +3.2%). Subsequently, we saw a decrease in the odds of ICU readmission of 0.7% per quarter, which in fact, represented a non-significant decrease in that proportion (-0.04% per quarter; 95% CI, -0.2% to +0.1%). At the end of the study the proportion of patients readmitted in the ICU was 6.0% (95% CI, 4.8% to 7.0%) (Table 4).

In-Hospital Mortality (Fig.8). The final model included the covariates age, gender, Charlson index, APACHE_greaterEqual_25, one interaction term with APACHE II and Charlson index, one interaction term with age, APACHE II ≥ 25 and Charlson index and a quadratic term with Charlson index. These interaction terms produced significant effect modification on the outcome, and they were also required for a good fit of the model with the data. Regression showed that 7.0% (95% confidence interval [CI] 6.0% to 9.0%) of the patients of our study population died in the hospital at the start of the study period. In the pre-intervention period, there was a decrease in the odds of in-hospital mortality of 0.2% per quarter, which represented a non-significant decrease of 0.01% (-0.01% 95% CI -0.09% to +0.07%) in the proportion of patients who died in the hospital per quarter of study. After implementation of the ICUOT program, there was an immediate non-significant increase of 22% in the odds of in-hospital mortality, which

means a 1.0% non-significant increase in that proportion (+1.0%, 95% CI - 0.3% to +2.4%). Subsequently, there was a decrease in the odds of in-hospital mortality of 3.5% per quarter, actually representing a significant small decrease in the proportion of patients who died in the hospital in the post-intervention study period (-0.2% per quarter; 95% CI, -0.3% to -0.05%). At the end of the study the proportion of in-hospital deaths was 4.0% (95% CI, 3.0% to 5.0%) (Table 4).

4.5 Sensitivity Analyses

Multivariable analyses were performed using various covariates of clinical relevance. Sex, age, Charlson Index of chronic comorbidities, APACHE II score, continuous renal replacement therapy, mechanical ventilation requirements, length of stay in ICU, ICU admission categories (Medical, Surgical, Cardiac Surgery, Trauma, Neurological) were used alone or composing two, three or four interaction terms in order to assess their effects on the outcomes. Also, quadratic or cubed terms were tested intending to find effect modification or attempting to find the best model that would fit the data. The best models were reported in the Results section of this document.

CHAPTER FIVE: DISCUSSION

5.0 Key Findings

Our study investigated the effects of the implementation of a critical care transition program, which was created to facilitate the transition of patient care from the ICU to the

hospital wards. We found that the ICUOT program had no significant impact on patient readmission to ICU.

Considering hospital mortality, we could appreciate a very small, but significant reduction in the proportion of in-hospital deaths in survivors of their first ICU admission. Our results remained the same, when performing sensitivity analyses with many different multivariable models using segmented logistic regression.

In the literature review section of this document, we described the findings of our recent systematic review and meta-analysis of Critical Care Transition Programs and the Risk of Readmission or Death After ICU Discharge. The pooled risk ratio estimates demonstrated a reduced risk of ICU readmission (0.87, 95% CI 0.76 – 0.99, p = 0.03) and a trend towards a reduction in hospital mortality (0.84, 95% CI 0.66 – 1.05, p = 0.1) associated with a critical care transition program.[32]

In our study, we could not find any significant impact of implementing a critical care transition program on ICU readmission, but a small significant reduction in hospital mortality among patients transferred from ICU to ward. One possible explanation is that differently from the majority of previous studies, which were conducted in single hospitals and employed before-and-after study designs that are at increased risk of bias, we evaluated our critical care transition program in three tertiary hospitals using a robust scientific approach comprised of an interrupted time series design with segmented logistic regression, involving a period of 9 years – 5 years before and 4 years after the implementation of the ICUOT program. Additionally, we assessed a multiprofessional critical care transition program with a systematized approach. That approach included the handing over of patient information and responsibility of care to the ward staff. These patients were then followed by

the team members for a range of 2 to 5 days - period when the outreach team worked collaborative with the ward staff in order to optimize care.

Some could argue that ICUOT might have been just beneficial for elderly patients, with high admission APACHE II scores or multiple comorbidities. Perhaps also beneficial for patients with longer ICU length of stay and prolonged mechanical ventilation - that is, very sick and complex patients. However, our sensitivity analyses using multivariable models were adjusted for those variables and produced similar results.

These results might bring out questions about what is the real role of ICUOT program on safety and quality of care of patients discharged from ICU. Would those services be just a tool to make ICU discharge faster, simply because they are perceived to improve the quality of care provided to seriously ill patients with complex medical problems when they arrive in the ward? Studies employing qualitative methods have suggested that critical care transition programs are thought to increase the comfort of less experienced nurses caring for them in the ward.[46,47] In other words, because the program is available, would intensivists be comfortable to faster transfer patients to the ward and ward staff comfortable to receive them? All in all, possibly it could improve ICU bed flow, making new beds available for very acute cases requiring ICU, while the ICUOT could keep continued care of those patients transferred from ICU to ward, until a readmission back to ICU would be required.

How come the ICUOT would not be able to help to avoid ICU readmissions, but somehow it would improve quality of care being associated with a decrease in the risk of patient death? Perhaps, appreciation of clinical deterioration of those patients requiring ICU would be faster and better noticed by the ICUOT and more effective resuscitative

maneuvers would be rapidly initiated by this team on the ward. These “golden hours” would not be enough to decrease their ICU readmission rates but could be good enough to improve their survival rates at the hospital discharge, maybe explaining at least in part our findings regarding the small, yet significant reduction in hospital mortality for that population of ICU survivors.

5.1 Relevance to existing scientific literature

This work, based on a robust methodology that uses an interrupted time-series with segmented logistic regression highlights one of the more important knowledge gaps in acute care medicine – the ability of the intensive care systems, hereby represented by one of its arms or extensions - the ICU outreach team, in trying to maintain stability and the achieved recovery on ICU survivors after a life-threatening health condition treated in the ICU.

Even using a systematic preventive approach on their follow-up after ICU discharge, ICU readmission rates remains the same based on the estimated change in intercept and slope from pre to post-intervention using segmented regression. There is insufficient evidence of a statistically significant effect of the ICUOT on ICU readmissions. However, it is possible that closer monitoring and faster actions on those ICU survivors who required or did not required ICU readmission lead to a small but significant improvement in mortality. Therefore, ICUOT may contribute to a better care of high-risk patients who have been transferred from ICU to ward, and I believe that this idea would add motivation for a continued support to our ICUOT program at least at this point in time.

5.2 Limitations

5.2.1 Internal Validity

A common challenge when using interrupted time series design to evaluate quality improvement interventions is that even small improvements in diagnostic methods and treatments, staff education and training, logistics and organizational factors introduced at different times over the study period will introduce biases to the effects of the intervention on the outcomes being measured.[33-40] Such possible improvements in quality of care may have taken place over the nine - year period of our study. When a regression analysis is used with time modeled as a single continuous variable, an estimate is obtained for the slope over time, but it is impossible to distinguish the effect of the intervention from the underlying secular trend and to make causal claims about the effects of the intervention, especially if no control group was simultaneous evaluated, which is the case in our study.[40]

ITS designs are also subject to threats to internal validity that are related to history (such as seasonality) that influence the dependent variable and maturation bias where there is a pattern of improvement in the experimental group prior to the intervention.[33-40] However, we performed correlograms, also called autocorrelation plots on our series and no seasonality pattern was seen. Also, instrumentation bias, a classic type of bias that occurs in time series design, where changes in the way records are kept or the way the outcomes are measured may change over time, did not occur in our study. The intervention was unlikely to affect data collection as well. Selection bias, which could cause a differential drop out in the post-intervention group probably did not happen, because our dataset covered 80 - 100% of the total number of survivors of their first admission to ICU in each hospital readmission. Also, patient baseline characteristics were very similar, comparing the pre and

post-intervention periods.

Like in many interrupted time series studies, we had different participating sites contributing data. In our analyses of these data, we used a single time series of data aggregated across all sites (etracer). An analysis of aggregated data is likely to have less power than a multilevel logistic regression analysis of the time series from the individual sites. As an alternative we could have conducted separate segmented regression analyses at each site, and then estimate the overall effect by pooling the estimates of intervention effect across sites using inverse variance weights in a meta-analytical model.[38,40] We also could have fitted a single model to the data from all sites and account for heterogeneity across sites by incorporating random effects for the sites.[38,40] It could be relevant, since we also assessed patients from a post-cardiac surgery ICU who may receive different types of care, protocols, treatment and diagnostic procedures.

We did not assess the presence of specific comorbidities, like Diabetes Mellitus, Chronic Obstructive Pulmonary Disease, Heart Failure, Cirrhosis or Malignancies, but instead, we used the Charlson Index score to quantify the presence of comorbidities. It may have been an important limitation of our study since different comorbidities may correlate with prognosis, even for short-term outcomes (e.g. ICU readmission and in-hospital mortality).

5.2.2 External Validity

Since it is difficult to measure how differently secular trends affect different institutions, or how simultaneously quality-improvement interventions and other activities affecting outcomes are implemented in different institutions over time, threats to external validity are

a major issue in studies like ours. Otherwise, different institutions may have different ICUOT programs with its own peculiar characteristics. For example, different ICUOT models, afferent limbs and warning scores systems, closed versus open intensive led model of ICUs and private versus publicly funded healthcare system may occur in different institutions. Also, allocation of resources and processes for ICU discharge frequent vary across healthcare jurisdictions. Hence, the results may not apply to other institutions.[36]

5.2.3 Time-Series versus Advanced Longitudinal Analysis

When dealing with Time-Series data, the most important problem we need to assess is the autocorrelation of the data that arises with clusters of measurements over time. That is, the data exhibits some level of dependency over time and it needs to be taken into account. In a stochastic process, randomness requires independency of successive events. It's also important to remember that random or independent variables must be uncorrelated.[33-40] One can find uncorrelated dependent data. Independence is a stronger condition. In our study, we find no evidence for correlation in our response variables taken quarterly, despite we were likely dealing with dependent data. However, since linear autocorrelation of the data was not found, we were safe enough to consider our model a stochastic process and go ahead.

The classical and simplest definition of longitudinal Studies is that they are studies in which individuals are measured repeatedly through time. However, the way most authors best deal with longitudinal data in longitudinal studies has been substantially different from the way they have been analyzing time-series data.[48,49] With longitudinal data, repeated measures are obtained from the same person who is followed over time and those

measures are usually positively correlated. Observations from different individuals are independent, while repeated measurements of the same individual are not assumed to be independent.

Those types of data shows:

- Between-Subject Variation: Different subjects respond differently; some are “high" responders, some are “low" responders, and some are “medium" responders.
- Within-Subject Variation: Random variation appears from the process of measurement; e.g. due to measurement error and/or sampling variability.

That is, the response for the i^{th} subject at the j^{th} occasion is assumed to differ from the population mean, $X_{ij}B$, by a subject effect, b_i, and a within-subject measurement error, e_{ij}. Then:

- $Y_i = X_i \beta + Z_i b_i + e_i$, where β is a (k x 1) vector of fixed effects;
- b_i is a (q x1) vector of random effects and bi ~N (0;G);
- X_i is a (p_i x k) matrix of covariates;
- Z_i is a (p_i x q) matrix of covariates (usually the columns of Z_i are a subset of the columns of X_i and q < k); e_i is a (p_i x 1) vector of errors and $e_i \sim N (0;R_i)$.

Again, $Y_i = X_i \beta + Z_i b_i + e_i$: the vectors of regression parameters β are the fixed effects, which are assumed to be the same for all individuals. In contrast to β, the b_i are subject-specific regression coefficients and describe the mean response profile of a specific individual (when combined with the fixed effects). The pillar of this approach is that we assume that there is natural heterogeneity across individuals in a subset of the regression parameters. That is, a subset of the regression parameters (e.g. intercepts) is assumed to vary across individuals according to some distribution. Then, conditional on the random

effects model, it is assumed that the responses for a single individual are independent observations from a distribution belonging to the exponential family (Normal, Bernouilli, Gamma, Poisson etc). These mixed (fixed plus random effects) models are most useful when the scientific objective is to make inferences about individuals rather than the population averages. That is, the main focus is on the individual and the influence of covariates on the individual.[48,49]

When dealing with analyses of longitudinal data, where repeated measures of the outcome are obtained on the same subject, we usually face 5 types of challenge that threat the internal validity of the study: 1) heterogeneity (random subject-specific effects), 2) correlated errors of measurement (short-term residual correlation which tends to decrease exponentially with the temporal distance between the measurement occasions), 3) missing data, 4) irregularly spaced measurement occasions, and 5) clusters (in our study, repeated measures of outcome over time – clusters – generates correlation).

For the 5 problems above - the most widely used statistical modeling include mixed-effects regression models and GEE or generalized estimating equations. Fundamentally, mixed-effects regression (MRM) models are useful to add individual-specific effects into the model that will account for the data dependency and describe differential time trends for different individuals. They provide estimates of person-specific effects (e.g., person-specific trend lines) that are quite useful in understanding inter-individual variability in the longitudinal response process and in predicting future responses for a given subject or set of subjects from a particular subgroup. This is precisely what they do. Mixed-effects regression models allow both the intercept and time-trend to vary by individuals. Because they make full use of all available data from each subject, they are called full-likelihood

methods. Missing data can be ignorable if the missing responses can be explained either by covariates in the model or by the available responses from a given subject. Therefore, subjects with incomplete data across time are included in the analysis. These methods allow for understanding how specific individuals change across time and are robust to missing data and irregularly spaced measurement occasions. Regression estimates from the mixed model are “subject specific” to reinforce the notion that they are conditional estimates, conditional on the random (subject) effect - conditional models. Thus, they represent the effect of a regressor on the outcome controlling for or holding constant the value of the random subject effect.

While in mixed-effects models, the conditional mean (conditional to random effects – as describe above,) of Y_i, given b_i, is $E(Y_{ij}b_i) = Xi\ \beta + Z_ib_i$. In marginal models, the marginal or population-averaged mean of Yi is $E(Yi) = Xi\ \beta$. The basic premise of marginal models is to make inferences about population averages. The term `marginal' is used to emphasize that the mean response modeled is conditional only on covariates and not on other responses (or random effects).

Differently from classical marginal fixed-effects models, GEE or generalized estimating equations, which are also marginal models, include an additional variance component to accommodate correlated data, and to allow for differences among individuals or clusters. In this marginal model, we model the regression of the response on covariates and the covariance structure separately. The main point, is that coefficients have population-averaged interpretations.[48,49] Excepting the intercept, the coefficients describe differences in mean response, but now across all observations (and hence across all clusters). The

random effects part of the model (which characterizes a mixed-effects regression) is not included in the equation.

They also generalize easily to a wide variety of outcome measures with different distributional forms. The price of this flexibility, however, is that partial likelihood methods (like GEE) are more restrictive in their assumptions regarding missing data. Also, parameter estimates and empirical standard errors are robust to misspecification of the correlation structure (repeated observations over time will produce a pattern of correlation of the data that we may not know).

All in all, GEE and MRM account for correlation or autocorrelation. GEE is a marginal model and MRM allow for understanding how specific individuals change across time with robustness to missing data and irregularly spaced measurement occasions.

Now, why we used a fixed-effect regression, which is a marginal model (segmented logistic regression) and not MRM or GEE for the analysis of our time-series data?

1. We used a conventional fixed-effect model (a segmented classic logistic regression) because we did not make repeated measurements on the same individual over time. We made repeated measurements of outcomes over time on our population of first admission ICU survivors, obtaining quarter clusters of outcomes along the study period. Specific random individual changes across time (intercept and trend lines, MRM) were out of context in this study.
2. We used what should be important to answer our questions – a marginal model too, that could give us population-averaged estimates, which is more useful when estimating effects of an intervention at a population level[26,27]. So, it would not be necessary to use GEE, since we opted for a simpler marginal model.

3. It's highly probable that our ICU database has cover 80 to 100% of all patients admitted to and transferred from ICU during the period of study. No concerns about missing data would arise. No use for MRM.
4. Measurements of outcome were made in spaced measurement occasions.
5. Finally, we tested our series for presence of autocorrelation. A stochastic stationary process generated our time series implying that the mean and variance did not change over time and it was checked using Phillips-Perron, and Augmented Dickey-Fuller tests in this study. In addition, the white noise Q test or the Portmanteau test for white noise showed us no evidence for autocorrelation. That is – we would not have a clear necessity to address correlation using the advanced longitudinal methods described above.

Therefore, we opted to make our analysis simple and easy, using a classic model that we were convinced that was going to be reliable for our study and familiar to readers and researchers in the health services research field.

5.3 Further Research

What we actually know is that survivors of critical illnesses who experienced intensive care treatments belong to a very complex population from which outcomes like ICU readmission and mortality are very difficult to predict despite our efforts, either due to overwhelming illness, co-morbidity or even genetic makeup.[36] We probably need to evaluate different combinations of multifaceted interventions in order to identify what patients are safe for being transfer to the ward, and when arriving there, what of those are

likely to require ICU readmission or die.[36] Perhaps alterations in ICUOT composition or in their protocols, better ward staff education and training, better warning scores systems, technological advances, identification of specific inflammatory prognostic markers and other still unknown tools, may allow more efficient preventive and reactive interventions towards those patients resulting in a better outcome profile. These are possible ways to continue to investigate the effects of ICUOT on ICU survivors.

5.4 Conclusions

There is insufficient evidence of a statistically significant effect of the ICUOT on ICU readmissions. However, it is possible that closer monitoring and faster actions on those ICU survivors who required or did not required ICU readmission have been lead to a small but significant improvement in mortality. Therefore, ICUOT may contribute to a better care of high-risk patients who have been transferred from ICU to ward, and I believe that this idea would add motivation for a continued support to our ICUOT program at least at this point in time.

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Figures and Tables

Fig 1. Rapid Response System Models

Model	Members	Assignments
Medical Emergency Team	Physicians (critical care or hospitalist) and nurses	Respond to emergencies
ICU Outreach	Critical care physicians and nurses	Respond to emergencies Follow up on patients discharged from ICU Proactively assess high-risk ward patients Educate ward staff
Rapid Response Team	Critical care nurse, respiratory therapist, and physician (critical care or hospitalist) backup	Respond to emergencies Follow up on patients discharged from ICU Proactively evaluate high-risk ward patients Educate and act as liaison to ward staff

Fig 2 Study Population Flow Diagram

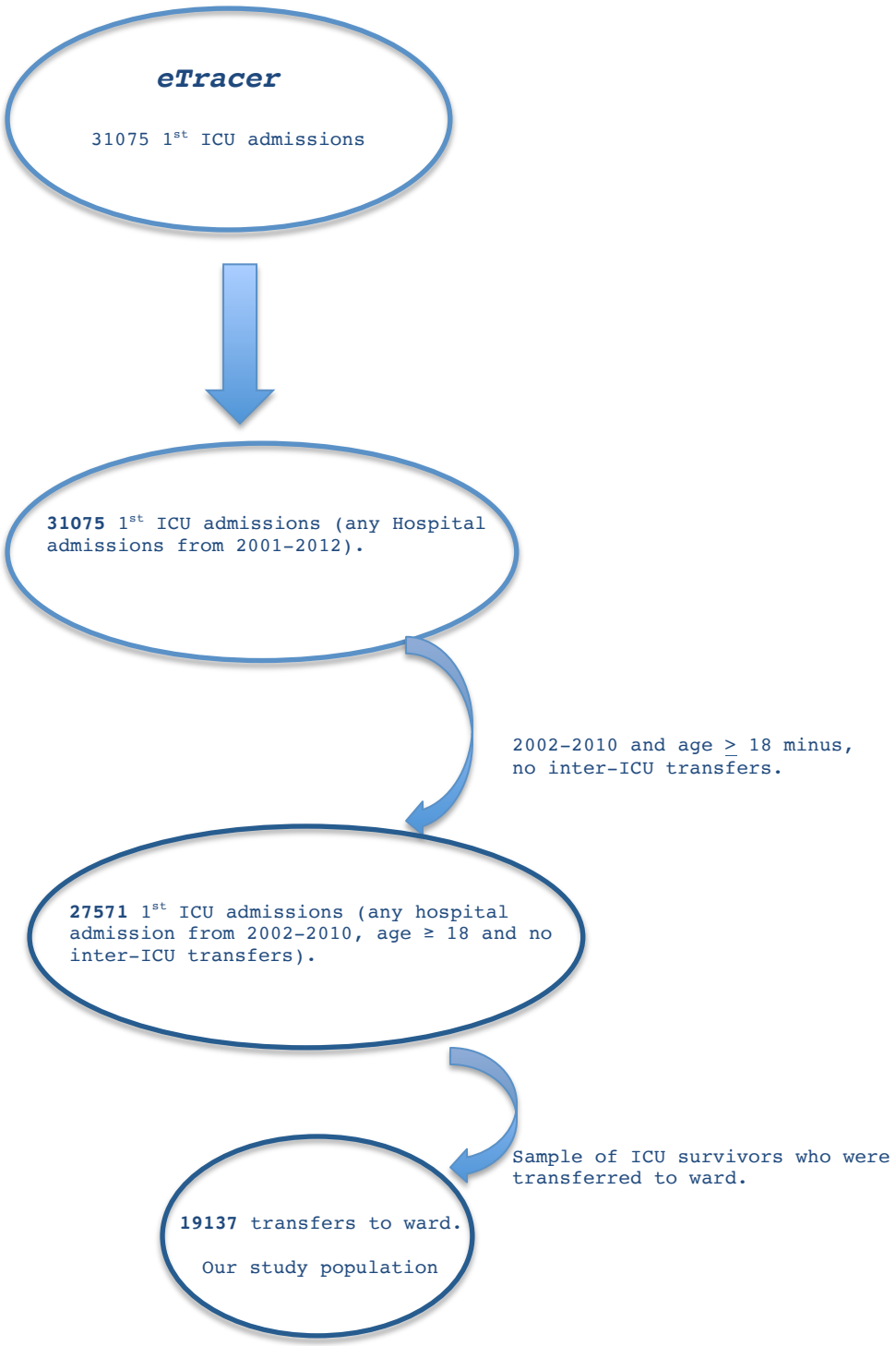
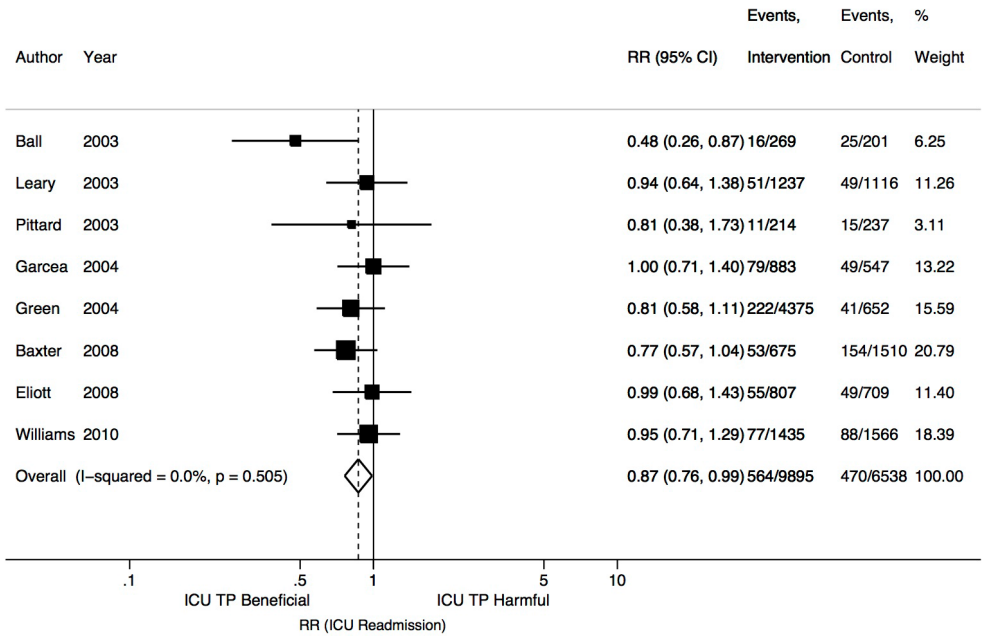


Fig 3. Forrest Plot Outreach Systematic Review

ICU readmissions



Hospital Mortality

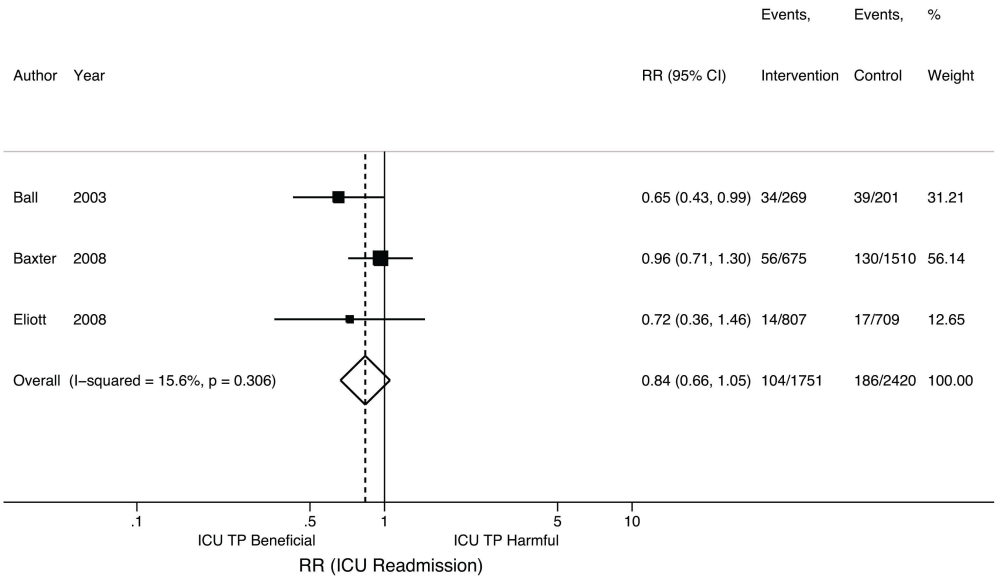


Fig 4. Segmented Regression Analysis on Interrupted Time-Series

$$Y_t = \beta_0 + \beta_1{}^{*}\text{time}_t + \beta_2{}^{*}\text{intervention}_t + \beta_3{}^{*}\text{time after intervention}_t + e_t$$

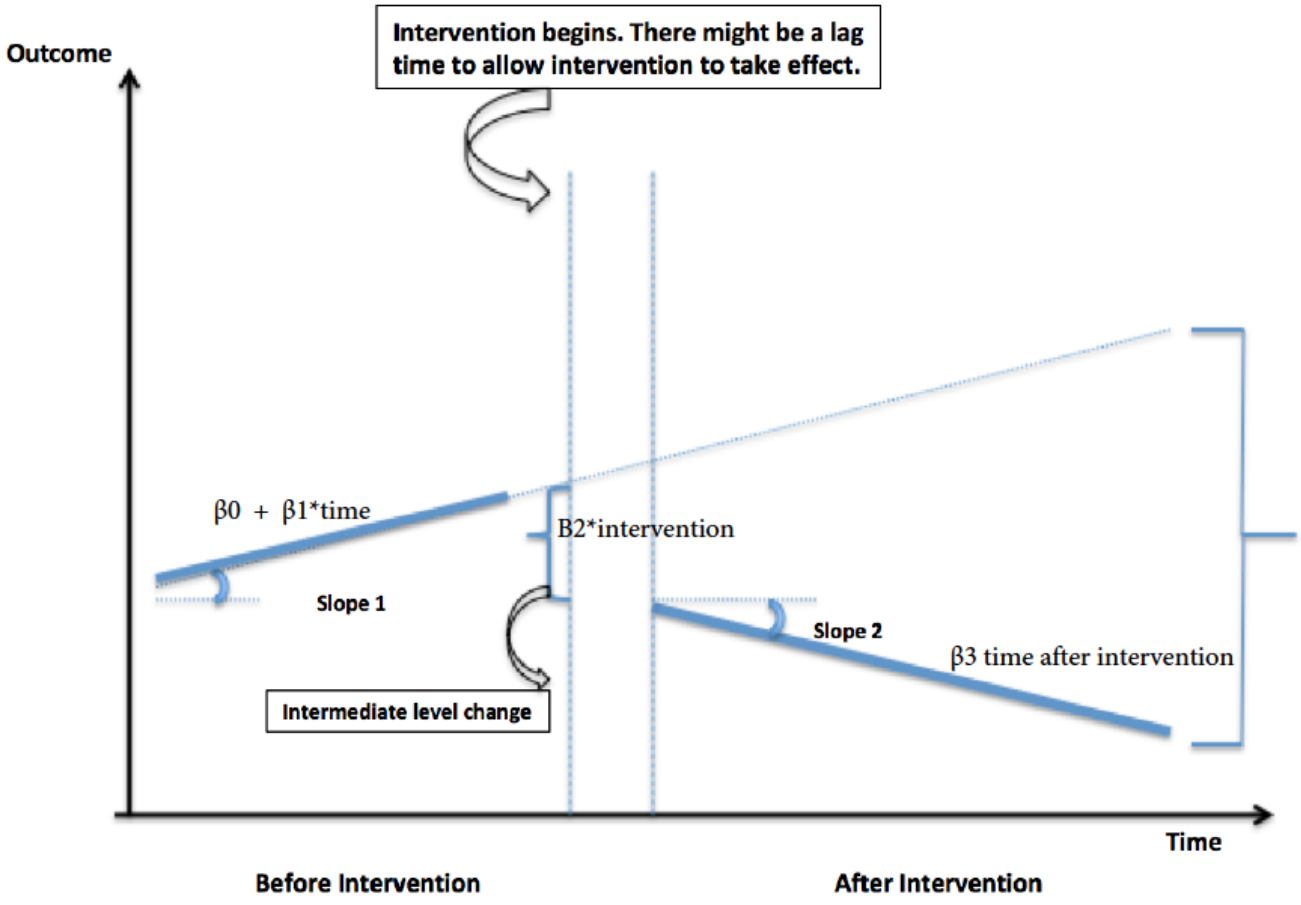
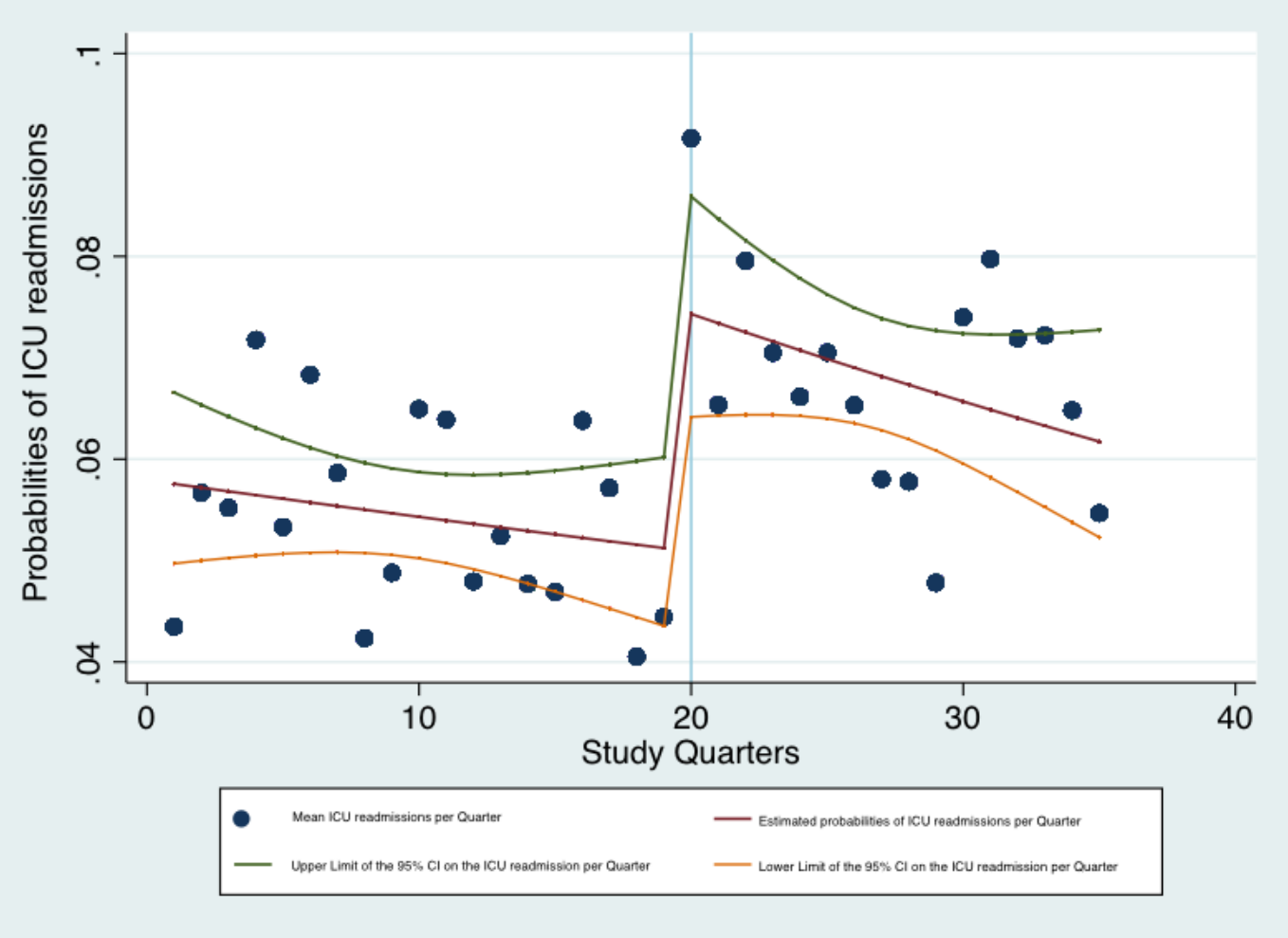
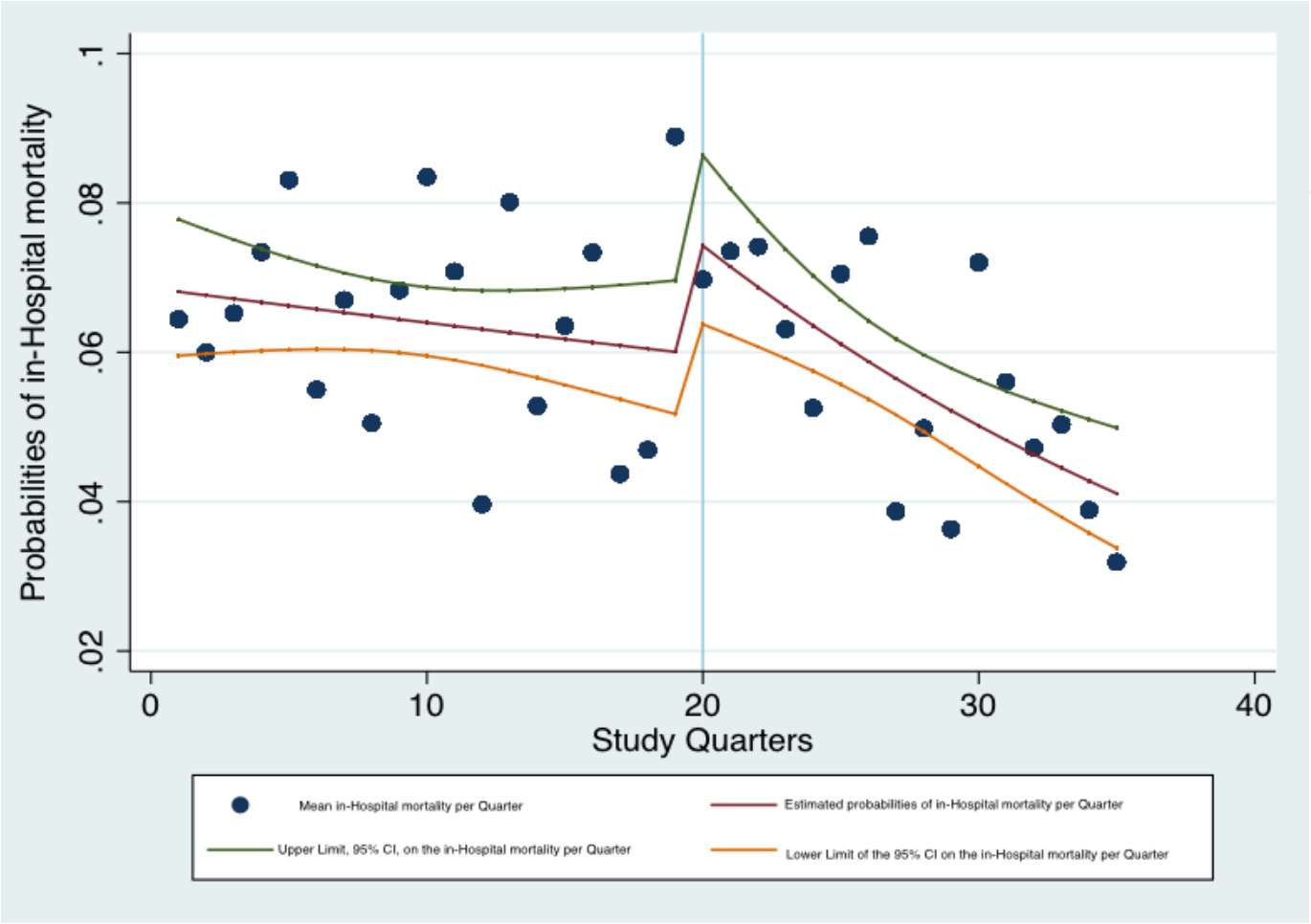


Fig 5. Unadjusted Segmented Logistic Regression for ICU Readmissions



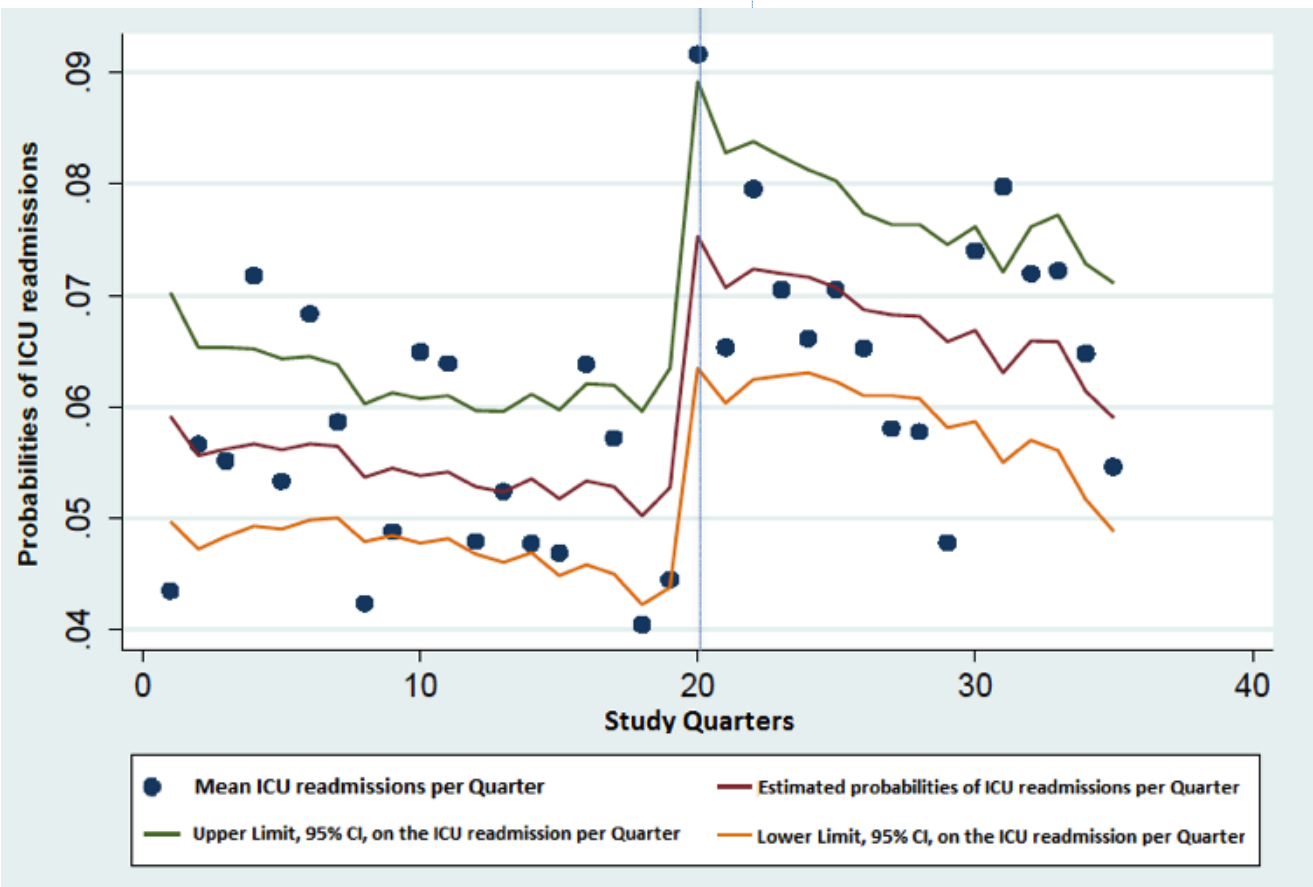
Probabilities of ICU readmissions per quarter during the period of study. A new trend is observed following a change in level, immediately the 20th quarter, meaning a non-significant -0.04% decrease ICU readmissions per quarter (95% CI, -0.2% to +0.1%) when ICUOT program starts.

Fig 6. Unadjusted Segmented Logistic Regression for In-Hospital Mortality



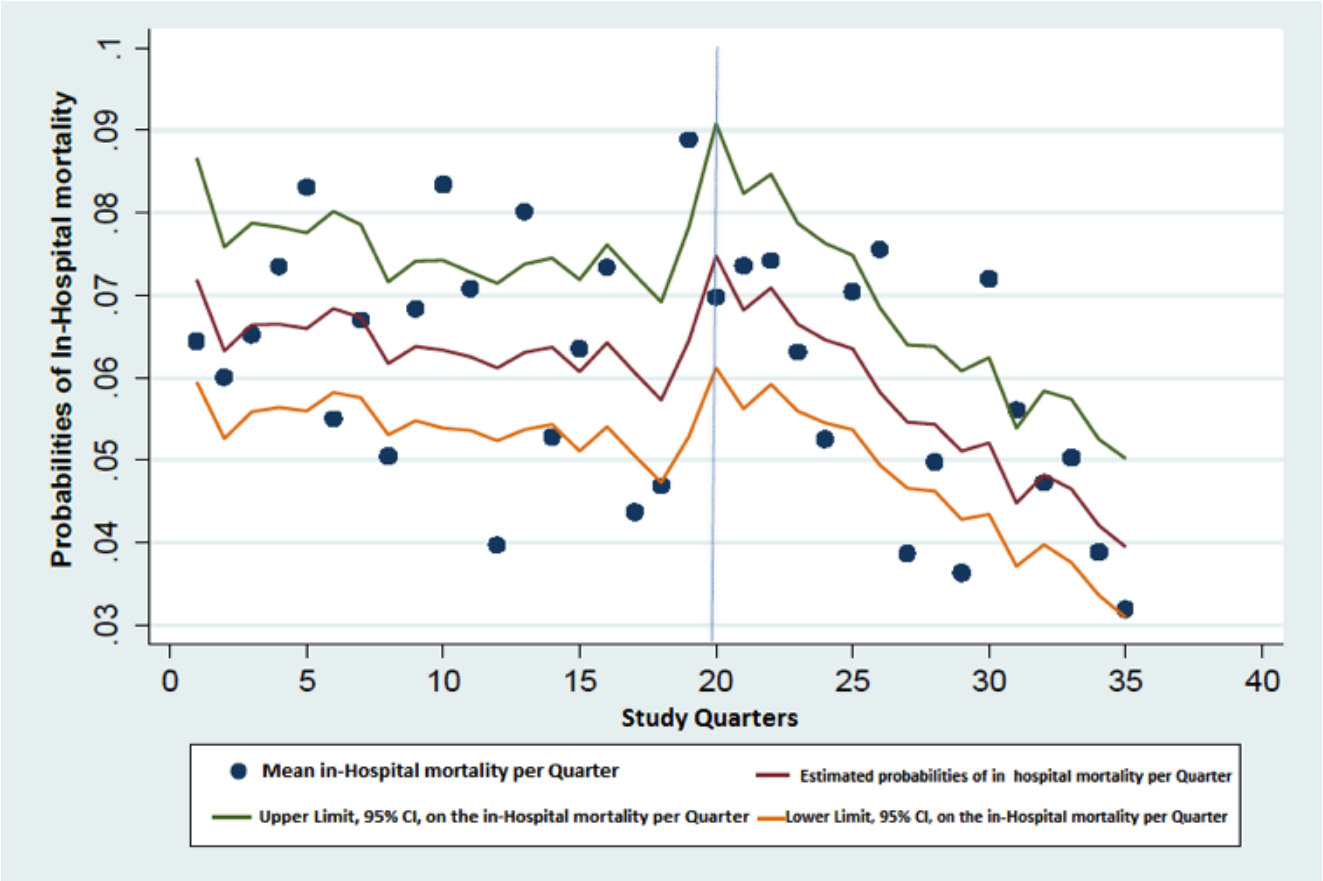
Probabilities of In-Hospital mortality per quarter during the period of study. A new trend is observed following a change in level, immediately the 20th quarter, meaning a significant -0.2% decrease in In-Hospital mortality per quarter (95% CI, -0.3% to -0.05%), when ICUOT program starts.

Fig 7. Adjusted (Multivariable) Segmented Logistic Regression for ICU Readmissions



Probabilities of ICU readmissions per quarter during the period of study. A new trend is observed following a change in level, immediately the 20th quarter, meaning a non-significant -0.04% decrease ICU readmissions per quarter (95% CI, -0.2% to +0.1%) when ICUOT program starts.

Fig 8. Adjusted (Multivariable) Segmented Logistic Regression for In-Hospital Mortality.



Probabilities of In-Hospital mortality per quarter during the period of study. A new trend is observed following a change in level, immediately the 20th quarter, meaning a significant -0.2% decrease in In-Hospital mortality per quarter (95% CI, -0.3% to -0.05%), when ICUOT program starts.

Table 1: Demographic characteristics of the study population before and after implementation of the Outreach program.

	Outreach Program		
	Before (n=10562)	**After (n = 8575)**	**p. value**
Age (years)	59.6 ± 16.5	59.4 ± 16.4	<0.001
Sex = M (n%)	6898 (65.3)	5660 (66.1)	0.41
Charlson Index (points)	1 Q1Q3: (0-2)	1 Q1Q3: (0-2)	0.89
CRRT (%)	208 (2.4)	214 (2.5)	0.014
CRRT days	5 Q1Q3: (3-10)	6 Q1Q3: (4-10)	0.05
Mech vent days	2 Q1Q3: (2-3)	2 Q1Q3: 2-4)	<0.001
LOS ICU days	2 Q1Q3: (1-5)	2 Q1Q3: (1-6)	<0.001
Apache2 (points)	16.04	15.74	<0.001
Admission Class: n (%)	10517 (99.6)	8575 (100)	
Cardiac Surgery	4537 (43.1)	3620 (42.2)	0.36
Medical	3322 (31.6)	2124 (24.8)	<0.001
Neuro	335 (3.2)	510 (5.9)	0.07
Surgical	2055 (19.5)	1.763 (2.0)	<0.001

Data are showed as mean values ± SD and median values with Q1Q3 interval. *M* - male, *CRRT* - Continuous Renal Replacement Therapy, *Mech Vent* - Mechanical Ventilation, *LOS ICU* - Length of Stay in Intensive Care Unit, Apache2 - Acute Physiologic Assessment and Chronic Health Evaluation II

Table 2. Outcomes, Before and After Intervention

Table 2: Outcomes before and after Outreach Program Implementation

	Before (n = 10562)	After (n = 8575)	p value
ICU readmission n (%)	451 (4.3)	469 (5.5)	<0.001
<48 hrs	150 (1.4)	149 (1.7)	0.08
>48 hrs	301 (2.8)	320 (3.7)	<0.001
In Hospital Mortality	683 (6.5)	488 (5.7)	0.02

Table 3. Unadjusted Proportions for ICU Readmissions and In-Hospital Mortality

	ICU Readmissions% (CI95%)	In-Hospital Mortality% (CI95%)
Beginning of Study	6.0 (4.91 to 7.12)	7.0 (6.02 to 9.01)
Baseline Trend Change Quarter-to-Quarter	0.04 (-0.11 to 0.05)	-0.04 (-0.12 to 0.04)
Immediate Change Post-Implementation	2.3 (0.90 to 3.70)	1.5 (0.20 to 3.02)
Change in Trend Post-Implementation	-0.04 (-0.20 to 0.11)	-0.2 (-0.30 to -0.05)
End of Study	6.0 (5.20 to 7.00)	4.0 (3.00 to 5.00)

Table 4. Adjusted Proportions for ICU Readmissions and In-Hospital Mortality

	ICU Readmissions% (CI95%)	In-Hospital Mortality% (CI95%)
Beginning of Study	6.00 (4.90 to 7.01)	7.0 (6.00 to 9.01)
Baseline Trend Change Quarter-to-Quarter	-0.02 (-0.10 to 0.07)	-0.01 (-0.09 to 0.07)
Immediate Change Post-Implementation	2.0 (0.50 to 3.20)	1.0 (-0.30 to 2.40)
Change in Trend Post-Implementation	-0.04 (-0.20 to 0.10)	-0.2 (-0.30 to -0.05)
End of Study	6.0 (4.80 to 7.00)	4.0 (3.00 to 5.00)

Table 5. Final Segmented Logistic Regression Model and Coefficients.

icu_readmit_hosp	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
stdy	.9970751	.0079813	-0.37	0.714	.9815541	1.012841
post_66	1.403229	.1757925	2.70	0.007	1.097722	1.793761
ta4_66	.9935158	.0125629	-0.51	0.607	.9691956	1.018446
Charlson_index	1.526111	.0592797	10.88	0.000	1.414237	1.646834
CAP	1.046507	.0201827	2.36	0.018	1.007688	1.086822
CI2	.9672815	.0044482	-7.23	0.000	.9586023	.9760392
_cons	.0321691	.0032032	-34.51	0.000	.0264656	.0391017

inhosp_death_dad	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
stdy	.9977129	.0075668	-0.30	0.763	.982992	1.012654
post_66	1.220927	.1544291	1.58	0.115	.9528519	1.564423
ta4_66	.9652571	.012891	-2.65	0.008	.9403191	.9908565
Age	2.606452	.2014139	12.40	0.000	2.240129	3.032678
Gender	.710312	.044953	-5.40	0.000	.6274509	.8041158
Charlson_index	1.726136	.0673545	13.99	0.000	1.599046	1.863328
APACHE_greaterEqual_25	.7747132	.0816868	-2.42	0.015	.6300704	.9525609
CAP	1.15971	.0432411	3.97	0.000	1.077982	1.247635
ACAP	.8852063	.0297108	-3.63	0.000	.8288483	.9453965
CI2	.9649851	.003986	-8.63	0.000	.9572043	.9728292
_cons	.021675	.0025804	-32.19	0.000	.0171642	.0273712

stdy: study quarter (pre–intervention period). post_66: moment of the intervention. ta4_66: after-intervention periods.
CAP:Charlson_index and Apache (interaction). ACAP: age, Charlson_index and Apache (interaction).CI2: Squared Charlson_index (quadratic)

Table 6: Change in probabilities of ICU readmission and In-Hospital mortality per study quarter, expressed by dy/dx coefficients.

ICU Readmissions

Delta-method

	dy/dx	Std. Err.	z	P>|z|	[95% Conf.	Interval]
stdy	-.0001633	.0004462	-0.37	0.714	-.0010379	.0007113
post_66	.0188848	.0069944	2.70	0.007	.005176	.0325937
ta4_66	-.0003626	.0007049	-0.51	0.607	-.0017442	.001019
Charlson_index	.0235644	.0022253	10.59	0.000	.0192029	.027926
CAP	.002534	.001076	2.36	0.019	.0004252	.0046429
CI2	-.0018544	.0002596	-7.14	0.000	-.0023632	-.0013455

In-Hospital Mortality

Delta-method

	dy/dx	Std. Err.	z	P>|z|	[95% Conf.	Interval]
stdy	-.0001243	.0004117	-0.30	0.763	-.0009313	.0006827
post_66	.0108368	.0068694	1.58	0.115	-.0026271	.0243006
ta4_66	-.0019197	.0007258	-2.65	0.008	-.0033422	-.0004972
Age	.0520088	.0043078	12.07	0.000	.0435656	.060452
Gender	-.0185698	.0034499	-5.38	0.000	-.0253314	-.0118081
Charlson_index	.0296359	.0021953	13.50	0.000	.0253332	.0339385
APACHE_greaterEqual_25	-.0138581	.0057267	-2.42	0.016	-.0250821	-.002634
CAP	.0080441	.0020285	3.97	0.000	.0040683	.0120199
ACAP	-.0066198	.0018268	-3.62	0.000	-.0102001	-.0030394
CI2	-.001935	.0002279	-8.49	0.000	-.0023817	-.0014883

stdy: study quarter (pre–intervention period). post_66: moment of the intervention. ta4_66: after-intervention periods.
CAP:Charlson_index and Apache (interaction). ACAP: age, Charlson_index and Apache (interaction).CI2: Squared Charlson_index (quadratic)