Impact of trauma center accreditation in Canada

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June 2020

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Doctor of Philosophy

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Abstract

The introduction of trauma systems in many countries over the last fifty years has led to important reductions in injury mortality and disability. Essential to the development of a trauma system is the designation of trauma centers, which are acute care hospitals where resources are prioritized to ensure that injured patients receive appropriate and timely care.

In North America, states or provinces are responsible for determining the optimal number of trauma centers in their jurisdictions, based on available resources and anticipated volume of trauma patients. Many injury organizations provide guidelines for optimal trauma care, which has led to the development of an external peer review process called accreditation or verification. This process aims to verify the capacity of a trauma center to deliver appropriate trauma care. Accreditation processes generally require centers to submit a prereview questionnaire and to complete an on-site visit by an experienced peer review team in trauma care. In Canada, accreditation is voluntary, except in the province of Quebec where it is mandatory.

Although accreditation has become a common practice, evidence of its effectiveness on patient outcomes is lacking. Proponents of accreditation argue that it enhances stakeholder engagement, strengthens collaboration through elements of the continuum of care and improves adherence to evidence-based protocols, all of which improve patient outcomes. Criticisms of accreditation include the mobilization of resources, and the possibility that improvements in care are only transitory.

In the **first manuscript** of this thesis, I present a systematic review of the literature on the impact of trauma center accreditation on adherence to evidence-based clinical processes of care and

patient outcomes, including in-hospital mortality, complications and hospital length of stay. This review highlighted some key findings. First, available studies have serious methodological limitations, including the lack of robust controls and competing-risk issues. Second, mixed and inconsistent results between accreditation and studied outcomes were found. Third, all available studies were conducted in the United States, limiting the generalizability of observed associations. Therefore, the actual state of knowledge adds little guidance to inform hospitals' decision to seek accreditation.

Disregarding the competing risk of in-hospital mortality when assessing the impact of accreditation on hospital length of stay was one of the primary issues identified in the review. The **second manuscript** of this thesis is a methodological study, which describes novel approaches to estimate the impact of hospital interventions on in-hospital length of stay while considering the competing risk of in-hospital mortality.

The **third and fourth manuscripts** present estimates of the impact of accreditation in mandatory (Quebec) and voluntary (British Columbia) settings, respectively. In both studies, I conducted an interrupted time series analysis to assess the effect of the first or subsequent accreditation cycles on in-hospital mortality, complications and hospital length of stay.

Overall, results suggest that in a mandatory context, accreditation is mostly beneficial for centers experiencing decreases in performance during the months preceding the visit. In a voluntary context, the impact of accreditation seems to be sustained after the first cycle and temporary for subsequent accreditation cycles. However, results did not support a universally beneficial impact of accreditation on studied outcomes, partly because some measured estimates were imprecise.

In conclusion, the collective findings presented in this work fill a gap in the literature regarding trauma center accreditation, particularly the important methodological limitations of existent observational work and its focus on the United States context. Further work evaluating other outcomes such as staff recruitment and retention is needed.

Résumé

L'introduction de systèmes de traumatologie dans de nombreux pays au cours des cinquante dernières années a contribué à d'importantes réductions de la mortalité liée aux traumatismes. La désignation de centres de traumatologie, qui sont des hôpitaux de soins aigus où les ressources sont rassemblées pour garantir que les patients victime de traumatismes reçoivent des soins appropriés en temps opportun, est essentielle pour le développement de systèmes de traumatologie.

En Amérique du Nord, les états et provinces sont responsables de déterminer le nombre optimal de centres de traumatologie dans leurs juridictions, en fonction des ressources disponibles et du volume anticipé de patients. De nombreuses organisations de traumatologie fournissent des recommandations pour une prise en charge optimale des patients victimes de traumatismes. Ces diverses recommandations ont conduit à l'élaboration d'un processus externe d'évaluation par des pairs appelé accréditation. Ce processus vise à vérifier la capacité d'un centre de traumatologie à fournir des soins de traumatologie optimaux. Les processus d'accréditation nécessitent généralement que les centres soumettent au préalable un questionnaire et accueillent une équipe d’examinateurs expérimentés en soins de traumatologie pour une visite des installations. Au Canada, l'accréditation est volontaire, sauf dans la province du Québec où elle est obligatoire.

Les partisans de l'accréditation soutiennent qu'elle améliore l'adhésion aux protocoles de soins fondés sur des données probantes, ce qui contribuerait à améliorer les résultats cliniques des

patients. Les critiques de l'accréditation mentionnent la mobilisation des ressources et la possibilité que l'amélioration des soins ne soit que transitoire.

Le **premier manuscrit** de cette thèse est une revue systématique de la littérature de l'impact de l'accréditation des centres de traumatologie sur l'adhésion aux processus cliniques de soins et les résultats cliniques des patients, incluant la mortalité hospitalière, les complications et la durée du séjour hospitalier. Cette revue a permis de mettre en évidence que les études disponibles ont de sérieuses limites méthodologiques tels que le manque de groupe témoins robuste. De plus, les effets observés étaient mitigés et incohérents. Finalement, toutes les études disponibles ont été menées aux États-Unis, limitant la généralisation des résultats. Par conséquent, l'état actuel des connaissances apporte peu d'orientation pour éclairer la décision des centres de se soumettre à un processus d'accréditation.

L'omission du risque compétitif que représente la mortalité hospitalière lors de l'évaluation de l'impact de l'accréditation sur la durée du séjour hospitalier a aussi été identifiée dans la revue de littérature. Le **second manuscrit** de cette thèse décrit de nouvelles approches pour estimer l'impact d'une intervention sur la durée du séjour hospitalier tout en tenant compte du risque compétitif de la mortalité.

Le **troisième et quatrième manuscrit** présentent l'évaluation de l'impact de l'accréditation sur la mortalité hospitalière, les complications et la durée du séjour hospitalier respectivement dans un contexte obligatoire (Québec) et volontaire (Colombie-Britannique). En utilisant des analyses de séries chronologiques interrompues, les résultats suggèrent que dans un contexte obligatoire, l'accréditation est principalement bénéfique pour les centres dont la performance diminuait au

cours des mois précédant la visite. Dans un contexte volontaire, l'impact de l'accréditation semble être soutenu après le premier cycle et temporaire pour les cycles subséquents. Cependant, je ne pouvais pas globalement conclure à une amélioration des issues étudiées, en partie parce que certaines les effets mesurés étaient imprécis.

L'évaluation d'autres indicateurs, tels que le recrutement et la rétention du personnel sont nécessaire pour compléter notre compréhension actuelle des possibles bénéfices de l'accréditation.

Acknowledgements

I would like to express my sincere gratitude to all the people who allow me to complete this thesis. I owe a massive debt of gratitude to my supervisors Dr. Arijit Nandi, Dr. Lynne Moore and committee member Dr. Erin Strumpf. It was an honor to complete this PhD under your supervision.

Ari, thanks again for accepting a stubborn student who only wanted to work on injuries. Thank you for giving me the freedom to do this work. You have been very patient, supportive, in short, an exceptional supervisor. Lynne, thanks for getting me through two degrees. You have been very supportive as well, specifically during data request processes and always responded in a timely manner. Dr. Erin Strumpf thank you for your valuable insight and for sharing your knowledge and expertise in interrupted time series analyses. I am also grateful to all Department of Epidemiology, Biostatistics, and Occupational Health (EBOH) professors, specifically Dr. Jay Kaufman who has and continues to be a mentor, always providing excellent advice. Thanks to the EBOH administrative office, especially Andre-Yves, Deirdre, Dolores, and Katherine who helped navigate through countless administrative procedures.

To the Institute for Health and Social Policy (IHSP), thank you to Anaik, Efe, Hellen and Holly for your support. To the Population Health and Optimal Health Practices Research Unit, Trauma – Emergency – Critical Care Medicine, Centre de Recherche du CHU de Québec, Amina, Marjorie, Pier-Alexandre and Xavier. Special mention to former colleague Dr. Ignacio Nazif-Munoz for his mentoring. I also thank the members of the Public Policy and Population Health Observatory (3PO) for their thoughtful questions and comments.

Thanks to the "*BEST COHORT EVER*" for making this learning experience a fun journey. To my friends, thank you for supporting me, and for providing an indispensable link to the real world.

A special thanks to CBS!

I would like to thank my parents Germain and Brigitte, my sisters, brothers and cousins. My uncle and mentor Fulbert and his wife Judith, and my aunt Mirielle. A special mention for my aunt Marie-Georgette, her husband Prosper and my cousin Rodrigue and his wife Dorice.

Finally, I will like to express my profound gratitude to the first respondents, epidemiologists, healthcare professionals and all other essential workers for their tireless work, for which they have and continue to pay a heavy price during this exceptional COVID-19 pandemic time.

Statement of financial support

I was extremely fortunate to receive different sources of financial support throughout my doctoral studies. My main funding source was the Doctoral Award from the Fonds de recherche - Santé Québec (FRQS). I received additional funding through the graduate award program of the Institute of Health and Social Policy (IHSP), as well as complementary support in the form of research assistantships and stipends to cover my tuition from my supervisor, Dr. Arijit Nandi. I also received several travel awards from the Department of Epidemiology, Biostatistics, and Occupational Health (EBOH) at McGill University, which were essential for the dissemination of my research.

Contribution of authors

My doctoral study has led to the production of five manuscripts, of which four are presented in this thesis. The data used in the analyses came either from my own data collection (manuscript 1) or from the Quebec trauma registry (manuscripts 2 and 3) and the British Columbia trauma registry (manuscript 4). I was responsible for developing the research questions and study design, cleaning the data, completing the analyses, and generating the draft versions of the manuscripts.

Dr. Arijit Nandi, my supervisor is an Associate Professor in epidemiologist jointly appointed in the Department of Epidemiology, Biostatistics and Occupational Health and the Institute for Health and Social Policy at McGill University. He has extensive experience in policy evaluations and provided guidance to refine my research questions and select the most appropriate design. Dr. Lynne Moore, my co-supervisor, is an Epidemiologist and Professor in the Department of Medicine Social and Preventive at Laval University. She is an expert on trauma care research, specifically the development, validation, implementation, and evaluation of comprehensive quality assessment tools for acute injury care. She deepened my subject matter knowledge, facilitated collaborations with accreditation agencies and was crucial in the interpretation of results. My committee member, Dr. Erin Strumpf, is a Health Economist and an Associate Professor jointly appointed in the Department of Epidemiology, Biostatistics and Occupational Health and the Department of Economics at McGill University. She reviewed, commented, and offered methodological guidance for manuscripts 2, 3 and 4.

Manuscript 1: Batomen B, Moore L, Carabali M, Tardif PA, Champion H, Nandi A. Effectiveness of trauma center verification: A Systematic Review and Meta-analysis (*Accepted for publication in the Canadian Journal of Surgery* 2020).

Manuscript 2: Batomen B, Moore L, Strumpf E, Nandi A. Addressing competing risks when assessing the impact of health services interventions on hospital length of stay: The example of trauma center accreditation *(Accepted for publication in Epidemiology).*

Manuscript 3: Batomen B, Moore L, Strumpf E, Champion H, Nandi A. Impact of trauma center accreditation on mortality and complications in a Canadian trauma system: An interrupted time series analysis *(Accepted for publication in BMJ Quality&Care).*

Manuscript 4: Batomen B, Moore L, Strumpf E, Yanchar N, Thakore J, Nandi A. Trauma system accreditation and patient outcomes in British Columbia: An interrupted time series analysis *(Accepted for publication in International Society for Quality in Health Care).*

The manuscript not included in this thesis is the protocol for the systematic review presented in manuscript 1. It is published in the journal *Systematic Reviews*.

Batomen B**,** Moore L, Carabali M, Tardif P-A, Champion H, Nandi A. Effectiveness of trauma center verification: Protocol for a systematic review. *Systematic reviews 2019; 8: 1-5.*

Dr. Howard Champion is a physician and world expert in trauma care research, who has developed several measures for trauma severity. Fellow of the American College of Surgeons, he has been instrumental in the development and implementation of trauma systems around the

world. He provided input on methodology and interpretation of the results for manuscripts 1 and 3.

Dr. Mabel Carabali is a physician and Infectious Disease Specialist. She is also my PhD classmate, and contributed to the data extraction, data synthesis, data analysis and drafting of manuscript 1.

Mr. Pier-Alexandre Tardif, M.Sc is a research assistant at the Population Health and Optimal Health Practices Research Unit, Trauma – Emergency – Critical Care Medicine, Centre de Recherche du CHU de Québec. He is an expert in systematic reviews and provided guidance in the development of the protocol and revised manuscript 1.

Dr. Natalie L Yanchar is a physician specialized in pediatric surgery and clinical professor of Surgery at the University of Calgary. She has extended knowledge of trauma research and is a former president of the Trauma Association of Canada. She provided insight in the interpretation of the results for the manuscripts 3 and 4.

Mr**.** Jaimini Thakore, BSc, MBA currently works at the Provincial Health Services Authority as the manager of the British Columbia provincial trauma registry. He provided essential information on the context of accreditation in British Columbia and helped with the interpretation of manuscript 4.

Statement of originality

Although I received guidance from my supervisors, committee member and co-authors on several aspects of this thesis, the works presented herein are my own. This thesis constitutes an original contribution to the advancement of epidemiology methods in general and the management of trauma systems in particular.

Manuscript 1 systematically reviewed and synthesized, both quantitatively and qualitatively, evidence on the association between trauma center accreditation and patients' outcomes. Manuscript 2 was framed as a practice of epidemiology paper, to describe novel approaches to estimate the impact of hospital interventions on in-hospital length of stay, while accounting for changes in patients' characteristics and the competing risk of in-hospital mortality. Manuscripts 3 and 4 are to my knowledge, the first studies to assess the impact of trauma center accreditation cycles in Canada, both in mandatory and voluntary contexts.

In addition to these four manuscripts, a manuscript detailing the protocol of the systematic review presented in manuscript 1 was published.

Ethical Statement

This thesis received ethics approval from the McGill University Faculty of Medicine Research Ethics committee (IRB Study Number A05-E26-18B).

List of abbreviations

AC	Accreditation Canada
ACF	Autocorrelation function
ACS	The American College of Surgeons
ACSCOT	The American College of Surgeons Committee on Trauma
AIS	The Abbreviated Injury Scale
AR	Autocorrelation
ARIMA	Autoregressive integrated moving average
BC	British Columbia
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CITS	Comparative interrupted time series
DALYs	Disability-adjusted life years
EMBASE	Excerpta Medica database
GEE	Generalized estimating equations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICD-9-CM	The Ninth Revision of the International Classification of Disease- Clinical Modification
ICD-10-CA	The Tenth Revision of the International Classification of Disease- with Canadian Enhancements
INESSS	Institut national d'excellence en santé et services sociaux
IRB	Institutional Review Board
ISS	Injury severity score

ITS	Interrupted time series
LOS	Hospital length of stay
MA	Moving average
MTOS	Major Trauma Outcome Study
NTDB	National Trauma Data Bank
PACF	Partial autocorrelation function
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PROMs	Patient-reported outcome measures
PROSPERO	International prospective register of systematic reviews
RAMQ	Régie de l'assurance maladie du Québec
ROBINS-I	The Risk Of Bias In Non-randomized Studies – of Interventions
SMR	Standardized mortality ratio
TAC	Trauma Association of Canada
TQIP	Trauma Quality Improvement Program
VIF	Variance inflated factor
WHO	World Health Organization

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CHAPTER 1. Introduction

Road traffic and unintentional injuries are responsible for millions of deaths globally and approximately 180 million disability-adjusted life years (DALYs) annually, which represents an estimated 10% of the global burden of disease(1-3). They are also the leading cause of death under 40 years of age in North America (4-6). Injuries cost Canadians more than $26.8 billion per year, including direct costs of $15.9 billion and indirect costs of $10.9 billion(5). Along with road safety and other prevention measures, the introduction of trauma systems in many high and upper-middle-income countries over the last fifty years has led to tremendous reductions in blunt injury mortality and disability(7-9). Many organizations, including the World Health Organization (WHO)(10), the American College of Surgeons (ACS)(11), the Trauma Association of Canada (TAC)(12) and Accreditation Canada (AC)(13) provide recommendations on the structure, processes of care and expected performance of trauma systems and centers. These criteria have led to the development of accreditation or verification processes,[1] which aim to determine whether trauma centers and systems are fulfilling the criteria for optimal care. Despite the growing trend towards accreditation of hospitals within trauma systems, evidence of it benefits are unclear(14, 15).

1.1 Trauma Systems

A trauma system is an organized and multidisciplinary response to injury from pre-hospital and acute care to rehabilitation and community integration(16). The redefinition of injury as a

[1] Accreditation and verification of trauma centers refer to the same process. In Canada, the word accreditation is used, while in the United States we used verification. Both terms are however, sometimes used as synonym for trauma center designation which is a different process.

preventable and treatable disease by the National Research Council in 1966 was a major stimulus to the development of trauma systems(17, 18). The first statewide trauma system was initiated in Maryland in 1973, and others followed in Illinois and Virginia(18). In Canada, the development of trauma systems started in early 1990s at the Vancouver Coastal Health Authority in British Columbia, followed by the Continuum of trauma services in the province of Quebec(19, 20).

Elements of an ideal trauma system are access to care, prehospital care, hospital care, rehabilitation, patient education and research (**Table 1.1**)(21, 22). We will characterize a trauma system as "*inclusive*" if it is comprised of all these elements, or "*exclusive*" when the focus is only on major trauma centers for hospital care(23). However, for a well-functioning trauma system, the presence of a legal authority which is usually a state, province, local agency or assigned non-profit organization is crucial(18). The legal authority is responsible for the designation of trauma centers according to levels of care. It is also in charge of anticipating patient volumes and assessing available resources to determine the optimal number and level of trauma centers in a given area(11).

Table 1.1: Trauma system criteria and components

Criteria	Explanation
Presence of a legal authority	State, province or regional health authority which designates and categorizes trauma centers, after determining the appropriate number of centers
Formal designation process	Formal process of designating some hospitals as trauma centers
On-site accreditation or verification	On-site external review to verify compliance with trauma center standards
Prehospital triage	Protocols allowing emergency medical services to bypass non-designated hospitals for major trauma patients
Process to measure systems outcomes	Formal process to monitor system performance
Full geographic coverage	Coordination between emergency medical services and hospital resources to ensure access to trauma care in a timely manner

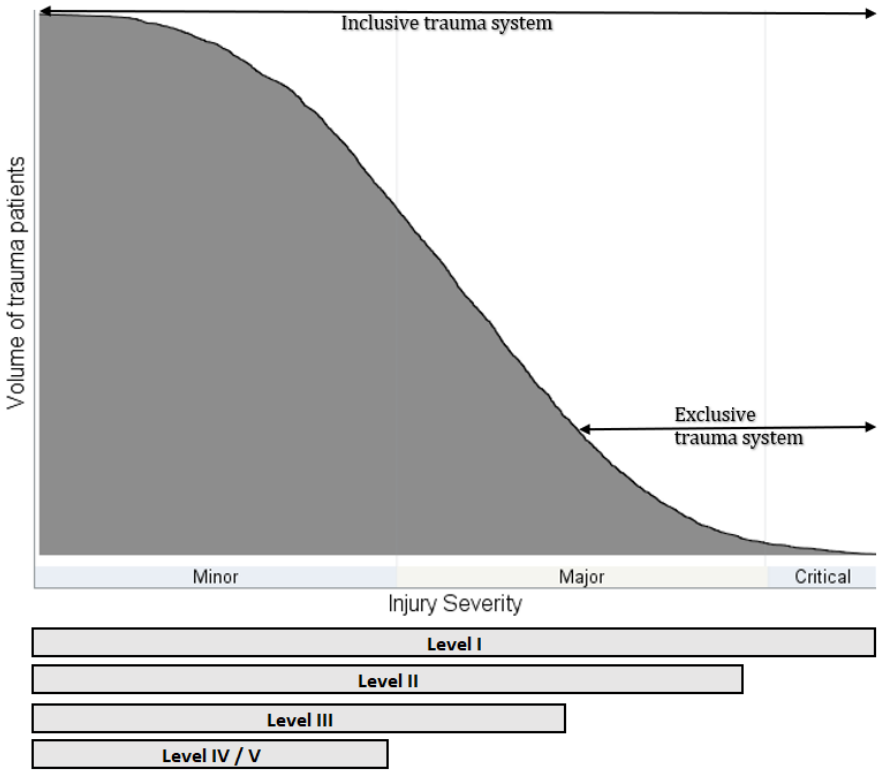
Adapted from West, J. G., Williams, M. J., Trunkey, D. D., & Wolferth, C. C. (1988). Trauma systems: current status—future challenges. *Jama*, *259*(24), 3597-3600, and David J. Ciesla AJK, Joseph J. Tepas III. Trauma Systems, Triage, and Transport. 2017. In: Trauma, Eighth Edition. Cenveo: McGraw-Hill Education.

1.2 Trauma Centers

Essential to the development of a trauma system is the presence of trauma centers. They are medical centers where resources are prioritized to ensure that injured patients receive full and timely resuscitation, assessment and definitive care. They are classified as levels I – V for adult trauma centers and levels I – II for pediatric trauma centers (**Figure 1.1**). In general, only one level I or level II trauma center and one level I or level II pediatric trauma center is required in a trauma system serving a population of 1 to 2 million. Both adult and pediatric level I trauma centers are usually university-affiliated, large metropolitan medical centers with a full array of medical specialties and ready access to advanced medical technology. Level II centers are required in jurisdictions without a level I center or where the major trauma volume is too large for a single level I center. Level II centers are similar to level I centers, but they may or may not be university affiliated(12). Level III centers are typically present in jurisdictions where there is no rapid access to level I or II centers, but where there is a significant volume of major trauma. Level IV and V facilities typically exist in urban jurisdictions near a level I or II trauma center or in smaller communities where they play a role in the initial stabilization of major trauma patients. In Quebec, level V centers are usually local community services hospitals (CLSC). System field triage guidelines should be in place to ensure that the majority of major trauma patients bypass lower level facilities and are transported to a level I/II center, or are stabilized before transfer if the closest level I/II center is outside a one hour catchment area(11, 12). In Canada, all provinces have

major trauma centers, except Prince Edward Island, which transfers all major trauma patients to Nova Scotia. Concerning the territories, Yukon, Northwest Territories, and Nunavut, all major trauma patients are transferred, respectively, to New Brunswick, British Columbia, Alberta, or Manitoba (24, 25).

Figure.1.1: Patient volume and injury severity



Adapted from Ernest E. Moore DVF, Kenneth L. Mattox. Trauma, Eighth Edition Cenveo: McGraw-Hill Education; 2017.

Although patients with minor trauma can receive effective and definitive care in non-designated hospitals, a trauma system should have protocols for inter-facility transfer of patients whenever a major trauma patient is inappropriately triaged to an undesignated facility(18, 26-28).

The first document to define criteria for categorization of hospital as trauma centers was the *Optimal Resources for the Care of the Seriously Injured* published by the American College of Surgeons (ACS) in 1976. This document established standard for comprehensive delivery of care and serves as the "gold-standard" for hospitals working towards a trauma center designation. It is periodically revised to reflect current knowledge(18).

1.3 Accreditation Process

Most states, provinces or local authorities use ACS criteria to designate trauma centers. However, the designation process may vary between jurisdictions and are typically outlined through a legislative or regulatory authority(29). Therefore, external peer reviews called verification (in the United States) or accreditation in (Canada) are often used to verify the abilities of specific trauma centers to deliver the appropriate level of care(12, 18, 30). Accreditation and verification refer to the same process. Hereafter the term accreditation is used for both.

Even though the terms accreditation and designation are sometimes used interchangeably they have different meanings(31-34). Accreditation organizations do not designate trauma centers. Instead, they verify the presence of resources and, assess the commitment, readiness, policies, patient care, and performance improvement of centers(12). A center should be designated before seeking accreditation, unless it does not fall under a designating authority. Donabedian quality of care principles suggest that, besides patient characteristics, institutional structures and clinical practices determine patient outcomes(35). While trauma center designation does not generally require compliance with specific practices, accreditation does assess compliance to regularly updated evidence-based practices(30, 36).

The accreditation process generally comprises submission of pre-review questionnaire by the center under evaluation followed by an on-site review by a peer review team experienced in trauma care. The pre-review questionnaire is usually completed and submitted at least one month before the on-site visit. It allows site reviewers to have a preliminary understanding of trauma care capabilities, and includes general information (name, tax status, trauma director), as well as information on general services (e.g. number of surgeons) and specialty services (e.g. pediatric, geriatric, rehabilitation)(12, 37, 38). In addition, most accreditation bodies now request that centers submit data on performance indicators such as trauma team activation and time to surgery(30). Centers are evaluated according to their designated level and the criteria assessed during the process cover broad aspects of trauma care including, for example, the role of the trauma center in the trauma system, staff qualifications and availability, presence of protocols for care delivery and benchmarking tools to measure performance and outcomes. Although criteria used for the evaluation are widely based on the ACS' *Resources for Optimal the Care of the patient*, they vary according to the accreditation body.

Accreditation was introduced in the United States in 1987, when the American College of Surgeons Committee on Trauma (ACSCOT) instituted the verification/consultation program(11, 18). In the United States accreditation is requested by individual trauma centers.[2] In Canada (except for the province of Quebec), trauma center accreditation was introduced in 1993 by the Trauma Association of Canada (TAC)(12). Accreditation is also voluntary and was sought by individual trauma centers until 2005. Thereafter, the focus of accreditation moved from trauma

[2] Some states like Pennsylvania have their own verification agencies and the ACS verification process is also shifting from center to system accreditation/verification.

centers to regional trauma systems. Nevertheless, each center in the system evaluated is still required to complete the pre-review questionnaire and host on-site reviewers. Prior to 2014, the accreditation process resulted in one of three outcomes: 1) successful, with a certificate valid for 5 years; 2) provisional, which confers a certificate valid for one year, during which the center or organization must correct deficiencies identified in the review, and a full accreditation may be granted; finally, 3) unsuccessful, in which case a new application for a full review is required. From 2014, the TAC entered a partnership with Accreditation Canada. Thereafter, accreditation resulted in success or failure, with a certificate valid for 4 years(12, 39).

In Quebec, accreditation is mandatory.[3] The process is very similar to that for the rest of Canada, and after completion a center can have one of the following results: unconditional accreditation, in which case the certificate lasts approximately 5 to 6 years; provisional accreditation**,** in which case a new site visit is conducted within 18 months; and accreditation postponed. The latter can result in a modification of the level of designation. Starting in 2017, the accreditation process in Quebec no longer involves on-site visits.

Accreditation is, however, an expensive and resource-consuming process(14, 32, 40). For example, the average estimated costs of readiness (including Administrative, Clinical Medical Staff, In-House Operating Room, and Education/Outreach) for a level I and level II trauma centers were $6.8 and $2.3 million, respectively, in the Georgia Trauma System(41).[4] Proponents of

[3] Given that an unsuccessful accreditation can result in a modification of the center level of designation, the words designation and accreditation are used interchangeably in Quebec official documents.

[4] Some of the centers evaluated in that study were not trauma center yet. Therefore, the costs presented may also comprise the preparation for designation by the legal authority.

accreditation argue that it enhances stakeholder engagement, strengthens collaboration through elements of the continuum of care, provides leverage for funding and improves adherence to evidenced-based protocols, all of which improve patient outcomes(25, 32, 42-44). Criticisms of accreditation include the mobilization of resources, as well as the possibility that improvements in care are only transitory. One hypothesis is that adherence to processes of care and patient outcomes improve during the preparation for accreditation but return to baseline levels not long after the accreditation visit(45). We currently lack data to support or refute these hypotheses.

1.4. Research objectives

My overarching goal was to assess if trauma center accreditation improves patients' clinical outcomes, including in-hospital mortality, major complications and hospital length of stay. My specific research objectives were to:

1. Systematically review and synthesize available evidence on the impact of trauma center accreditation on patient outcomes and adherence to evidence-based processes of care;

2. Assess the effect of trauma center accreditation on patient outcomes after adjustment for patient and center-level confounding factors.

The latter has two sub aims, specifically

2.1 To evaluate the impact of accreditation on investigated outcomes in mandatory and voluntary settings separately;

2.2 To assess if change in the accreditation body impacts investigated outcomes.

1.5 Structure of the Thesis

This thesis is manuscript-based and contains seven chapters with four corresponding to original research manuscripts. Each manuscript chapter begins with a preface explaining its rationale, the research question(s) addressed and the connection with thesis objectives. In chapter 1, I present the overarching thesis rationale and state my research objectives. Chapter 2 consists of a systematic literature review (manuscript 1). Chapter 3 briefly presents the data source, design and analytical methods I used to complete my thesis objectives and sub-objectives. Chapter 4 describes novel analytical approaches to address serious methodological concerns identified in the literature review (manuscript 2). In Chapter 5, I evaluate the impact of accreditation on investigated outcomes in a mandatory context (manuscript 3). In chapter 6, I assess the impact of accreditation on investigated outcomes in a voluntary context and evaluate whether a change of the accreditation body has any impact (manuscript 4). Chapter 7 discusses the overall findings of this thesis, its implications and future directions, and makes concluding remarks. References to the documents (articles, book chapters, reports and webpages) cited in this work are provided at the end.

CHAPTER 2. Effectiveness of trauma center verification: A systematic review and metanalysis

2.1 Preface: Manuscript 1

Systematic reviews are a robust attempt to collate and synthesize evidence that fits pre-specified eligibility criteria in order to answer a specific research question(46). To minimize bias in the evaluation of available evidence, my methodology was documented a priori in a protocol that was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database, CRD42018107083(47), and published in *Systematic Reviews(48)***.**

This review addresses the first objective of my thesis, which is to synthesize evidence on the effectiveness of trauma center accreditation for improving hospital mortality, morbidity, resource utilization and adherence to evidence-based processes of care. It was presented orally at *the International Public Policy Association meeting* (Montreal, June 2019) and was accepted for a poster presentation at the *Trauma Association of Canada Congress* (Halifax, March 2020), and the 21st European Congress of Trauma & Emergency Surgery (Oslo, Norway, cancelled).[5] It was accepted for publication in the *Canadian Journal of Surgery(47)*.

[5] The Trauma Association of Canada was held virtually, and the European Congress of Trauma & Emergency Surgery was cancelled due to the COVID-19 pandemic.

2.2 Manuscript 1

Title: Effectiveness of trauma center verification: A systematic review and metanalysis

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Funding

Funds for this project are covered by the Fonds de recherche du Québec – Santé (FRQS) PhD scholarship (BB) and a Canadian Institute of health Research (CIHR) Foundation grant (FRN 353374 for LM and FRN 148467 for AN).

Acknowledgements

To Andrea Quaiattini Ms., who was the librarian helping to refine the research question, keywords, and Mesh terms for the preliminary search strategy.

Abstract

Background: There is a growing trend towards verification of trauma centers, but its impact remains unclear. This systematic review aims to synthesize available evidence on trauma center verification effectiveness.

Study Design: We conducted a search in CINAHL, EMBASE, HealthStar, MEDLINE, and ProQuest databases, as well as key injury organization websites for grey literature, up to June 2019. Our population consisted of injured patients treated at trauma centers. The intervention was trauma center verification. Comparison groups comprised non-verified trauma centers, or the same center before it was first verified or "re-verified". Investigated outcomes were in-hospital mortality (primary outcome), as well as adverse events, resource utilization, and processes of care (secondary outcomes). Pooled summary estimates were computed using random effects meta-analysis.

Results We included 29 articles, all conducted in the United States. Mortality was the most frequently investigated outcome (n=20), followed by processes of care (n=12), resource utilization (n=12) and adverse events (n=7). The risk of bias was serious to critical in 22 studies. We observed an imprecise association between verification and decreased mortality (RR 0.74; 95% CI 0.52 to 1.06) in severe injured patients.

Conclusions Our review found mixed and inconsistent results between verification and processes of care or patient outcomes. The validity of the published literature is limited by the lack of robust controls, as well as any evidence from outside the United States, which preclude extrapolations

to other health care jurisdictions. Quasi-experimental studies are needed to assess the impact of trauma center verification.

Systematic reviews registration: PROSPERO number CRD42018107083**.**

Keywords: Verification; Accreditation; Trauma Centers; American College of Surgeons.

BACKGROUND

The introduction of trauma systems, defined as an organized and multidisciplinary response to injury from pre-hospital care to rehabilitation and community integration, has led to important reductions in injury burdens in many high-income countries(1, 2). Essential to the development of a trauma system is the designation of trauma centers according to levels of care (levels I – V for adults and I or II for pediatric centers), which is commonly the role of states or provinces(3). Trauma centers are acute care hospitals where resources are prioritized to ensure that injured patients receive appropriate and timely care(4, 5). Injury organizations, including the American College of Surgeons (ACS), have established trauma facility standard guidelines(3). These criteria have been used to develop trauma center verification or accreditation processes, aimed to determine whether trauma centers are fulfilling the criteria for optimal care. Accreditation and verification of trauma centers refer to the same process, hereafter we use the term verification to refer to both(5, 6).

The terms verification and designation are sometimes used interchangeably despite having different meanings(7-10). Designation is conducted by regional health authorities at the local or state stage where centers are categorized in levels (I – V for adults and I or II for pediatric centers),

while verification or accreditation is generally an optional program to verify that a facility is performing as a trauma center and meets the criteria its designation level(5, 8, 11). For example verification is offered, by the American College of Surgeons (ACS) in the USA(3, 12, 13) and accreditation by Accreditation Canada in Canada(6), who are not responsible for designation(11). A center can be designated at a particular level without having received verification(8, 9). In some USA states or Canada provinces, regulatory agencies may require regular verification for a trauma center to maintain designation within their systems. Verification allows for standardization of personnel, equipment and a facility's commitment to trauma care(8). Perceived advantages of verification include commitment as well as, identification of opportunities and priorities for improvement(14). Verification is, however, an expensive and resource-intensive process(15, 16). It generally requires a center to submit a prereview questionnaire and to complete an on-site visit by an experienced peer review team(3). A summary of verification modalities in different countries is presented in **Table 2.1.**

Although verification has become a common practice(14, 17), the evidence of its effectiveness on patient outcomes has not been systematically assessed and synthesized. It is essential to know whether the allocation of financial and human resources used in the verification process has its intended effect(17, 18). This systematic review aims to synthesize available evidence on trauma center verification, to evaluate whether verification reduces in-hospital mortality, adverse events, resource utilization and improves processes of care.

Table 2.1: Some examples of verification agencies

Countries	Verification Agencies	Certificate Duration	First Verification
United States†	American College of Surgeons	3 years	1987 - Ongoing
Canada (except Quebec)	Trauma Association of Canada	5 years	1995 - 2014
	Accreditation Canada	4 years	2014 - Ongoing
Quebec‡	Institut national d'excellence en santé et services sociaux	~ 6 years	1995 - Ongoing
Australia	Royal Australasian College of Surgeons	3 years	2000 - Ongoing

†Some states (e.g. Pennsylvania) have their own verification agencies.

‡Verification is mandatory in Quebec.

Methods

The protocol of this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database, CRD42018107083, and published (19, 20)**.** It was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (**eFigure 2.1 Supplement materials**)(21).

Literature Search and Selection of Studies

We conducted a systematic search of CINAHL, EMBASE, HealthStar, MEDLINE, and ProQuest databases, as well as key injury organization websites for grey literature from inception up to June 2019, without language restrictions. Manual searches for additional eligible studies were performed by reviewing the reference lists of included studies. The search strategy is available in (**eTable 2.1 Supplement materials**). Conference abstracts were included unless they were subsequently published as full articles (**Figure 2.1**).

Study Population and Intervention

Our study population consists of injured patients treated at trauma centers. The intervention under evaluation was trauma center verification. Comparison groups comprised non-verified centers, or the same center before it was first verified or "re-verified". All study designs were considered, however, narrative studies without a quantitative estimate of the association between verification and the investigated outcomes were excluded.

Outcomes

Our primary outcome was in-hospital mortality. Secondary outcomes included, population-based injury related mortality, adverse events (e.g. complications), resource utilization [e.g. length of stay (LOS) and costs], and adherence to evidence-based processes of care (e.g. non-surgical management of splenic injuries).

Data Collection and Extraction

After removing duplicates from database search results(22), titles and abstracts were independently screened by two authors (BB and MC) using a web and mobile app for systematic reviews(23). In case of disagreement or uncertainty, full papers were retrieved and discussed with a third author (LM). Full texts of selected studies were retrieved and examined to determine eligibility by two authors (BB and MC), who also independently extracted the data using standardized forms. When available, data recorded included country of the study, the number of centers, study design, patient demographics and outcome results. Efforts were made to contact the corresponding author for further information when needed. Descriptive statistics and measures of associations were directly extracted from the studies or computed if enough information was provided(24-26).

We assessed the risk of bias using the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool(27). We evaluated the quality of the collective evidence and strength of recommendations using Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology(28).

Statistical Analysis

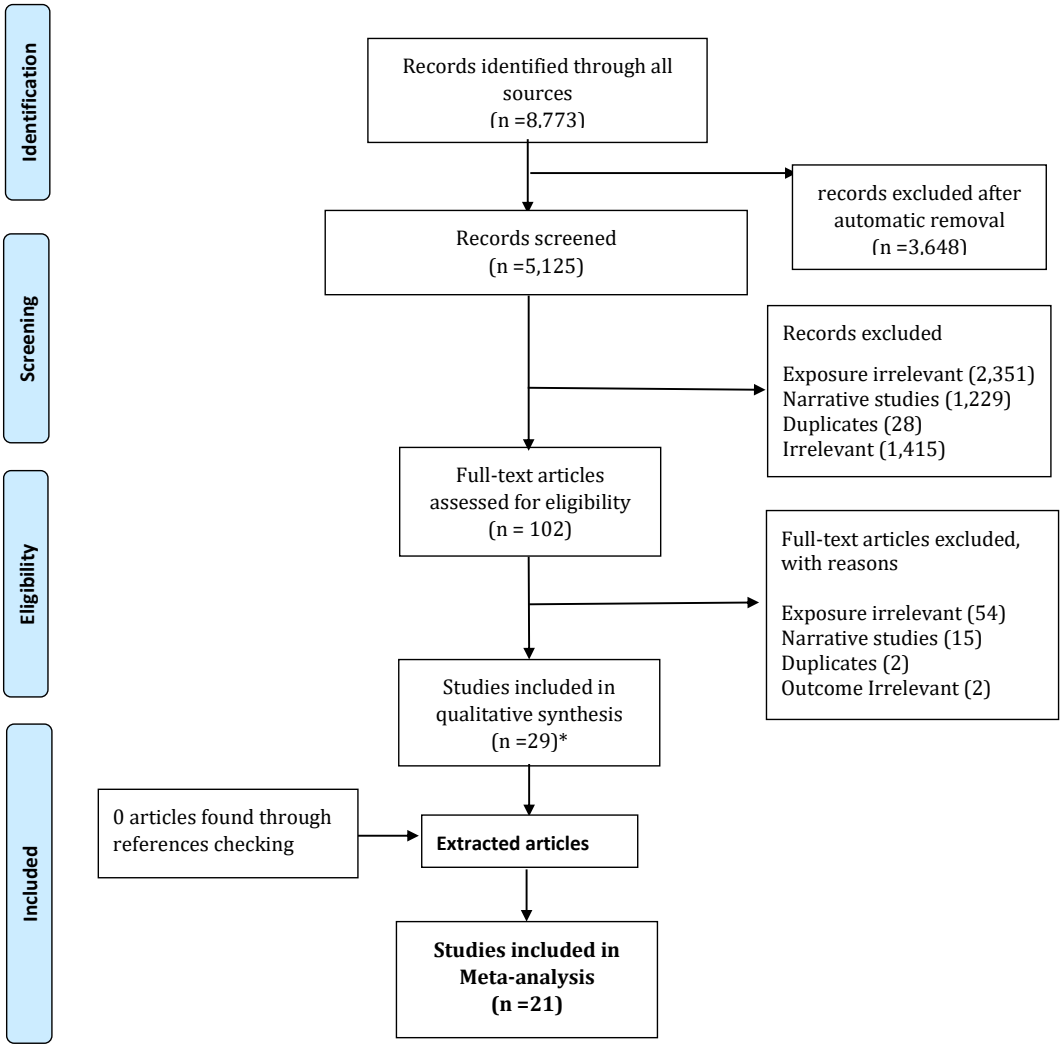
Included studies were summarized descriptively. Due to the diverse type of measures of association used and missing standard errors or confidence intervals, some studies were not included in the meta-analysis. These studies were summarized narratively.

For studies included in the meta-analysis, we calculated the overall summary estimates, including relative risks (RR), odds ratio (OR) and weighted mean difference (WMD) using random effects meta-analysis(29). Heterogeneity was quantified with the I^2 statistic(30). We also produced funnel plots to examine the potential for publication bias. Sensitivity analyses according to the risk of bias was planned but could not be done due to the low number of studies included. All analyses were performed with "*admetan*" and "*metafunnel*" packages in STATA 15(31, 32).

Results

A total of 5,125 citations were initially identified by the search strategy after de-duplication. Among them, 102 articles were selected for full text review and 29 satisfied our inclusion criteria (**Figure 2.1, eTable 2.2 Supplement materials**).

Figure 2.1: Study selection flow chart



*Including three conference abstracts and one thesis.

All included studies assessed ACS verification in the USA and, were observational, including 18 cross-sectional(8-10, 14, 16, 33-45), 10 pre-post(7, 46-54) and one time-series design(55). Mortality was the most commonly investigated outcome (n=20), followed by processes of care (n=12), resource utilization (n=12) and adverse events (n=7). A summary of study characteristics is presented in **Table 2.2.** It was not possible to compute confidence intervals for the measure of

associations in 24% (7/29) of the studies. Almost half of included studies (13/29) did not adjust for either center or patient case-mix characteristics(7, 37, 40-42, 46, 48-54), and only a third (6/18) of multicenter studies considered the clustered nature of the data in their analyses. The risk of bias was serious to critical for 22 studies, and moderate for the others (**Table 2.3**).

Mortality

Mortality was investigated in 20 articles(7-10, 14, 16, 33, 35, 36, 39, 44-47, 49-53, 55), of which 18 looked at in-hospital mortality. Thirty percent of studies (7/20) focused on pediatric injured patients, twenty percent (4/20) on adults and the rest on both. Most studies were cross-sectional (11/20) or pre-post designs (8/20), with only one time-series study. One-half of studies presented only crude estimates.

Due to the different effect measure scales used and missing standard errors, five studies were not included in the meta-analysis (**Table 2.2**). Jenkins et al(45) found that mortality increased during surgery conferences compared to non-conference dates in trauma centers lacking verification (OR 1.2; 95% CI 1.1 to 1.4). However, among verified trauma centers, no association was observed (OR 0.9; 95% CI 0.8 to 1.1). Piontek et al(47) showed a 22% reduction in standardized mortality ratio following the verification of a level II trauma center. Schubert et al(8) one of the few studies accounting for time-varying verification status during the study period, found a protective association in lower level centers (RR 0.84; 95% CI 0.72 to 0.99) for level III and (RR 0.25; 95% CI 0.12 to 0.54) for level IV. Notrica et al(39) showed that states with level I verified pediatric trauma centers (vPTCs) had 37% lower population-based pediatric injury mortality rates than states without a vPTC. The only time series analysis(55) found that the number of level I

vPTCs was protective and contributed to a decline (12%; 95% CI 4% to 18%) in the rate of change of adolescent injury mortality in the USA between 1999 and 2015. A similar, but smaller, protective effect was observed for combined adult/pediatric verified level I trauma centers.

We included 15 studies in the meta-analyses. Analyses of crude RR (n=11) showed that verification was generally associated with decreased mortality (**Figure 2.2a**). This association was also observed in analyses of adjusted estimates (n=7), except among severely injured patients, defined as those with an Injury Severity Score>24 (OR 1.1; 95% CI: 1.05 to 1.30) (**Figure 2.2b**).

Funnel plots (**Figure 2.2c and 2.2d**) indicated a certain degree of asymmetry, which was more pronounced among studies providing crude estimates, suggestive of publication bias. These figures also showed substantial variability among studies with larger sample size. The GRADE results suggest that the quality of evidence is very low (**eTable 2.3 Supplement**).

Table 2.2: Summary of study characteristics

Author (year) / Outcomes investigated	Population/Age range	Number of centers/patients	Data collection periods	Summary of results
Osler et al (2001) † • Mortality	Pediatrics (All injuries) / <18 years	53 centers /49,428 patients	1985-1996	Survival of children at verified centers is higher than at nonverified centers (OR: 0.75, 95%CI: 0.58 – 97). They cannot, however, conclude that it is the process of verification itself that improves outcomes. It is possible that only trauma centers with better results pursue verification. If this were the case, verification would recognize, but not contribute to, improved outcomes.
Hesdorffer et al (2002) † • Processes of care	Adults (TBI) / No details	411 centers/ No details	1999-2000	Surveyed all designated U.S. TCs caring for adults with severe TBI to determine the degree of guideline compliance and to identify predictors. centers. Full compliance occurred more commonly among hospitals with level I designation, a neurosurgery residency program, treatment protocols, a neurologic ICU, and ACS verification (23% vs 15%).
Demetriades et al (2006) † • Mortality	Adults (All severe injuries, ISS>15) / >14 years	256 centers/ 130,154 patients	1994-2003	Compared verified centers and non-verified centers and found that adjusted mortality in non-verified centers was higher than in level I verified centers (OR 1.09; 95%CI 1.05 to 1.13). They, however, highlighted that this finding needs cautious interpretation, because the group of non-verified centers includes facilities that are only state-designated and facilities with no trauma center designation.
Kim et al (2006) † • Mortality • Processes of care • Resources	All patients (Head injuries) / 0 to 89 years	17 centers/ 493 patients	2002-2003	There were 12 verified centers and 4 state centers. There were no associations between verification and the outcomes investigated (mortality, LOS, home discharge disposition and time to surgery).
Hesdorffer et al (2007) † • Processes of care	Adults (TBI) / No details	413 centers/ No details	2006	A web-based survey was conducted in 413 designated trauma centers admitting patients with severe TBI. Good adherence was defined as adherence to the median number of guidelines. A higher proportion of good adherence was found in verified TCS (70.6%, n=153) compared to state designated centers (60.8%, n=232).

Horton et al (2008) † • Processes of care • Resources	All patients (All injuries) / No details	156 centers/ No details	2005	Surveyed 435 trauma centers (level I and II) throughout the USA. 156 surveys were returned. ACS verification and trauma level I designation were independent predictors of recombinant factor VIIa use.
Smith et al (2011) † • Mortality • Adverse events	All patients (All injuries) /> 16 years	No details/ 519,402 patients	2002-2006	Level I verified facility were compared to state designated centers. Overall, there was no adjusted survival advantage. However, among acute respiratory distress syndrome (ARDS) cases, mortality following admission to the verified centers was lower(20.3% versus 27.1%).
Theologis et al (2012) † • Processes of care	All patients (Spine injuries)/ No details	No details	No details	They contacted trauma managers in all level I TCs in the US, to analyze institutions official C-spine clearance protocols if applicable. The response rate was 83%. Two-third of participants had an official C-spine clearance protocol. ACS verified centers had a higher rate of protocols (75%) when compared non-verified centers (54%).
Notrica et al (2012) † • Mortality	Pediatrics (All injuries) / <18 years	N. A	2008	Population-based study of state pediatric injury mortality rates (per 100,000). The availability of vPTCs and vATC in each state was determined and compared with mortality rates. Their findings highlight a protective association between state pediatric injury mortality rates and presence of Level I vPTCs..
Brown et al (2013) † • Mortality	Adults (All injuries) / >15 years	374 centers/ 900,274 patients	2007-2008	Retrospective analyses of 246 verified vs 128 state designated centers. Level I verified centers had a lower median SMR than State (0.95 [IQR 0.82–1.05] vs 1.02 [0.87–1.15]), with no difference in level II centers. Level II State centers had higher SMR outliers.
Russell et al (2015) † • Resources	Pediatrics et al (All injuries) / No details	102 centers/ No details	No details	The authors conducted a structured, telephone survey of emergency departments registered with the National Association of Children's Hospitals (NACH) and/or American verified PTC. They found that Bedside ultrasound has become largely ubiquitous for the care of children at designated pediatric trauma centers, and no significant differences between verified PTC 97% (56/58) vs only 89% for designated trauma centers (39/44).

Alarhayem et al (2015) [†] • Processes of care	Pediatrics (splenic injuries) / <17 years	No details/2,342 patients	2012	The authors found that the majority of children with splenic injuries are treated in non-verified PTC. Level I vPTCs had the highest success with non-operative management of high-grade splenic injuries (6%) followed by ACS level II vPTCs (10%) and non-verified PTC (13%).
Bogumil et al (2017)[†] • Processes of care	Pediatrics (All injuries) / <18 years	No details/475,527	2007-2014	The authors utilized the National Trauma Data Bank, to compare the prevalence of non-accidental trauma (NAT) between ACS vPTCs relative to non-ACS vPTCs to produce both crude and Injury Severity Score (ISS) adjusted prevalence ratio estimates. They found that the prevalence of NAT was higher among ACS vPTCs.
Grossman et al (2017) [†] • Mortality • Adverse events	All patients (All injuries)/All ages	94 centers/ 392,997	2012	The authors analysed a national representative sample of 94 TCs (72 verified vs 22 non-verified). Measurable benefits in complications were observed only among major trauma (ISS>25) in all age groups.
Roubik et al (2017) [†] • Mortality	All patients (Ground level fall)/ >15 year	794 centers/ 812,051	2007-2014	Retrospective analyses comparing 335 verified vs 459 state designated centers. SMR was lowest for verified level III/IV, (0.97; 95% CI 0.97 to 0.98) and highest for state level III/IV centers (1.04; 95% CI 1.04 to 1.04).
Agrawal et al (2018)[†] • Mortality • Adverse events • Resources	All patients (All injuries)/ <16 years	109 centers/ 1,504,848	2002-2009 2013-2014	After risk adjustment, a lower ICU length of stay (-0.2 ± 0.02), hospital length of stay (-0.3 ± 0.019), mortality (OR 0.94, [95% CI: 0.92 to 0.96]) and number of patients who developed complications was noted in verified centers relative to state centers.
Schubert et al (2018)[†] • Mortality • Adverse events	Adults (All injuries)/>17 years	863 centers /4,044,449 patients	2010-2015	Overall, patients admitted to verified vs state centers had similar adjusted mortality risk (RR 1.00; 95% CI 0.91 to 1.03) and unplanned return to operative room (RR 1.10; 95% CI 0.92 to 1.31), but higher unplanned intubation (RR 1.30; 95% CI 1.11 to 1.52). However, verified level III and IV facilities had lower adjusted mortality risk, with much lower mortality risk in ACS-verified level IV facilities.
Jenkins et al (2019) [†] • Mortality	Adults (All injuries) />16 years	155 centers / 94,655	2010-2011	The authors examined the association between national surgery conferences and in-hospital trauma mortality. Mortality increased significantly during meetings among trauma patients admitted to hospitals that lacked ACS trauma verification. That association was

				particularly pronounced at non-ACS verified trauma centers among patients with penetrating injuries.
Richardson et al (1997) ‡ • Mortality • Processes of care	All patients (All injuries) /No details	2 centers / 381 patients	1988 and 1995	Concurrent review of all trauma patients admitted to 2 levels III in 1988 and 1995. One hospital received level III verification, and the other had changes that lessened the general surgeon's involvement with initial evaluation and treatment. The verified center had an increase in patients transferred to the level I hospital and an increase in patient acuity. More operations were performed locally, and the care was more efficiently delivered. The other hospital had a large increase in transfers and decreased admissions locally as general surgical involvement decreased.
Piontek et al (2003) ‡ • Mortality • Adverse events • Resources	All patients (All injuries)/No details	One/7,811 patients	1993-2001	Pre-post with internal and external negative control outcomes of level II center. Results suggest that the efforts and resources consumed achieving ACS level II trauma center verification appear to result in decreased LOS (10%), reduced in-hospital mortality proportions (0.81 before versus 0.59) and reduced costs (5%).
Ehrlich et al (2005) ‡ • Processes of care	Pediatrics (All injuries) / <16 years	One/No details	1997-2002	Verification process at an already level I ATC seeking level I PTC verification affected patient care through changes in care indicators. Mortality and Injury Severity Score distributions remained unaltered. Trauma patient evaluation including radiology and disposition out of the emergency department (<120 minutes) improved. Pediatric ICU duration of stay increased and prehospital and emergency department fluid monitoring remained unsatisfactory.
Maggio et al (2009) ‡ • Mortality • Resources	All patients (All injuries)/No details	One/3,891 patients	2001 and 2007	Commitment to trauma verification had increased admissions, interfacility and transfers. Despite admitting more seriously injured patients, sustained reduction in mortality (47% in patients with ISS>24) and a trend toward decreased intensive care unit length of stay. Were observed They also found a 78% increase in revenue and a sustained increase in hospital profitability.
Norwood et al (2011)‡ • Mortality • Resources	All patients (Major torso vascular Injuries)/No details	One/274 patients	1992-2008	That center was already a level II verified centers before getting level I verification in 1998. The authors found that the commitment of hospital resources that are required to achieve Level I verification

				in a community hospital improves survival, particularly in patients with blunt and penetrating thoracic injuries (30% vs 73%).
Murphy et al (2015) ‡ • Mortality • Processes of care • Resource	Pediatrics (splenic injuries) / <16 years	No details/231 patients	1998-2012	The addition of a verified PTC within an inclusive trauma system was associated with a significant reduction of splenectomy proportions. However, they showed inconclusive results regarding mortality (RR 0.70; 95% CI 0.12 to 4.09).
Choi et al (2016) ‡ • Mortality • Adverse events • Resources	Pediatrics (All injuries) / No details	One/4,353 patients	2009-2010 and 2012-2014	Retrospective review of a level I- state-designated PTC, comparing 2 years before and 2 years after verification. Overall, there were no differences in the mean age or injury severity score. Hospital and PICU LOS, ventilator days, and mortality were also unchanged. The number of PICU admissions decreased from17.2% to 13.7%. Adverse events in the form of hospital-acquired conditions also decreased following verification, most notably through reduction in pneumonia.
Alexander et al (2018) ‡ • Mortality • Adverse events • Processes of care • Resources	Pediatrics (splenic injuries) / <18 years	One/126 patients	2005-2017	Pre-post comparison of an already verified level I ATC, following PTC verification. They found a higher rate of splenic intervention under ATC compared to PTC verification (19.6% vs 7.1%). The primary driver of this decrease was the reduction in operative rates (14.3% vs 4.3%). Average hospital LOS (7.4 vs 6.5 days) and average ICU LOS (2.7 vs 2.3 days) were similar. There was no change in hospital mortality.
Schlegel et al (2018) ‡ • Mortality • Resource	Pediatrics (All injuries) / <18 years	One/1,190 patients	2004-2016	Retrospective analysis divided into 3 chronological treatment eras: adult, early pediatric, and late pediatric trauma center after American College of Surgeons verification. A decrease in intensive care admissions was identified during late pediatric trauma center compared with early pediatric trauma center and adult trauma center (51% vs 62.4% vs 67%), but overall mortality was unchanged.
El-Shafy et al (2019) ‡ • Processes of care • Resources	Pediatrics (All injuries) / No details	One/1293 patients	2011 to 2016	Process changes associated with ACS level I pediatric verification and reductions in nonsurgical admission rate (29% in 2011 versus 5% in 2016) were also marked by a reduction in inpatient hospital length of stay(3.78 days versus 3 days).

Notrica et al (2018) [§] • Mortality	Pediatrics (All injuries) / 15 to 17 years	N. A	1999-2015	Prospective data on motor vehicle fatalities, crash characteristics, state-driving laws, and verified trauma centers were collected for the 50 U.S. states. vPTCs during the study time period are associated with a 12% decrease in the rate of change in adolescent crude fatalities.

[†]=cross-sectional; [‡] =Pre-post; [§]=Time-series; **N. A**: Not Applicable.

ACS: American college of Surgeons; **ATC**: Adult Trauma center; **ICU:** Intensive Care Unit; **ISS**: Injury severity score; **LOS**: Length of stay; PICU: pediatric intensive care unit; NAT: **PICU:** Pediatric Intensive Care Unit; **PTC**: Pediatric Trauma Center; **SMR**: Standardised mortality ratio; **TBI**: Trauma brain injuries; **vATC**: Verified Adult Trauma Center; **vPTC**: Verified Pediatric Trauma Center.

Table 2.3: Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) results

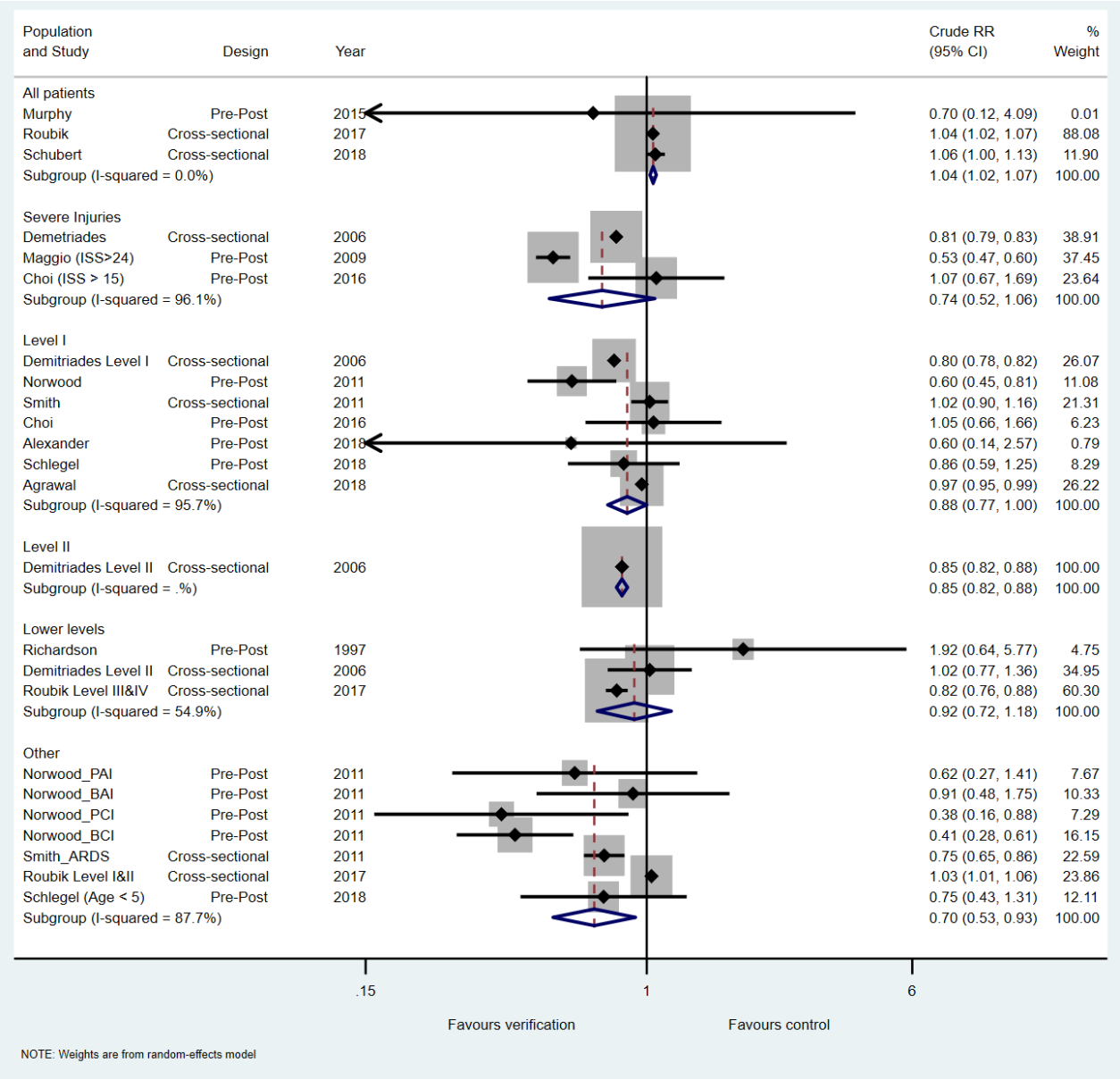
Author, year	Confounding	Selection of participants into the study	Classification of interventions	Deviations from intended of interventions	Missing data	Measurement of outcomes	Selection of the reported result	Overall bias	Direction
Osler et al 2011[†]	Serious	Serious	Serious	Serious	Serious	Low	Low	Serious	Unpredictable
Hesdorffer et al 2002[†]	Serious	Serious	Serious	NI	Serious	Moderate	Serious	Serious	Unpredictable
Demetriades et al 2006[†]	Critical	Serious	Serious	NI	NI	Low	Moderate	Serious	Favour experimental
Kim et al 2006[†]	Moderate	Serious	Moderate	Moderate	Critical	Low	Low	Moderate	Unpredictable
Hesdorffer et al 2007[†]	Critical	Serious	Critical	Low	Serious	Moderate	Serious	Serious	Unpredictable
Horton et al 2008[†]	Critical	Critical	Moderate	NI	Critical	Critical	Moderate	Critical	Unpredictable
Smith et al 2011[†]	Serious	Serious	Moderate	Moderate	NI	Low	Serious	Serious	Unpredictable
Theologis et al 2012[†]	Critical	Serious	Serious	NI	NI	Moderate	NI	Critical	Unpredictable
Notrica et al 2012[†]	Critical	Serious	Moderate	NI	NI	Moderate	Moderate	Serious	Unpredictable
Brown et al 2013[†]	Moderate	Serious	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Towards the Null
Alarhayem et al 2015[†]	Critical	Critical	Moderate	NI	NI	Low	Serious	Critical	Unpredictable
Russell et al 2015[†]	Critical	Critical	Serious	NI	NI	Critical	Moderate	Critical	Unpredictable
Bogumil et al 2017[†]	Critical	Moderate	Moderate	NI	Serious	Moderate	Low	Serious	Unpredictable
Grossman et al 2017[†]	Serious	Serious	Serious	NI	NI	Low	Moderate	Serious	Unpredictable
Roubik et al 2017[†]	Moderate	Serious	Moderate	Serious	Critical	Low	Moderate	Serious	Unpredictable

Agrawal et al 2018†	Serious	Moderate	Low	NI	Serious	Moderate	Serious	Moderate	Unpredictable
Schubert et al 2018†	Moderate	Moderate	Moderate	Low	NI	Low	Moderate	Moderate	Unpredictable
Jenkins et al 2019†	Low	Moderate	Low	NI	Serious	Moderate	Serious	Serious	Unpredictable
Richardson et al 1997‡	Critical	Low	Low	Moderate	NI	Moderate	Serious	Serious	Unpredictable
Piontek et al 2003‡	Moderate	Low	Low	Low	NI	Moderate	Moderate	Moderate	Unpredictable
Ehrlich et al 2005‡	Critical	Low	Low	Serious	NI	Moderate	Low	Serious	Unpredictable
Maggio et al 2009‡	Critical	Moderate	Moderate	Moderate	NI	Serious	Serious	Serious	Favor experimental
Norwood et al 2011‡	Critical	Low	Low	Moderate	NI	Low	Moderate	Serious	Favour experimental
Murphy et al 2015‡	Critical	Low	Low	Moderate	NI	Moderate	Moderate	Serious	Unpredictable
Choi et al 2016‡	Critical	Low	Moderate	Moderate	NI	Low	Moderate	Serious	Favour Comparator
Alexander et al 2018‡	Serious	Low	Low	Low	NI	Moderate	Serious	Moderate	Favour experimental
Schlegel et al 2018‡	Critical	Low	Low	Moderate	NI	Moderate	Moderate	Serious	Favour experimental
El-Shafy et al 2019‡	Critical	Low	Low	Moderate	NI	Moderate	Moderate	Serious	Unpredictable
Notrica et al 2018§	Moderate	Moderate	Moderate	NI	Serious	Low	Moderate	Moderate	Unpredictable

†=cross-sectional; ‡=Pre-post; §=Time-series; **NI**: No Information.

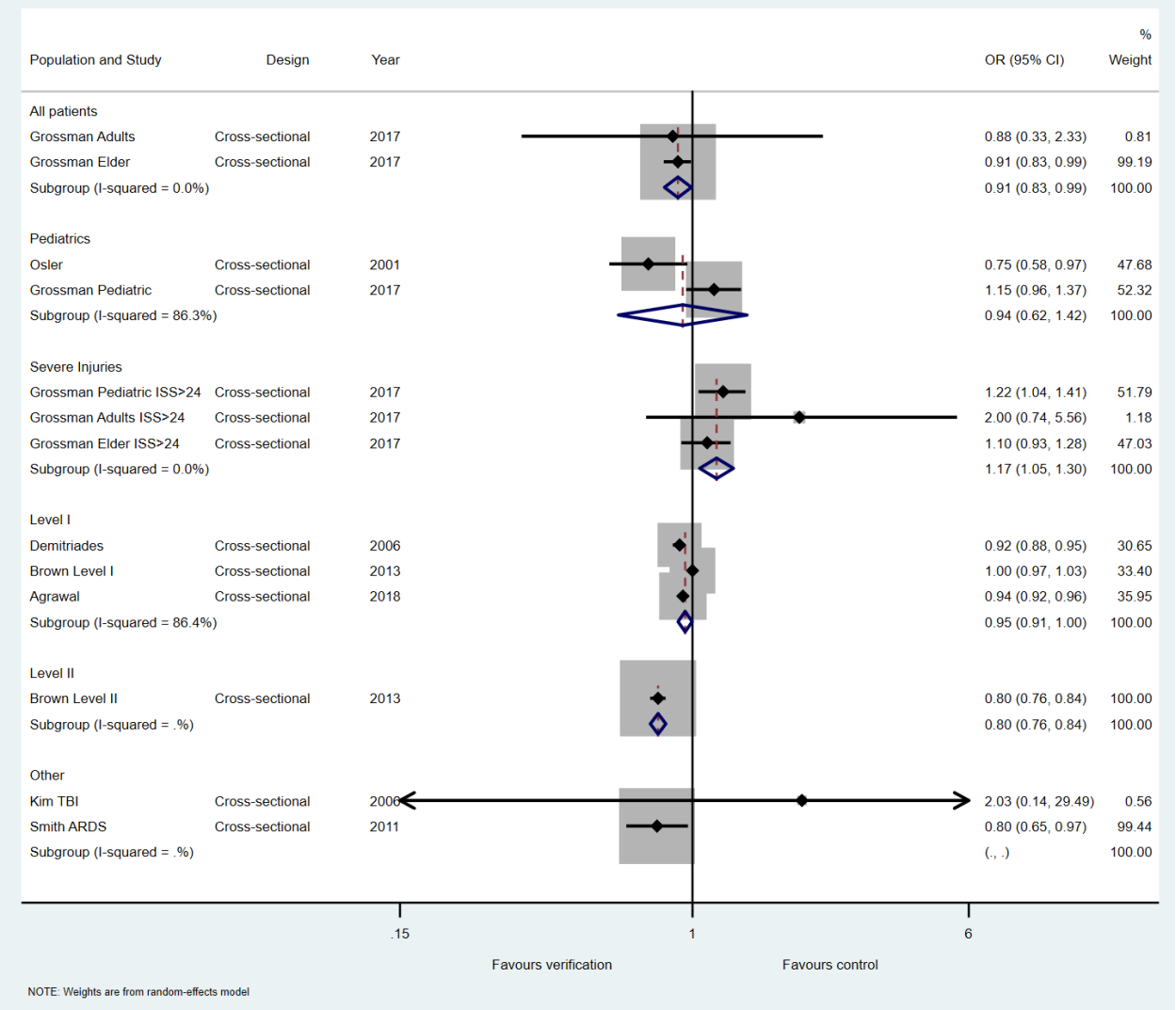
Figure 2.2

A : Metanalysis of crude association between trauma center verification and in-hospital mortality



ARDS: Acquired Respiratory Distress Syndrome; **BAI**: Blunt Abdominal Injuries; **BCI**: Blunt Cardiovascular Injuries; **CI**: Confidence Intervals; **ISS**: Injury Severity Score; **PAI**: Penetrating Abdominal Injuries; **PCI**: Penetrating Cardiovascular Injuries; **RR**: Relative Risks.

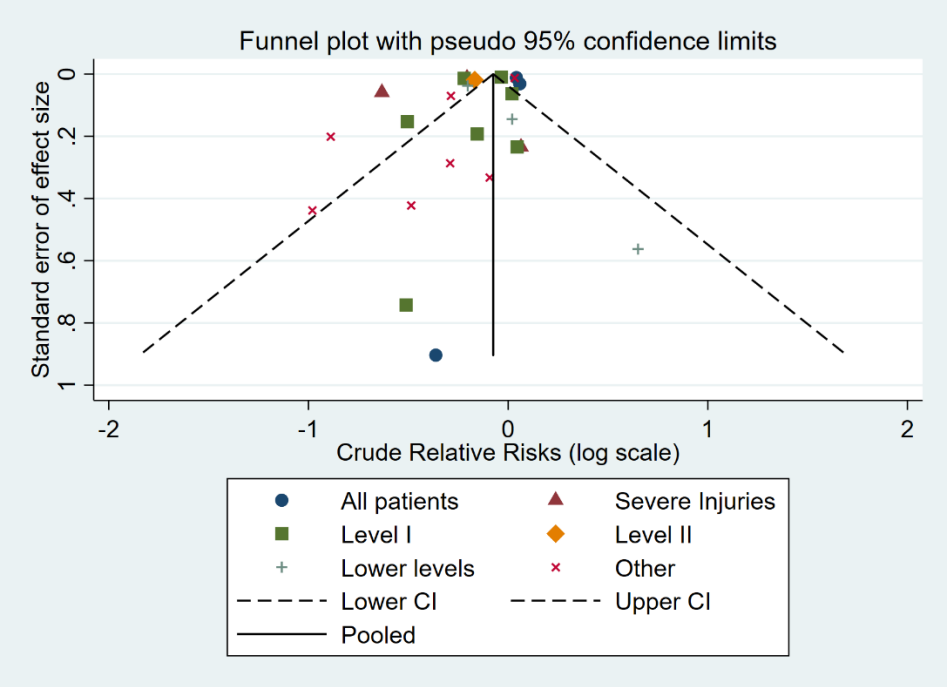
B : Metanalysis of risk-adjusted association between trauma center verification and in-hospital mortality



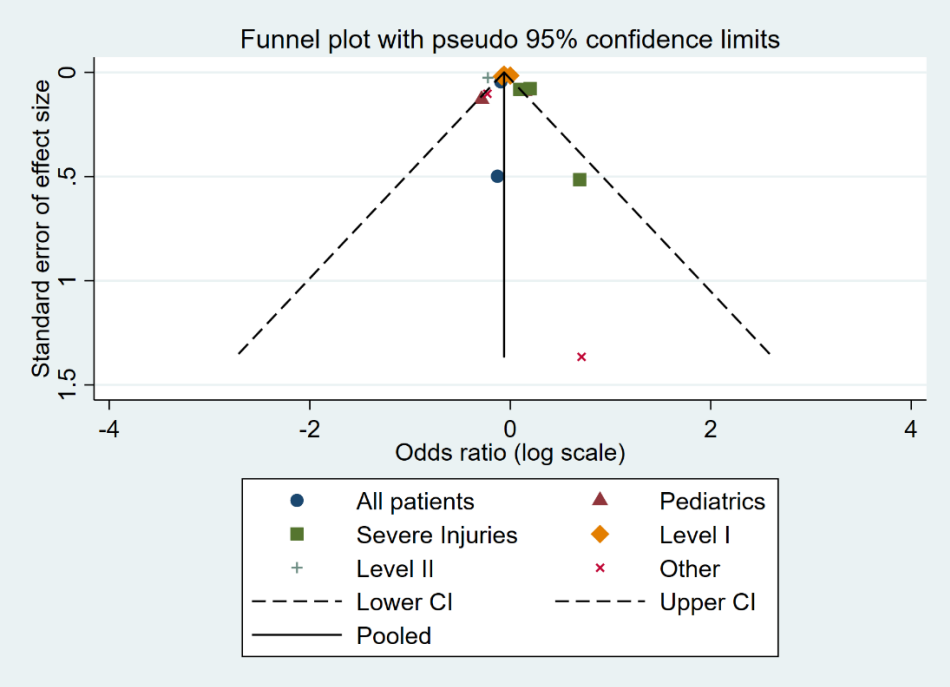
ISS: Injury Severity Score; **OR**: Odds Ratio; **TBI**: Trauma Brain Injuries.

Odds Ratios are presented instead of relative risks because it was the effect measure reported by studies with adjusted analyses, and they did not provide enough details to compute adjusted relative risks.

C : Funnel plot of studies reporting the crude association between trauma center verification and in-hospital mortality



D : Funnel plot of studies reporting the adjusted association between trauma center verification and in-hospital mortality



Resource Utilization

Length of stay (LOS), including overall and Intensive Care Unit (ICU), were the most studied outcomes in this category (10/12)(7, 10, 36, 47, 49-54). Other outcomes were blood products transfused, hospital charges, mechanical ventilation, bedside use of ultrasound, and recombinant factor VIIa(rFVIIa) use(38, 42). Half of studies (6/12) focused on pediatric injured patients. Only four studies adjusted for at least one potential confounder.

We meta-analyzed seven studies assessing LOS. Three studies described the distribution of LOS using the median and the interquartile range, while four presented the mean and standard deviation. We used a well-established technique to combine results reported on log-transformed or raw scales(24, 25) to conduct the analysis. Because of the skewed distribution of LOS, only weighted mean differences of the log-transformed LOS (which can be interpreted as the geometric mean ratio when exponentiated) were computed. Our results suggest that ACS verification was associated with longer ICU LOS. This association, however, was not observed with hospital LOS (**Figure 2.3a**).

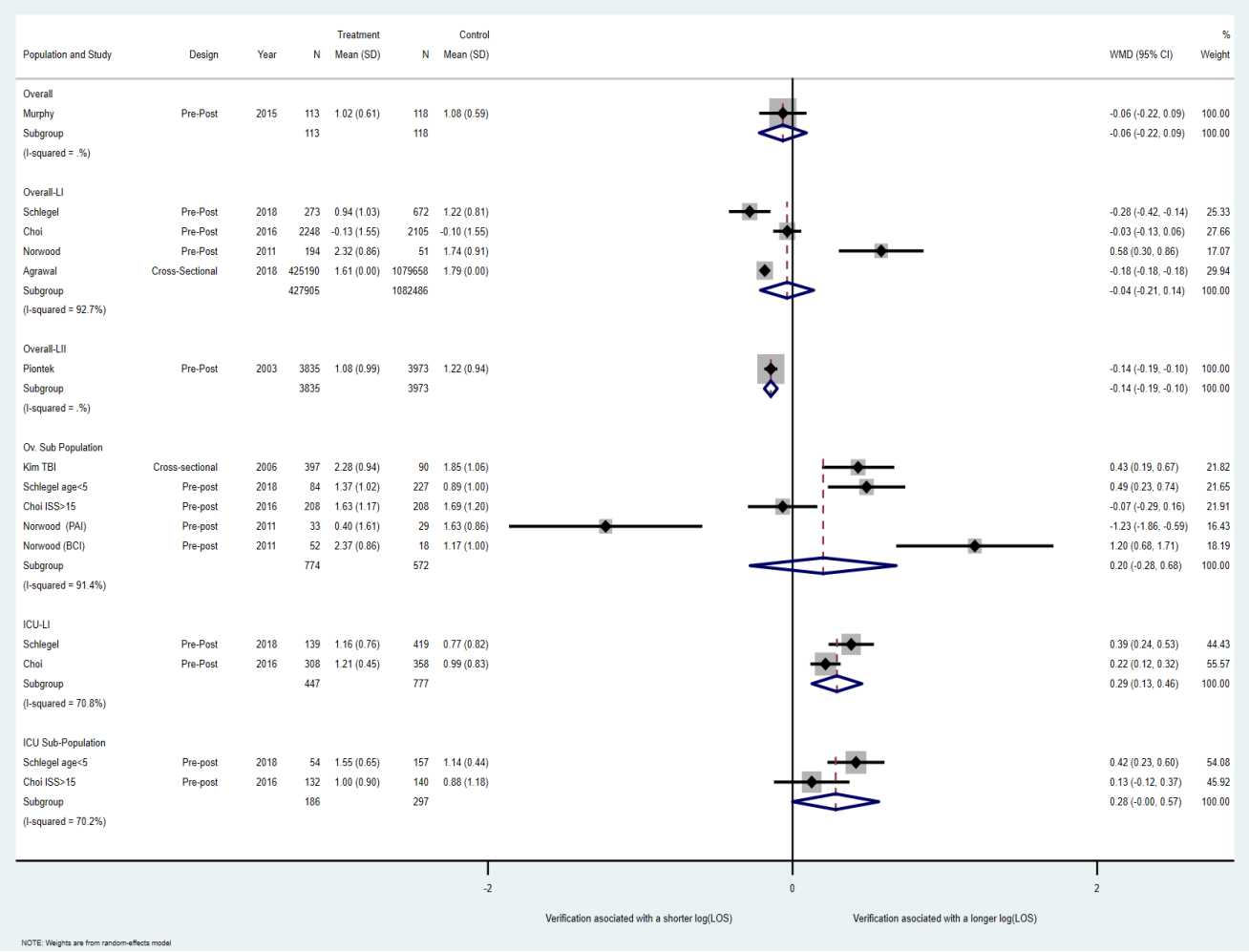
Funnel plots displayed asymmetry, in favour of studies with an increased LOS among verified centers (**Figure 2.3b**). Our GRADE assessment suggested that the evidence was of very low quality (**eTable 2.3 Supplement)**.

Studies excluded from meta-analysis showed mixed and inconsistent results concerning the association between verification and different resources. For instance, Alexander et al(52) found that pediatric verification was associated with a decrease in the average number of blood products transfused per patient (7.2 units vs 2.4 units; 95% CI -10.1 to 0.6). They also found a

decrease in professional charges (-$16,171; 95% CI -30,898 to -1,362). Piontek et al(47) found that after the verification of a level II trauma center, there was an increase in ventilation use (RR 1.30; 95% CI 1.12 to 1.51). Finally, Horton et al(38) surveyed Level I and II trauma centers and found that ACS verification was a predictor of rFVIIa use (OR 3.74; 95% CI 1.53 to 9.09), cf. (**Table 2.2**).

Figures 2.3

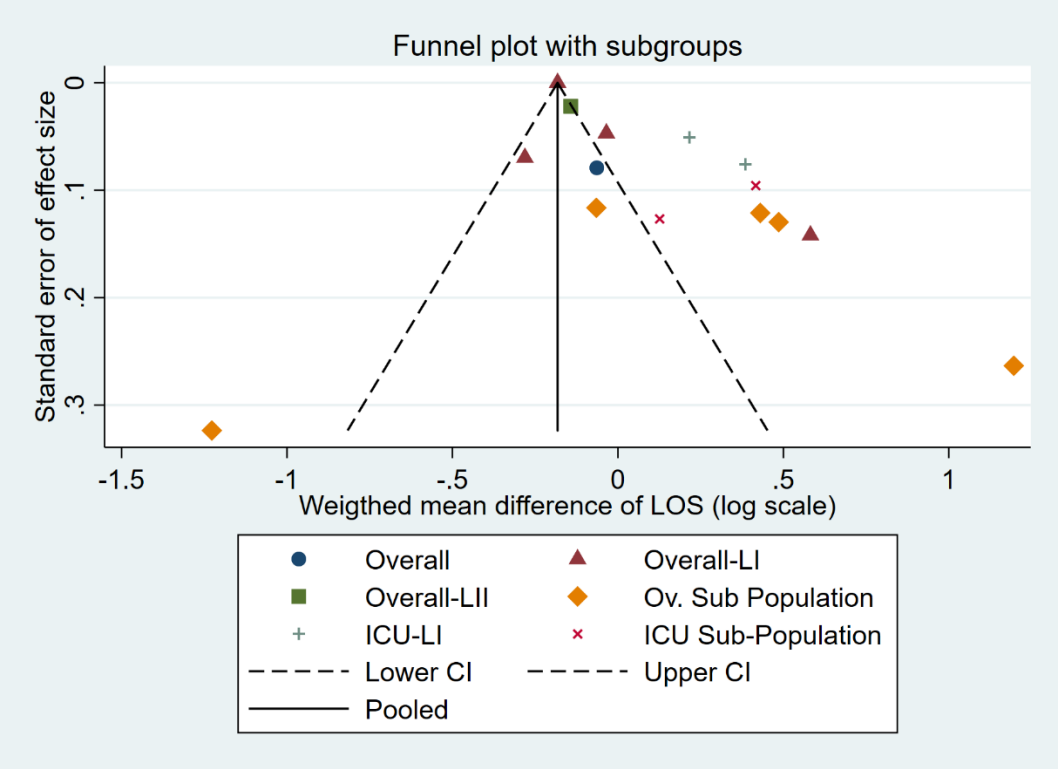
A : Metanalysis of studies reporting the association between trauma center verification and length of stay (log scale)



BCI: Blunt Cardiovascular Injuries; **CI**: Confidence Intervals; **ICU:** Intensive Care Unit; **ISS**: Injury Severity Score; **Ov. Sub Population**: Total length of stay estimate in a sub group**; PAI**: Penetrating Abdominal Injuries; **WMD**: Weighted Mean Differences.

Exponentiate of weighted mean differences can be interpreted as geometric mean ratio.

B : Funnel plot of studies reporting the association between trauma center verification and length of stay (log scale)



ICU: Intensive Care Unit; **LOS:** Length of Stay; **Ov. Sub Population**: Total length of stay estimate in a sub group**.**

Adverse Events

Among the seven studies included in this category(7-10, 14, 47, 52), three adjusted for potential confounders(8, 10, 14). Four studies were cross-sectional and three pre-post designs. Two studies focused on pediatric injured patients, one on adults and the remaining on both. Investigated outcomes included a wide range of complications such as pneumonia, pulmonary emboli, unplanned intubation, unplanned return to the operative room, and unplanned readmissions.

Adverse events results were not meta-analyzed due to the diversity of outcomes investigated but are reported narratively. Agrawal et al(10) after risk adjustment, found a lower odd of complications in verified centers compared to state centers (OR 0.88; 95% CI 0.87 to 0.90).

Schubert et al(8) found a positive association between verified centers and unplanned intubation, especially among level I trauma centers (RR 1.53; 95% CI 1.11 to 1.65) after adjusting for hospital and patient characteristics. Also, they did not observe an association between verification and unplanned return to the operative room. Following the verification of a level II trauma center, Piontek et al(47) found low evidence for changes in the incidence of complications (RR 1.27; 95% CI 0.86 to 1.89) or unplanned 30-day readmissions (RR 0.91; 95% CI 0.77 to 1.08). Likewise, in an already verified adult level I center, Alexander et al(52) did not find association between pediatric "re-verification" and unplanned 30-day readmissions. The low number patients (n=126) and readmissions (n=2), however, limit the interpretation of their findings. On the other hand, Choi et al(7) found a decrease in unplanned hospital readmissions (RR 0.36; 95% CI 0.15 to 0.87) and hospital-acquired pneumonia (RR 0.41; 95% CI 0.17 to 0.99) two years following verification of a level I trauma center. Grossman et al(14) found that verified trauma centers had a lower incidence of major complications (based on the National Trauma Data Bank definition)(56) than non-verified trauma centers, using a representative sample (n=94) of USA trauma centers. This association was higher among elders (OR 0.40; 95% CI 0.27 to 0.60) and pediatric patients (OR 0.23; 95% CI 0.12 to 0.47) with an Injury Severity Score >24. Finally, Smith et al(9) observed fewer acute respiratory distress syndrome cases in verified level I trauma centers than state centers (RR 0.91; 95% CI 0.84 to 0.99) (**Table 2.2**).

Processes of Care

Four of the 12 included studies adjusted for at least one potential confounder(36, 37, 43, 54). Six studies focused on pediatric injured patients(41, 43, 48, 51, 52, 54), two on adults(34, 37) and the

rest on both(36, 38, 40, 46). There were seven cross-sectional studies and the rest were pre-post designs. We did not conduct a meta-analysis due to the diversity of outcomes investigated.

In the pediatric population, reduction in the incidence of splenectomy were found by Murphy et al (2.7% among verified vs 11% non-verified trauma centers)(51) and Alarhayem et al (6% among verified vs 13% non-verified trauma centers)(41) following verification of a pediatric level 1 center. Among children with blunt splenic injuries, Alexander et al(52) observed a decrease in splenic interventions (i.e. splenectomy, splenorrhaphy, or embolization) following pediatric verification (RR 0.36; 95% CI 0.13 to 0.99). Ehrlich et al(48) observed an improvement in pediatric trauma patient evaluation (including radiology) and emergency department discharge (<120 minutes) following the verification of a combined adult/pediatric level I trauma center. Finally, Bogumil et al(43) observed a higher prevalence ratio (PR) of non-accidental trauma in verified pediatric centers compared to non-verified centers (PR 1.81; 95% CI 1.73 to 1.90). This association was higher in level I (PR 1.89; 95% CI 1.80 to 1.98) than level II centers (PR 1.62; 95% CI 1.51 to 1.75).

Surveys of all designated USA trauma centers in 2000 and 2006, showed that verified trauma centers had a higher likelihood of full compliance to published guidelines for the management of severe traumatic brain injury for the years 2000 (OR 5.1; 95% CI 1.1 to 23) and 2006 (OR 1.55; 95% CI: 1.00 to 2.40), respectively(34, 37). Similarly, Theologis et al(40) found that verified level I trauma centers had a higher proportion of compliance to C-spine clearance protocol presence (75%) when compared to non-verified centers (54%). Kim et al(36) did not find any association between verification and time to surgery in patients with head injuries. Richardson et al(46) found

that the verification of a level III trauma center was associated with an increase in the proportion of admission of transferred patients into a referent level I center (RR 1.19; 95% CI 1.03 to 1.36), cf. (**Table 2.2**).

Discussion

Main Findings

This systematic review synthesized, both quantitatively and narratively, evidence on the association between trauma center verification and in-hospital mortality, adverse events, resource utilization and processes of care. This review found mixed and inconsistent results on the association between ACS verification and all outcomes studied. Nonetheless, verification was imprecisely associated with decreased mortality and longer LOS. Finally, some evidence pointed to positive associations between verification and some processes of care, including adherence to published guidelines and reductions in the occurrence of complications. These findings, however, should be interpreted with caution given serious methodological concerns about the quality of the empirical evidence.

First, the inference of the obtained estimates is limited by the unclear nature of the "control group" in each study. For instance, in cross-sectional studies (18/29) it was not possible to distinguish those that failed during the verification process from those that never applied among non-verified centers. In addition, a quarter of multicenter studies (5/18) combined centers that had no trauma designation and state-designated centers as non-verified centers. The results obtained from these studies would be neither intention to treat nor per protocol estimates, if we placed ourselves in a trial framework. This issue leads to selection and healthy user biases, in the

sense that high-performing centers might be more willing to seek verification than low-performing centers. This may affect the validity and generalizability of the observed associations. It is important to note that not all included studies assessed the impact of verification as their primary objective.

Although pre-post studies are less vulnerable to the biases mentioned above, they cannot account for the underlying trend in the measured outcomes before verification(57), which can bias estimates in either direction. An interesting alternative to assess verification benefits would be the use of quasi-experimental designs such as differences in differences and interrupted time-series, frequently used to assess the impact of policy and other population-level interventions in health research. These methods can account for unobservable or unmeasured variables that are fixed over time, and for underlying trends in outcomes(58, 59).

Second, preparation for the verification visits might lead to improvements in measured outcomes and therefore bias the estimates. Only three studies(7, 48, 53) accounted for this, either by removing the period just before the verification in their analysis or via stratification. In fact, among the 73 articles excluded from our review, six(60-65) were excluded because they only assessed the preparation for verification visits.

Finally, issues related analytical methods might have biased the results. For instance, 45% of studies did not adjust for center level or patient-level risk factors. The latter is necessary to account for the changing epidemiology of trauma population (for example due to population ageing and possible change in referral patterns generally attributed to increased marketability(7). Additionally, several papers reported odds ratios as a measure of the association, which are

known to overestimate relative risks, especially when the outcome is common(66). Only one third (6/18) of multicenter studies accounted for it in their analysis, which may lead to type I errors and confidence intervals that are too narrow(33). Also, the competing risk of death was not considered when assessing LOS and missing data was rarely handled appropriately (**Table 2.3**).

Our findings are similar to those observed in previous systematic reviews assessing verification in other healthcare fields(67-71), which concluded that many of the studies were heterogeneous, highly vulnerable to confounding, and added little clarity or guidance. They also highlighted significant methodological challenges such as self-selection and lack of robust controls, limiting their inference.

Limitations

There are some limitations related to the review itself that are noteworthy. Although the uptake of verification is rising worldwide, all included articles were from the USA. Pediatric trauma patients were overrepresented, whereas the vast majority of injuries and deaths are non-pediatric. Altogether, despite the absence of language, country or population restrictions and grey literature searches(20). The inclusion of multiple study designs, while providing a more comprehensive assessment of the relevant literature, does introduce significant heterogeneity that in turn affects the robustness of meta-analysis estimates. Our choice of random-effects meta-analysis was based on the assumption that there might not be a common RR or OR applicable to all trauma populations(72). The low number of studies included in our meta-analysis make it difficult to properly summarize estimates and interpret funnel plots. Nonetheless, publication bias seems to be more likely in crude than in adjusted analysis. We also noted that

several large studies fell outside the projected lines of the funnel plots, indicating substantial variability among studies with small standard errors(73). We were unable to stratify our results by time, since trauma verification standards has evolved with time, which may have introduced a bias(3). Studies were excluded from meta-analyses due to missing confidence intervals or standard errors and the scale of effect measure used, despite our efforts to compute desired statistics when raw data were available. Finally, the quality and the strength of the cumulative evidence (using the GRADE framework) was very low(74).

Conclusion

Our review illustrated the inability to extrapolate or infer causality on trauma center verification effectiveness from the published literature due to significant methodological challenges, such as the lack of robust controls and the concentration of all the available studies in the USA. Considering the prevalence and spread of trauma verification globally, this systematic review and meta-analysis underscores the need for quasi-experimental studies that assess the impact of trauma center verification on changes in clinical processes of care and outcomes. Such studies could provide solid evidence to guide policy-making and individual hospitals' decisions to seek verification.

Ethics approval and consent to participate

We have received ethics approval for this project from McGill University Faculty of Medicine Research Ethics committee.

Authors' Contributions

BB, LM, AN, MC, PA led the development of the protocol. BB, LM and AN contributed to the development of research objectives, elaborated inclusion criteria and clinically significant outcomes. BB and MC conducted data extraction, data synthesis, data analysis and drafted the manuscript. AN, PA, LM and HC revised the manuscript and approved the final version.

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2.3 Supplemental material: Manuscript 1

eFigure 2.1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	34
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	36
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	37
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	37
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	38-39
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	38
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	eTable 2.1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	39
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	39
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	39
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	40
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	40
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	40
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	40
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	40
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	41; Figure 2.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2.2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2.3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	41-53; Figures (2.2a,2.2b,2.3)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures (2.2a,2.2b,2.3)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2.3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figures (2.2a,2.2b,2.3)
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	59-60
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	61
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	62
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title Page

eTable 2.1: Search strategy

EMBASE

1. exp emergency health service/
2. (trauma adj (system* or care or network* or health care or model* or center* or centre* or service*)).tw,kf
3. (injury adj (system* or care or network* or health care or model* or center* or centre* or service*)).tw,kf.
4. 1 or 2 or 3
5. quality assuran*/ or quality improv*/ or benchmark*/ or clinical audit*.tw,kf. or medical audit*.tw,kf.
6. licensing/ or professional standard/ or certification/ or recertification/
7. "american college of surgeon*".tw,kf.
8. "trauma association of canada".tw,kf.
9. accreditation canada.tw,kf.
10. INESSS.tw,kf.
11. "Institut national d'excellence en santé et en services sociaux".tw,kf.
12. (designated or designation or designate).tw,kf.
13. (accredited or accreditation).tw,kf.
14. (verified or verification or reverification).tw,kf.
15. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 4 and 15
17. remove duplicates from 16

MEDLINE

1. exp Trauma Centers/
2. (trauma adj (system* or network* or care or health care or model* or center* or centre* or service*)).tw,kf.
3. (injury adj (system* or care or network* or health care or model* or center* or centre* or service*)).tw,kf.
4. 1 or 2 or 3
5. exp Benchmarking/
6. clinical audit/ or exp medical audit/
7. quality assuran*/ or quality improv*/ or benchmark*/ or clinical audit*.tw,kf. or medical audit*.tw,kf.
8. (accredited or accreditation).tw,kf.
9. (verified or verification or reverification).tw,kf.
10. "american college of surgeon*".tw,kf.
11. "trauma association of canada".tw,kf.
12. accreditation canada.tw,kf.
13. INESSS.tw,kf.
14. "Institut national d'excellence en santé et en services sociaux".tw,kf.
15. (designated or designation or designate).tw,kf.
16. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. 4 and 16
18. remove duplicates from 17

HEALTHSTAR

1. Trauma Centers/
2. (trauma adj (system* or care or network* or health care or model* or center* or centre* or service*)).tw,kf.
3. (injury adj (system* or care or network* or health care or model* or center* or centre* or service*)).tw,kf.
4. 1 or 2 or 3
5. Benchmarking/
6. clinical audit/ or exp medical audit/
7. quality assuran*/ or quality improv*/ or benchmark*/ or clinical audit*.tw,kf. or medical audit*.tw,kf.
8. accreditation/ or certification/ or licensure/
9. (accredited or accreditation).tw,kf.
10. (verified or verification or reverification).tw,kf.
11. "american college of surgeon*".tw,kf.
12. "trauma association of canada".tw,kf.
13. accreditation canada.tw,kf.
14. INESSS.tw,kf.
15. "Institut national d'excellence en santé et en services sociaux".tw,kf.
16. (designated or designation or designate).tw,kf.
17. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 4 and 17
19. remove duplicates from 18

CINAHL

S1	TI (trauma N1 (system* or network* or care or "health care" or model* or center* or centre* or service*)) OR AB (trauma N1 (system* or network* or care or "health care" or model* or center* or centre* or service*))
S2	TI (injury N1 (system* or network* or care or "health care" or model* or center* or centre* or service*)) OR AB (injury N1 (system* or network* or care or "health care" or model* or center* or centre* or service*))
S3	S1 OR S2
S4	(MH "Accreditation+") OR (MH "American Accreditation Healthcare Commission")
S5	"""'accredited'' OR "accreditation"""
S6	(MH "Quality Assurance") OR "''clinical audit'' or ''quality assurance''
S7	(MH "Benchmarking") OR "benchmarking" OR (MH "Process Assessment (Health Care)+")
S8	""designation""
S9	""American College of Surgeons""
S10	""Trauma Association of Canada""
S11	""Accreditation Canada""
S12	""INESSS""
S13	""Institut national d'excellence en santé et en services sociaux""
S14	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S15	S3 AND S14

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((ti(accredited OR accreditation) OR ab(accredited OR accreditation)) OR (ti(verified OR verification OR reverification) OR ab(verified OR verification OR reverification)) OR (ti("clinical audit" OR benchmarking) OR ab("clinical audit" OR benchmarking)) OR (ti(designation OR designated) OR ab(designation OR designated)) OR (ti("American College of Surgeons") OR ab("American College of Surgeons")) OR (ti("Trauma Association of Canada") OR ab("Trauma Association of Canada")) OR (ti("Accreditation Canada") OR ab("Accreditation Canada")) OR (ti("Institut national d'excellence en santé et en services sociaux") OR ab("Institut national d'excellence en santé et en services sociaux")) OR (ti("INESSS") OR ab("INESSS"))) AND ((ti(trauma NEAR/1 (system* OR network* OR care OR "health care" OR model* OR center* OR centre* OR service*)) OR ab(trauma NEAR/1 (system* OR network* OR care OR "health care" OR model* OR center* OR centre* OR service*))) OR (ti(Injur* NEAR/1 (system* OR network* OR care OR "health care" OR model* OR center* OR centre* OR service*)) OR ab(Injur* NEAR/1 (system* OR network* OR care OR "health care" OR model* OR center* OR centre* OR service*))))

List of key injury organisations

The American College of Surgeons, Trauma Association of Canada, International Association for Trauma Surgery and Intensive Care, Australasian Trauma Society, Trauma Audit Research Network, American Association for the Surgery of Trauma, Eastern Association for the Surgery of Trauma, American Trauma Society, British Trauma Society, Orthopaedic Trauma Association, Western Trauma Association, Trauma.org, The Society of Trauma Nurses, International Trauma Anaesthesia and Critical Care Society, BrainTrauma Foundation.

eTable 2.2: Reason for the exclusion of full-text reviewed studies

Author, Year	Title	Reason for exclusion
Anonymous, 1988(49)	Pediatric trauma standards: Pennsylvania Trauma Systems Foundation standards for trauma center accreditation	Narrative studies, they listed the standard requirements for pediatrics verification.
Berk, 1994(50)	Infection control for health care workers caring for critically injured patients: A national survey	Exposure Irrelevant.
Howell, 1996(51)	Level I trauma certification and emergency medicine resident major trauma experience	Exposure Irrelevant, compared verified Level 1 to all other centers.
Buechler, 1998(52)	Variation among trauma centers' calculation of Glasgow Coma Scale score: results of a national survey	Exposure Irrelevant.
Nichols, 1997(53)	Magnetic resonance imaging: utilization in the management of central nervous system trauma	Exposure Irrelevant.
Gagneux, 1998(54)	Trauma emergency unit: long term evaluation of a quality assurance programme	Exposure irrelevant, assessed the effect of a self-established quality assurance program in an emergency department.
DiRusso, 2001(55)	Preparation and achievement of American College of Surgeons Level I trauma verification raises hospital performance and improves patient outcome	Exposure Irrelevant, assessed preparation to verification.
Nathens, 2001(56)	The relationship between trauma center volume and outcome	Exposure irrelevant.
Pasquale, 2001(57)	Outcome analysis of Pennsylvania trauma centers: Factors predictive of nonsurvival in seriously injured patients	Exposure Irrelevant
Rogers, 2001(58)	Population-based study of hospital trauma care in a rural state without a formal trauma system	Exposure Irrelevant, compared verified Level 1 to non-designated centers.
Abernathy, 2002(59)	Impact of a voluntary trauma system on mortality, length of stay, and cost at a Level I trauma center	Exposure Irrelevant.
Ehrlich, 2002(60)	American College of Surgeons, Committee on Trauma verification review: Does it really make a difference?	Exposure irrelevant, assessed preparation to verification.
Ehrlich, 2002(61)	The need for a statewide pediatric trauma program	Exposure irrelevant.
Meldom, 2002(62)	Trauma in the very elderly: A community-based study of outcomes at trauma and nontrauma centers	Exposure Irrelevant, compared verified centers to non-designated hospitals.
Simons, 2002(19)	Relative importance of designation and accreditation of trauma centers during evolution of a regional trauma system	Exposure irrelevant, accreditation occurred after the end of the study.

Ciraulo, 2004(63)	A survey assessment of the level of preparedness for domestic terrorism and mass casualty incidents among Eastern Association for the Surgery of Trauma Members	Exposure Irrelevant.
Simons, 2004(64)	Optimising trauma care: Role of trauma systems and trauma centres	Narrative studies.
Biffl, 2005(65)	The evolution of trauma care at a Level I trauma center	Exposure irrelevant, unable to attribute the change to verification which occurred in 1995 while the post period started in 1999.
Demetriades, 2005(66)	The effect of trauma center designation and trauma volume on outcome in specific severe injuries	Exposure irrelevant, compared level II verified centers to other verified III or IV and non-verified centers.
Bowman, 2006(67)	Hospital characteristics associated with trauma outcomes	Exposure irrelevant.
DeBritz, 2006(42)	The impact of trauma centre accreditation on patient outcome	Narrative studies.
Eldich, 2006(68)	Level I trauma certification and emergency medicine resident major trauma experience	Narrative studies.
Nathens, 2006(69)	The delivery of critical care services in US trauma centers: is the standard being met?	Exposure irrelevant, described Intensive Unit Care standards.
Udekwu, 2006(70)	Trauma Center Designation and Outcomes	Narrative studies, letter to editor.
Shackford, 2007(71)	The increasing use of vena cava filters in adult trauma victims: data from the American College of Surgeons National Trauma Data Bank	Exposure Irrelevant, all included centers were verified.
DuBose, 2008(72)	Effect of trauma center designation on outcome in patients with severe traumatic brain injury	Exposure Irrelevant, compared Level I versus Level II verified centers.
Fang, 2008(73)	Critical care at Landstuhl Regional Medical Center	Narrative studies
Shafi, 2008(74)	Trauma quality improvement using risk-adjusted outcomes	Exposure irrelevant, compared outcomes among verified ACS centers.
Terrell, 2008(75)	Nationwide Survey of Alcohol Screening and Brief Intervention Practices at US Level I Trauma Centers	Narrative studies, the part comparing verified to non-verified centers was narrative.
DuBose, 2009(76)	American College of Surgeons trauma centre designation and mechanical ventilation outcomes	Exposure irrelevant, compared Level I versus Level II verified centers.
Mikhail, 2009(77)	Midlevel practitioner role evolution in an American College of Surgeons-verified trauma surgery service: the 23-year experience at Hurley Medical Center	Narrative studies.

Milham, 2009(78)	Are there racial disparities in trauma care?	Exposure irrelevant, look at outcomes difference due to race irrespective of verification status.
Nance, 2009(79)	Access to pediatric trauma care in the United States	Exposure irrelevant, assessed access to care.
Recinos, 2009(80)	ACS trauma centre designation and outcomes of post-traumatic ARDS: NTDB analysis and implications for trauma quality improvement	Exposure Irrelevant, compared Level I versus Level II verified centers.
Ropele, 2009(81)	Cervical spine clearance in the non-alert, non-communicative, or unreliable pediatric blunt trauma patient	Exposure Irrelevant, just described current practices for clearing the cervical spine in a special pediatric population.
Salottolo, 2009(82)	Effects of a nonsurgical hospitalist service on trauma patient outcomes	Exposure irrelevant.
Bennett, 2010(83)	The volume-outcomes relationship for United States level one trauma centers	Duplicate.
Brown, 2010(84)	Trauma center designation correlates with functional independence after severe but not moderate traumatic brain injury	Exposure Irrelevant, compared Level I versus Level II.
Cudnik, 2010(85)	Are all trauma centers created equally? A statewide analysis	Exposure irrelevant, all included centers were verified.
Hemmilia, 2010(86)	The trauma quality improvement program: pilot study and initial demonstration of feasibility	Exposure Irrelevant.
Nyberg, 2010(87)	A national survey: acceptance of physician assistants and nurse practitioners in trauma centers	Outcome irrelevant, no patient outcomes.
DuBose, 2011(88)	The relationship between post-traumatic ventilator-associated pneumonia outcomes and American College of Surgeons trauma centre designation	Exposure Irrelevant, compared Level I versus Level II verified centers.
Bennett, 2011(89)	The volume-outcomes relationship for United States level I trauma centers	Narrative studies, comparison between verified and non-verified centers.
Kesler, 2011(90)	Demographic factors and outcomes in patients with epidural hematoma	Narrative studies.
Plurard, 2011(91)	Trauma center designation and the decreasing incidence of post-traumatic acute respiratory distress syndrome: A potential guidepost for quality improvement	Exposure Irrelevant.
Testerman, 2011(92)	Full-time orthopedic traumatologists enhance rural trauma center pelvic fracture outcomes and financials	Exposure irrelevant, assessed preparation to preparation.
Bailey, 2012(93)	Verification and Regionalization of Trauma Systems. The Impact of These Efforts on Trauma Care in the United States	Narrative studies.

Bukur, 2012(94)	The impact of American College of Surgeons trauma center designation and outcomes after early thoracotomy: A national trauma databank analysis	Exposure Irrelevant, assessed differences between levels of verified centers.
Moore, 2013(95)	Evaluating trauma center structural performance: The experience of a Canadian provincial trauma system	Exposure irrelevant.
Anonymous, 2014(96)	Hasbro designated Level 1 Pediatric Trauma Center by ACS	Narrative studies
Badjie, 2014(97)	Metamorphosis of a massive blood transfusion protocol at a level I trauma center	Exposure Irrelevant, no comparison of outcomes before and after verification.
Balogh, 2014(43)	Trauma verification: for the trauma centre or for the trauma system?	Narrative studies which described Australia verification process.
Carr, 2014(98)	Impact of adding Level II and III trauma centers on volume and disease severity at a nearby Level I trauma center	Exposure Irrelevant, assessed the impact of the designation of new centers on patient volume of an existing center.
Clark, 2014(99)	The effect of hospital care on early survival after penetrating trauma	Exposure irrelevant, they compared verified level I to all other hospitals which may include verified level II.
Guess, 2014(100)	Do level I trauma centers address the psychological responses associated with trauma?	Narrative studies.
Kim, 2014(101)	Relationship of trauma centre characteristics and patient outcomes: a systematic review	Narrative studies.
Shafi, 2014(36)	Compliance with recommended care at trauma centers: Association with patient outcomes	Exposure Irrelevant, did not assess verification.
Nikolis, 2015(102)	Establishing a massive transfusion protocol (MTP): A collaborative effort	Exposure irrelevant, described an aspect of preparation to verification.
Santy, 2015(103)	Variations in the implementation of acute care surgery: Results from a national survey of university-affiliated hospitals	Exposure Irrelevant.
Drefyus, 2016(104)	Comparison of pediatric motor vehicle collision injury outcomes at Level I trauma centers	Exposure irrelevant, only verified Level I was included.
Falcone, 2016(105)	A paradigm for achieving successful pediatric trauma verification in the absence of pediatric surgical specialists while ensuring quality of care	Exposure Irrelevant, they evaluated the impact of the collaborative partnership on improving regional pediatric trauma care
Grossman, 2016(106)	Effect of American college of surgeons trauma center designation on outcomes: Measurable benefit at the extremes of age	Duplicate. Was an abstract and the full paper was published the next year and included.
Myers, 2016(107)	A National Analysis of Pediatric Trauma Care Utilization and Outcomes in the United States	Exposure Irrelevant, compared centers regardless of verification status.
Brown, 2017(108)	Impact of Volume Change over Time on Trauma Mortality in the United States	Exposure Irrelevant, assessed the volume outcome relationship

Joseph, 2017(109)	American College of Surgeons Level I trauma centers outcomes do not correlate with patients' perception of hospital experience	Exposure Irrelevant, only included verified centers.
Kaufman, 2017(26)	Triage of injured patients in New York state prior to implementation of the American college of surgeons committee on trauma verification system	Exposure Irrelevant, described triage prior verification.
Bank, 2018(110)	Collaborative implementation of a massive transfusion protocol at a level one trauma center	Exposure irrelevant, they summarized the necessary blood bank resources implemented to ensure successful ACS verification/re-verification.
Bjurlin, 2018(111)	Impact of Trauma Center Designation and Interfacility Transfer on Renal Trauma Outcomes: Evidence for Universal Management	Exposure irrelevant, only included verified centers.
Polites, 2018(27)	Undertriage after severe injury among United States trauma centers and the impact on mortality	Exposure irrelevant, the purpose of this study was to determine the undertriage rate between trauma centers. No stratification between ACS and State centers.
Hamidi, 2019(112)	Outcomes After Massive Transfusion in Trauma Patients: Variability Among Trauma Centers	Exposure irrelevant.
Spaulding, 2019(113)	Hospital Value-Based Purchasing and Trauma-Certified Hospital Performance	Exposure irrelevant, compared trauma centers to non-trauma centers.
Swartz, 2019(114)	Geriatric trauma collaboration: Feasibility, sustainability and improved outcomes	Exposure irrelevant.
Ukwuoma, 2019(115)	Does an Emergency Department Trauma Status Upgrade Impact the Timeliness of Nontrauma Computed Tomography Scans	Irrelevant, non-trauma patients.

eTable 2.3: GRADE evidence profile: effectiveness of trauma center verification

Quality assessment						Summary of findings				
						Number of patients			Absolute risk	
No of Studies	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Controls**	**Verified**	**OR (95% CI)**	**WMD ¥ (95% CI)**	**Quality**
Hospital Mortality (number of studies)										
All patients (1)	Serious	N.A	N.A	N.A	N.A	No details	No details	0.91 (0.83 – 0.99)	-	N.A
Pediatrics (2)	Serious	Serious	No Serious*	Serious	Unlikely	No details	No details	0.94 (0.62 – 1.42)	-	Very Low
Severe Injuries (1)	Serious	N.A	N.A	N.A	N.A	No details	No details	1.17 (1.05 – 1.30)	-	N.A
Level I (3)	Serious	Serious	No Serious*	No Serious	Unlikely	No details	No details	0.95 (0.91 – 1.00)	-	Very Low
Level II (1)	No Serious	N.A	N.A	N.A	N.A	No details	No details		-	N.A
Other (2)	Serious	N.A	Serious	N.A	Unlikely	No details	No details	-	-	N.A
Length of Stay(number of studies)										
Overall (1)	Serious	N.A	N.A	N.A	N.A	118	113	-	-0.06 (-0.22, 0.09)	N.A
Overall Level I (4)	Serious	Serious	No Serious	Serious	Unlikely	2,828	2,715	-	-0.04 (-0.21, 0.14)	Very Low
Overall Level II (1)	No Serious	N.A	N.A	N.A	N.A	3,973	3,835	-	-0.14 (-0.19,-0.10)	N.A
Overall Sub-population (4)	Serious	Serious	No Serious	Serious	Likely	572	774	-	0.20 (-0.8, 0.68)	Very Low
ICU Level I (2)	Serious	No Serious	No Serious	No Serious	Likely	777	447	-	0.29 (0.13, 0.46)	Very Low
ICU Sub-population (2)	Serious	No Serious	No Serious	No Serious	Likely	297	186	-	0.28 (0.00, 0.57)	Very Low

*There is minor indirectness of the interventions due to comparison groups. ¥Exponentiate of weighted mean differences can be interpreted as geometric mean ratio. **N.A**: Not Applicable; **OR**: Odds Ratio; **WMD**: Weighted mean difference

CHAPTER 3. Overview of data and methods

The literature review described in the previous chapter identified several methodological gaps that limit the inference that can be drawn concerning the impact of accreditation process. Moreover, the review uncovered that all available studies were derived from the United States. In this chapter, I describe different approaches designed to tackle these concerns and fill existing knowledge gaps.

3.1 Study Population

The study population consisted of major trauma patients, defined as those with an Injury Severity Score (ISS) ≥12, treated in designated level I or II trauma centers(25, 116, 117). ISS is the most ubiquitous summary score of trauma injury and is frequently used to classify patients as 'major trauma'(117). The focus is on major trauma patients because they are the primary target of trauma systems. Indeed, each trauma system has triage protocols, to ensure that major trauma patients are transported rapidly to highly specialized trauma centers (level I and II) (**Table 1.1**)(11, 28).

Further criteria were applied to exclude the following:

- Patients dead on arrival, including patients admitted with no functional signs and who died within 30 minutes;
- Patients aged 65 years or more with isolated orthopedic fractures due to a fall, because the trauma is often the result of an underlying chronic diseases (e.g. osteoporosis).

3.2. Data sources

Two datasets were used in this thesis, the Quebec and the British Columbia Trauma registries.

3.2.1. Quebec Trauma Registry

The province of Quebec has an inclusive trauma system. All 59 designated trauma centers are required to collect data on all trauma admissions, which are then transferred and stored in a central database managed by Québec's health insurance board (Régie de l'assurance maladie du Québec, RAMQ)(118). It includes information on patient demographics (for example, sex and age); injury mechanisms and diagnoses; anatomical injury severity (i.e., the Injury Severity Score); physiological parameters (e.g. Glasgow Coma Scale, systolic blood pressure); and outcomes (e.g. mortality, complications, length of stay, intensive care unit days)(119, 120). Trauma registry analysts are present in each center to ensure rigorous data quality checks. I secured access to data from April 2008 to March 2017. Accreditation status of centers over time was obtained through our collaboration with the Institut national d'excellence en Santé et Service Sociaux (INESSS).

3.2.2. British Columbia Trauma Registry

The British Columbia (BC) trauma service consists of a collaboration of regional health authorities which have their own, inclusive local systems(121). The BC trauma registry is the combination of two datasets: 1) the minimum dataset, which contains information on all trauma patients who have been sent by ambulance or have been in an emergency department, or who have been admitted to hospital; 2) the comprehensive dataset, which contains extensive clinical and administrative data specific to trauma patients with moderate to major trauma. Trauma registry analysts are present in each of the 11 designated centers to collect data and ensure rigorous data

quality checks(121). I secured data from January 2008 to March 2018 and details about accreditation visits (date and results) were obtained through our collaboration with the BC trauma services.

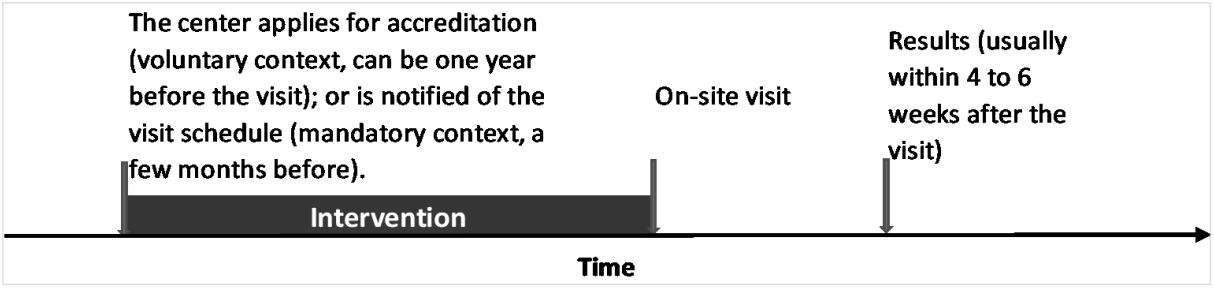
Using these two datasets contributes to filling one of the gaps identified in the literature, specifically that all previous studies were performed in the United States, and these results may not be transportable to other contexts.

3.3. Measures

3.3.1. Exposure or Intervention

The **exposure or intervention** is accreditation, defined as the center being successful at obtaining accreditation. The focus here is on the process of accreditation, which ends with the on-site visit, rather than just possessing the certificate(**Figure 3.1**). Depending on the setting (mandatory or voluntary) the comparison group will be the same center before accreditation, centers who failed the accreditation process, or non-accredited centers.

Figure 3.1: Visual description of the accreditation process



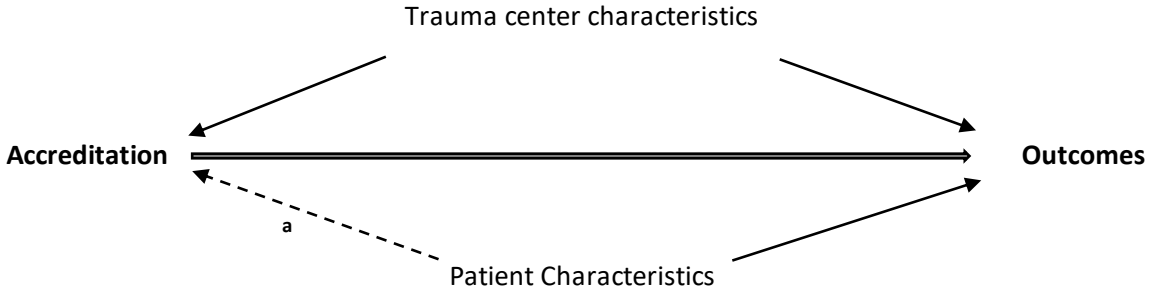
3.3.2. Outcomes

Three outcomes were assessed throughout this thesis: 1) hospital mortality defined as any death occurring between arrival in the emergency department and discharge; 2) major complications, focusing on conditions established by consensus in the trauma literature: acquired respiratory distress syndrome, cardiac arrest, myocardial infarction, pneumonia, pulmonary emboli, renal failure, respiratory failure, sepsis, stroke and death(74, 122-125); and finally 3) total hospital length of stay defined as time in days between admission and being discharged alive.

3.3.3. Potential confounders and effect measure modifiers

Data on covariates were collected from the trauma registries. They are listed below as center or patient level characteristics and were identified through the literature and consultations with expert in trauma care.

Figure 3.2: Conceptual framework



[a]Although in a voluntary context, the case-mix of patients may be one of the factor leading a center to seek accreditation, in a mandatory context it mostly modifies the effect of accreditation on studied outcomes.

a) Center characteristics: The designation level of trauma centers can confound and or modify an effect between accreditation on our primary outcomes (**Figure 3.2**). There is ample evidence indicating higher survival and better functional outcomes for injured patients treated at level I

centers compared to those treated at level II centers(126, 127)**.** Center type (university affiliated versus community) was considered given that university-affiliated facilities employ more surgeons, and have more subspecialty services compared to community-based centers(128). Details on other time-varying center characteristics that could have changed independently of accreditation like the designation of some hospitals as specialized centers for spinal cord injury or neurotrauma was collected after consultation with hospital and trauma system administrators in each setting.

b) Patients characteristics: Included age, sex, physiological parameters on arrival at the emergency department or admission (systolic and diastolic blood pressure, pulse, Glasgow Coma Scale, respiration rate), injury mechanism (motor vehicle collision, falls, penetrating and others), anatomic injury severity measured using the Abbreviated Injury Scale score(129), body region of the most severe injury, and whether the patient was transferred from another acute care hospital. To account for changes in the Abbreviated Injury Scale version (AIS 98 to AIS 2005) used to record injury severity over the study period, published conversion tools were applied (130, 131).

International Classification of Disease (ICD-9-CM and ICD-10-CA) codes were used to identify major complications and comorbidities in both datasets.

3.4 Case-Mix Standardization

Half of the included studies in the systematic review did not account for differences in patient characteristics between centers or for changes in the composition of patients over time(47). If

changes in the patient case-mix are correlated with accreditation, it could result in confounding bias due to the non-exchangeability of patients over time, which threatens the internal validity of these studies.

Standardized mortality ratios (SMRs), calculated as the ratio of the number of events observed in the trauma center under evaluation to the number that would be expected if the patients were treated in a “standard population” is the most commonly used method to adjust for changes in patient case-mix in trauma research(40, 132). Commonly used “standard populations” include the Major Trauma Outcome Study (MTOS) and the US National Trauma Data Bank (NTDB)(132-134). However, directly comparing the SMRs of two different centers may be inappropriate as the SMRs for two centers performing equally for each patient type will not necessarily take the same value if the centers' population structures are different(119, 135, 136). The size of this bias depends on the magnitude of the differences in the case-mix structure between centers(135). To circumvent these issues, direct standardization to obtain the expected number of events, which is the approach adopted by the Trauma Quality Improvement Program (TQIP) of the ACS Committee on Trauma, or regression-adjusted mortality according to the global case-mix distribution of all trauma centers have been proposed(74, 132, 137). However, these approaches are problematic when the aim is to evaluate the impact of an intervention, given that the distinction between exposed and control patients is ignored, leading to bias if the intervention has an effect on the investigated outcome(138).

For this thesis, prognostic or disease risk score were used to adjust for changes in case-mix(138). A prognostic score describes a person’s risk of the outcome given its observed covariate pattern.

Compared to traditional multivariate models, which include each covariate, conditioning on prognostic score protects against a loss of precision and produces balance of covariates strongly associated with the outcome(138-142). More importantly, it is recommended for the evaluation of interventions when treatment heterogeneity is expected across several patient characteristics, and the process by which outcomes are generated is repeatable, understood and more carefully controlled than the process of assigning units to interventions(138, 141, 142). In fact, there is more knowledge on the main predictors of in-hospital mortality, complications and length of stay than on the reasons why a center decides to seek accreditation.

A series of logistic regression models were used to estimate the prognostic score. First, using a sample of "control patients" i.e., patients treated in non-accredited centers or during the pre-accredited periods in accredited centers, a pooled logistic regression was run: $logit\, Y_{ic} = \beta_0 + \beta_z Z_{ic}$ **(3.1)**. From **(eq3.1)**, Y_{ic} represents the outcome of interest for a patient i in center c and Z_{ic} is a vector of patient risk factors, such as age, sex, number of comorbidities, etc. The coefficients β_z, from **eq3.1** were then used to estimate the probability of the respective outcome or prognostic score ($Score_{ic}$) for all patients during the study period based on their observed covariates Z_{ic}. Second, another logistic model was executed: $logit\, Y_{ic} = \beta_0 + \beta_1 Unit + \beta_2 Center + \beta_3 Unit * Center + \beta_4\, logit(Score_{ic})$ **(eq3.2)**, with $Unit$ being months or trimesters, modeled as factors. From equation **eq3.2**, marginal predictions of Y_{ic} were aggregated at the unit level to obtain a time series of monthly or quarterly standardized proportions of studied outcomes for each center. This was necessary to obtain a regular repeated measurement of outcomes, which is a basic requirement for interrupted-time series analyses used to assess the impact of accreditation.

A sample of “control patients” was used in equation **eq3.1** to avoid issues related to overfitting, and relax the assumption of a uniform intervention effect across categories of the prognostic score(138). A violation of this assumption could overestimate intervention benefits in the high-risk group (patients with a higher risk of death or acquiring a complication) and underestimate intervention harms in the low-risk group. However, using a sample of “control patients” assumes that the effects of risk factors on outcomes and coding practices do not change over time.

3.5. Study Designs

The most important limitation identified in the literature review pertained to the study designs used in prior research, which were either cross-sectional or pre-post comparisons(47). In cross-sectional studies included in the literature review, it was not possible to distinguish centers that failed during the accreditation process from those that never applied. Concerning pre-post studies, they cannot account for the underlying trend in measured outcomes before accreditation(143). These limitations can lead to selection and confounding biases, affecting the validity of observed associations.

I therefore, decided to opt for an interrupted time-series (ITS) design, which is a quasi-experimental design frequently used to assess the impact of policy and other population-level interventions in health research(143-150). Although ITS accounts for unobservable or unmeasured variables that are fixed over time, and for underlying trends in outcomes, it requires strong assumptions and a careful planning of each analytic step(143, 151). In the following paragraphs, I will briefly describe the framework based on seven steps, used to conduct ITS analyses.

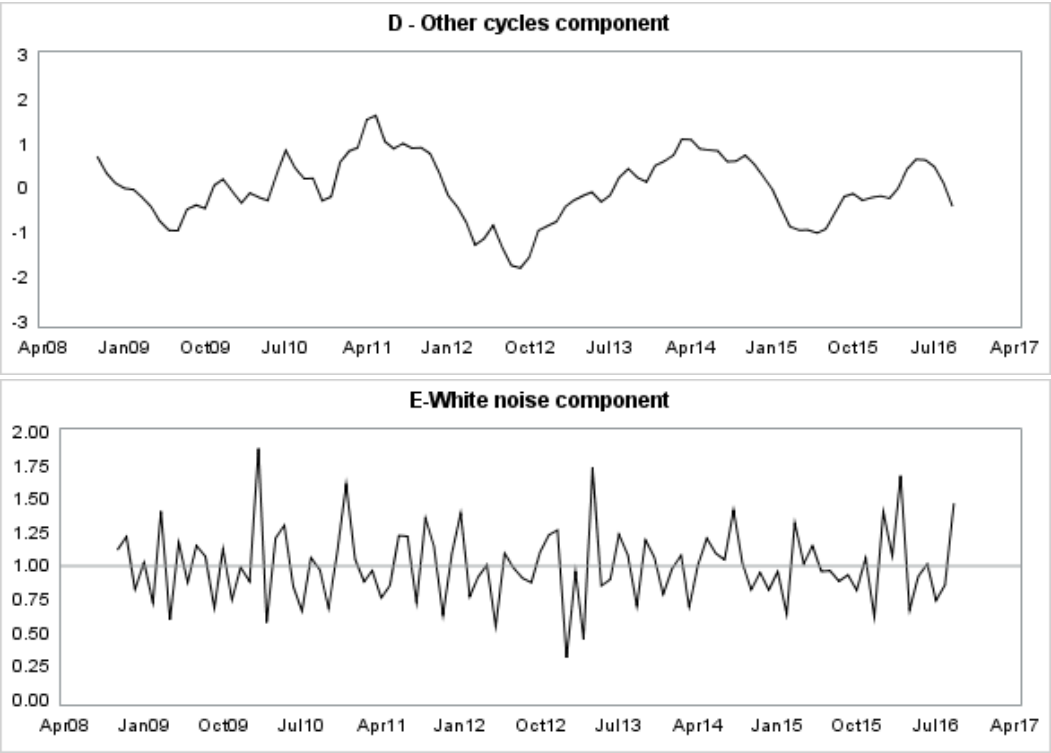
3.5.1. Verify conditions for an interrupted time series (ITS) design

Interrupted time series designs require two basic characteristics. First, presence of regular repeated measurements of an outcome of interest (i.e. measures taken at multiple months, quarters or years), which represents the time series. Second, the intervention must be introduced at a clearly defined time point(143, 144, 150, 152, 153). Depending on data and the nature of intervention (e.g., gradual or abrupt intervention onset), different analytical methods can be applied.

3.5.2. Examine the series of interest

Any time series can be described using four components which are: 1) a trend which refers to long-term direction; 2) seasonal cycles which are repeating patterns of increase or decrease in the series that occurs consistently and are associated with some aspect of the calendar (e.g., months, quarter); 3) other cycles, which are patterns that are not of fixed duration like seasonal patterns; and 4) random variation or white noise which constitutes any remaining variation in a time series after the three systematic components have been removed (**Figures 3.3a to e**)(154). For this thesis, this step involved plotting the monthly or quarterly proportions of investigated outcomes adjusted for patient case-mix over the study period, to visually assess the presence of any underlying trend prior to the intervention, seasonal or other cycle patterns, data dispersion and outliers. Each of these characteristics provide clues for the most appropriate analytics methods.

Figure 3.3: Decomposition of a time series*



*Example of a time series and its components. (A) corresponds to the series of interest; (B) is the trend component of the series, which suggests an increase in the mortality until April 2011 followed by a one year rapid decline and a plateau; (C) indicates the presence of a small seasonal pattern; (D) indicates the presence of small irregular cycles; (E) is the random error. Multiplicative decomposition was applied.

Another characteristic of time series data is the possible presence of data dependency due to autocorrelations and moving average processes. For an in-depth discussion of these processes we refer the reader elsewhere(155, 156), but they are briefly described as follows. If $\{Y(t);\ t \in T\}$ is a time series, the value of Y at a given time point t is comprised of a random component $\mathcal{E}_t$ as well as components of the values of Y at previous time intervals, represented by lags 1 through p: $Y_t = \Phi Y_{t-1} + \Phi Y_{t-p} + \cdots + \Phi_p Y_{t-p} + \mathcal{E}_t$ (143). The autocorrelation measures the extent to which data collected closer together in time are correlated with each other and is bounded between -1 and 1.[6] A negative autocorrelation suggests that outcomes taken close together in

[6] This is also true for higher order models. For an AR(n) model incorporating n AR terms the sum of the n terms must be < |1| in absolute magnitude.

time are likely to be dissimilar (a high outcome is followed by a low outcome that is then followed by a high outcome and so on). In contrast, a positive autocorrelation suggests that outcomes measured closer together in time are more similar to each other, which is manifest as "runs" in the data(151, 157). Moving averages are conceptualized in terms of the pure random shock components $\mathcal{E}_t$ which comprised one part of the autoregressive processes, and are also bounded between -1 and 1(143, 158). These processes can be examined by plotting the Autocorrelation Function (ACF) and Partial Autocorrelation Function (PACF)(143, 159).

3.5.3. Assess the stationarity of the series

Before applying any modeling to time series data, the series need to be stationary(143). The time series $Y(t)$ is said to be stationary if for any $t_{1,}t_{2,\ldots,}t_{k,} \epsilon T$ and any $h \epsilon T$, the distributions of $Y(t_1)$ and $Y(t_2)$ and the bivariate distributions of $\{Y(t); Y(t+h)\}$ are the same. However, this assumption is too strong for most applications(160), and a milder version called "weak stationarity" is generally used. A time series is said to be weakly stationary if its mean ($E[Y(t)]$=μ) and its variance (Var[Y(t)=σ^2]) are constant over time, and the autocovariance function $\gamma(t_1, t_k) = E\{[Y(t_1) - \mu(t_1)][Y(t_k) - \mu(t_k)]\}$ depends only on the distance between the two time points ($t_{k-}\ t_1$)(160, 161). The stationarity concept in time series analysis is essential because a series' mean and variance are only accurate population estimates if they remain constant throughout the series(143, 154).

Two approaches are commonly used to render a series stationary: 1) removing any trend by regressing the outcome on a deterministic trend term using segmented or piecewise generalized regressions (for trend stationary series); or 2) differencing by computing the differences between

consecutive observations , usually within an autoregressive integrative moving average (ARIMA) modeling framework (for difference stationary series)(143, 154). Deciding between the differencing and the regression approaches is often a function of the dominant method that had been taught in a discipline. In public health, the regression approach is commonly used because most health outcomes tend to have an attraction to the mean when we adjust for other variables, and we generally have shorter time series data which are not suitable for ARIMA models, which require longer series (i.e. at least 50 time points)(154, 158). For this thesis, it was necessary to determine whether the series required differencing, considering that the study period from 2008 to 2017 allows for at least 100 monthly estimates of the investigated outcomes. A series of tools was used to guide this decision, including:

- Unit root testing, using procedures such as the Augmented Dickey-Fuller's test to assess the presence of a unit root or stochastic trend. Should the null hypothesis of a unit root be rejected, it can be safely assumed that the series does not require differencing. However, these tests have low power to reject the null hypothesis(143, 162, 163).

- Plotting the Autocorrelation Function (ACF). As shown in (**Figure 3.4a**), the ACF from a non-stationary series is characterized by slowly damping autocorrelations, i.e., very high correlation coefficients across successive lags (143, 159).

- Overfitting several autoregressive models with high order of lags can also be used(164).[7]

[7]Since autocorrelations and moving averages are bounded within the interval -1 and +1, an estimated first-order autocorrelations (AR1) or moving averages (MA1) parameter which is >|1| is indicative of a time series process which has not in fact be rendered stationary.

Finally, it is worth noting that sometimes neither approach will give a definitive answer, especially when one of the roots of the series is around 1. For example, a model such as $Y_t = 0.96Y_{t-1} + \varepsilon_t$ can exhibit a difference stationary behavior. Therefore, subject matter knowledge must guide the decision. As mentioned earlier, a trend stationary series generally tends to have an attraction to the mean and a decay in the autocorrelations at lengths of interest (**Figure 3.4b**)(164). In this case it is appropriate to use generalized regressions with a deterministic trend.

Figure 3.4: Autocorrelation Function

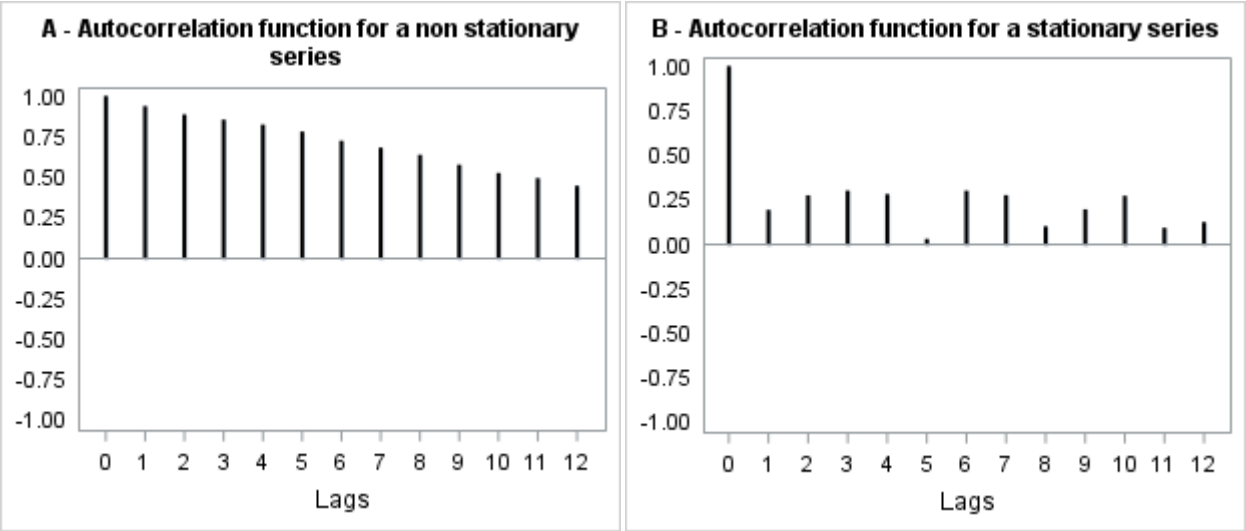


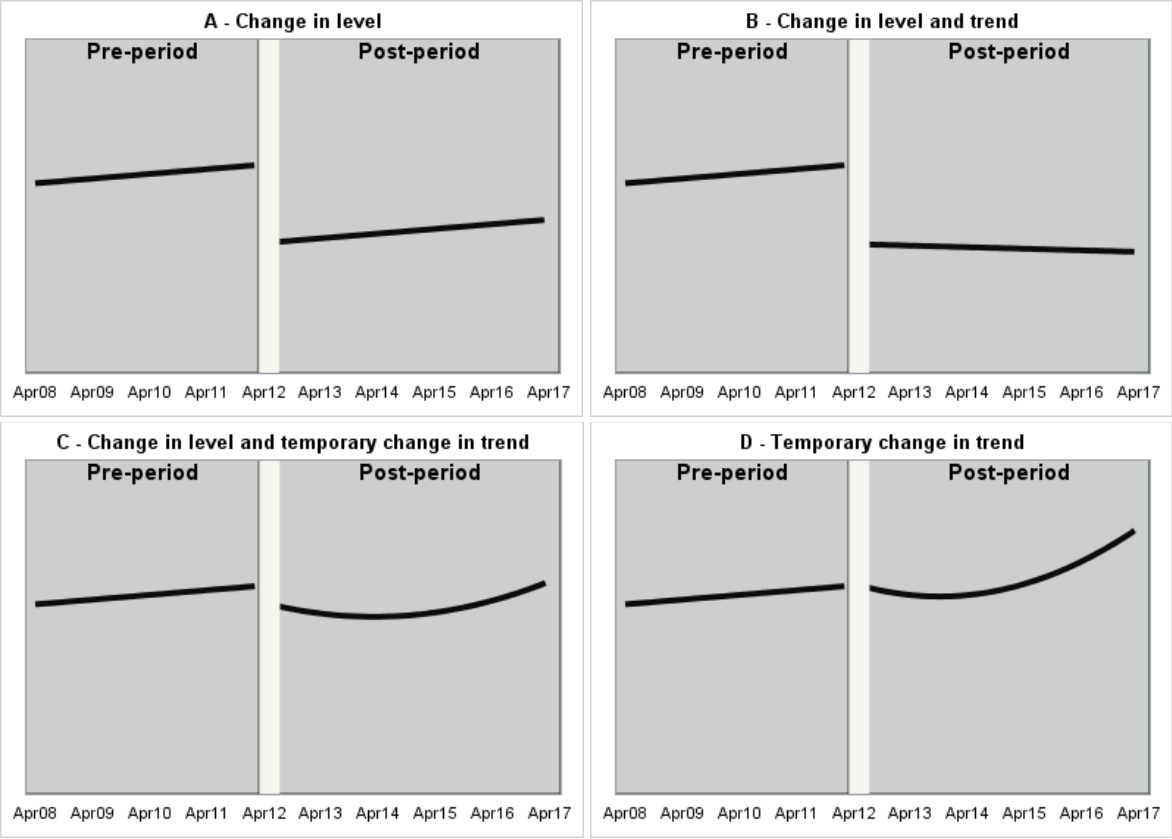
Figure 3.4a displays the very high correlation coefficients across successive lags which die out slowly; while in 3.4b the sample autocorrelations damp quite quickly suggesting a stationary series.

3.5.4. Fit the intervention models

Depending on the nature of the series (trend or difference stationary), generalized linear regression for the former or ARIMA models with transfer function for the latter was used. In both cases pre-specified impact models need to be defined, i.e., whether the intervention effect is abrupt or gradual, immediate or delayed, and whether or not the effect persists or is temporary(144). For this thesis I assumed that the accreditation has a transition or preparation

period, and that following that period, we may observe a change in levels and/or trends of the outcomes(**Figure 3.5**)(152). This was based on previous studies indicating improvements in patients' outcomes during the preparation for the accreditation visit(31, 45, 165).

Figure 3.5: Interrupted time series impact models for accreditation



The y-axis represents the investigated outcome. The light grey represents the transition period, a few months preceding the on-site visit. (A) corresponds to an abrupt level change after the transition period; (B) assumes accreditation has an abrupt and permanent effect; (C) abrupt level change followed by a gradual waning effect; (D) gradual waning effect. Adapted from Bernal JL, Soumerai S, Gasparrini A. A methodological framework for model selection in interrupted time series studies. Journal of clinical epidemiology. 2018;103:82-91.

ARIMA based ITS models already consider the presence of autocorrelations when estimating the effect of an intervention(166, 167). By contrast, generalized regression based ITS requires control for any autocorrelation, if needed. An example of generalized regression based ITS is piecewise regression using maximum likelihood for estimation (143, 153, 168) : $Y_t = \beta_0 + \beta_1 time +$

$\beta_2 Accred + \beta_3 Post\_period + R_t$ **(eq3.3)**. From equation **(eq3.3)**, Y_t is the proportion of the outcome at a given time unit *t*, β_0 is the intercept for the pre-accreditation series, $time$ is coded 1 to T, and its coefficient $\beta_1$is the slope (trend) of the regression line for the pre-accreditation period. The dummy variable $Accred$ indicates whether each time point occurred before or after the accreditation (0 for all period prior and 1 for all period after). The coefficient β_2 is the change in the level of Y_t due to the preparation for the visit. The variable $Post\_period$ represents the number of time points since accreditation (0 for all time points until the event;1,2,3...for subsequent periods), and its coefficient β_3 the change in the trend of the post-accreditation series.

Should evidence of autocorrelations in the residuals R_t be identified after inspecting an ACF plot of residuals, using the Durbin Watson and the Ljung-Box tests(143, 148, 156), new parameters are added to equations **eq3.3** : $Y_t = \beta_0 + \beta_1 time + \beta_2 Accred + \beta_3 Post\_period + R_t$, with R_t= $\Phi_1 R_{t-1} + \Phi_p R_{t-p} + \mathcal{E}_t$.**(eq3.4)**. R_t is the autoregressive component comprised of Φ_p, which is the autoregressive parameter for lag *p,* and $\mathcal{E}_t$, the white noise or random error. Non-linearity in the pre- or post-intervention trends can be modeled using quadratic terms or splines(169, 170).

3.5.5. Adjust for seasonality If necessary

There are different approaches to adjust for seasonality in time-series analyses, including the following commonly used methods:

- Adding fixed effect terms (deterministic approach) for months or trimesters, depending on the series. This approach is easy to implement but adds several degrees of freedoms and may lead to over-parameterization(143, 154).

- Flexible modeling using seasonal harmonic models. These models use sine and cosine functions to describe the pattern of fluctuations seen across periods. Although more realistic than the deterministic approach, they are more complex, and assume that the series exhibits the same pattern for each year or period(154, 170).

- Decomposition of the initial series into distinct components (trend, seasonal patterns, other cycles and noise) and fitting the intervention model on the seasonally adjusted series. However, this technique is mostly recommended when the magnitude of the seasonal pattern in a series appears to get either larger or smaller over time(143).

- Adding autoregressive (AR) or moving average (MA) terms to residuals from the impact model at given seasonal lags. This approach was adopted in this thesis, because it requires fewer terms than the deterministic approach (2 versus 11 degrees of freedom terms in the case of monthly time series data) and is less complex than decomposition and harmonic seasonal approaches(143, 153).

The final model will be the one where residuals could be considered white noise, not exhibiting any autocorrelations, seasonal cycles or trend.

3.5.6. Assess multicollinearity

Underlying trend and change in trend coefficients in ITS models tend to be highly correlated with one another. Therefore, when there are few time points between two interventions modeled, their coefficients for the impact on the time trend are likely to be almost perfectly correlated(143). While moderate multicollinearity may not be problematic, severe multicollinearity can increase the variance of the intervention effects and make the estimates

very sensitive to minor changes in model specification(143). Examination of the correlation between each pair of explanatory variables, the variance inflation factor (VIF) and the tolerance statistic were used to assess multicollinearity(171, 172). When severe multicollinearity was identified, i.e., VIF factor above 10(143, 172), only a change in the outcome level following accreditation was assessed (equivalent of removing coefficient β_3 from equation **eq3.4**).

3.5.7. Sensitivity analyses

To discriminate between the effect of accreditation and those of co-occurring events, non-accredited centers (more specifically their outcomes series) were used when the parallel trends assumption was satisfied. The parallel trends assumption implies that accredited and non-accredited centers may have different levels of the investigated outcome prior to the start of the intervention, but their trends in pre-treatment outcomes should be the same(173). When an accredited center and one or several non-accredited centers have parallel trends, a comparative interrupted time series (CITS) was applied. While CITS is more robust than single ITS, the availability of control centers satisfying the parallel trend assumptions is not guaranteed. Alternative options are the use of synthetic controls or a propensity score-based weighted ITS model. In the former, a synthetic control group is constructed using a complex data-driven approach and estimates of the intervention effect are obtained by comparing the trajectory of the outcome for a treated unit to the evolution of the same aggregate outcome for the synthetic control group(174). The latter, follows three steps: 1) a propensity score is estimated for the intervention group and all potential controls; 2) weights are constructed based on the target population of interest; and 3) these weights are then used within a regression equation like **(eq3.4)** to provide an intervention effect estimate(175-177). For this thesis the propensity score-

based weighted ITS model was used in sensitivity analyses, because of the small pool of potential control centers.

Finally, other sensitivity analyses were used to investigate the robustness of the results to potential unmeasured confounding and differential errors in the measurement of the outcome, due to a possible change in coding practices following accreditation. Specifically, bounding factors for risk difference using sensitivity parameters on the relative risk scale and formula for differential measurement errors in outcomes were used(178, 179).

3.6 Missing Data

Missing data, especially for patients' physiological parameters on arrival to the center are common in trauma registries(180). Although it is recognized that missing data can lead to biased estimates, standard errors and loss of power, the systematic review (Chapter 2 – manuscript 1) highlighted that most studies disregarded missing data(47, 181). To tackle this issue, multiple imputation using chained equations was applied following published recommendations(182). In addition to the covariates listed in **section 3.3,** all potential predictors of missingness (variables that are not used in the analysis but could improve the imputations), a dummy indicator for the pre vs post-accreditation period, and study outcomes were included in the imputation models(183). Predictive mean matching was used to impute skewed continuous variables, the discriminant function method for categorical variables and the number of imputed datasets was equal to the percentage of incomplete cases (20 imputed datasets for 20% of missing data)(182, 184). Due to practical considerations, a single imputation model was used by setting (Quebec and British Columbia).

All analyses i.e., prognostic score computation and ITS, were performed in each imputed dataset and the estimates of interest were combined using Rubin's rule(185). Appropriate transformations were applied before combining statistics such as autoregressive terms (182, 186).

3.7 Competing Risks

Another methodological limitation highlighted by the literature review was the disregard of competing risks. Competing risks arise when subjects are exposed to more than one cause of failure and failure due to one cause excludes failure due to other causes(187). This is the case for studies evaluating the impact of accreditation on hospital length of stay, given that the relevant length of stay for deceased patients is truncated. Although there is a vast literature on time-to event analysis in the presence of competing risks(188-192), it remains that competing risks are rarely considered in trauma research when hospital length of stay is the studied outcome(193). Furthermore, there is no guidance on how to integrate commonly used competing risk models within an ITS framework. To address these limitations, in the next chapter I describe, two approaches to handle the competing risks of in-hospital mortality when assessing the impact of an intervention on hospital length of stay, within an ITS framework.

CHAPTER 4. Addressing competing risks when assessing the impact of health services interventions on hospital length of stay: The example of trauma center accreditation

4.1 Preface: Manuscript 2

Length of stay (LOS) is among the most commonly analyzed outcome measures when assessing the impact of hospital interventions, including accreditation(165). In trauma research, LOS is used as a proxy for resource use(194). However, most studies disregard the competing risk of in-hospital mortality(47). In addition, commonly used multivariable competing-risk models i.e., cause-specific and subdistribution hazards, produce estimates which are difficult to interpret(189).

This manuscript aims to illustrate how to estimate the impact of hospital accreditation on LOS while accounting for changes in patient case-mix and the competing risk of in-hospital mortality using an interrupted time series (ITS) design. The manuscript is framed as a practice of epidemiology paper, and it was presented orally at local meetings (McGill Statistic; Epidemiology, Biostatistics and Occupational Health research day); accepted for oral presentation at a national and international conferences (the Trauma Association of Canada Congress, Halifax 2020 and the Society for epidemiology research, Boston 2020).[8] It also received several awards, including the second prize at the Epidemiology, Biostatistics and Occupational Health research day, and the Society for Epidemiologic Research Student and Postdoc Travel Scholarship. It is now accepted for publication in *Epidemiology*.

[8] The Trauma Association of Canada congress and the Society for epidemiology research conferences have been held virtually due to the COVID-19 pandemic.

4.2 Manuscript 2

Title: Addressing competing risks when assessing the impact of health services interventions on hospital length of stay: The example of trauma center accreditation**.**

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Funding

Funds for this project are covered by the Fonds de recherche du Québec – Santé (FRQS) PhD scholarship (BB) and a Canadian Institute of health Research (CIHR) Foundation grant (FRN 353374 for LM and FRN 148467 for AN).

Acknowledgement

The authors will like to thank Dr. Stephen R. Cole, of University of North Carolina for his help in the design of this study.

The data that support the findings of this study are from the Quebec trauma registry and are not publicly available. However, the computing code are available in the supplemental materials.

Abstract

Background: Although LOS is generally studied as a continuous outcome, it is increasingly recommended that LOS should be considered as a time-to-event outcome. In addition, in-hospital mortality is a competing risk, given that it makes it impossible for a patient to be discharged alive. We estimate the effect of a health service intervention, trauma center accreditation, on the risk of being discharged alive, while considering in-hospital mortality as a competing risk. We also compared our results with those obtained from the "naïve" approach, with LOS modeled continuously.

Methods: Data are from admissions to a level I adult trauma center in Quebec, Canada between 2008 and 2017. We computed the standardized risk of being discharged alive at specific days after admission following accreditation of the center in March 2012, by combining inverse probability weighting and the Aalen-Johansen estimator of the cumulative incidence function. Estimates of the accreditation effect were obtained using interrupted time series analyses.

Results: 5,300 patients were admitted in the hospital during the study period, 11.7% died, and 83.3% were discharged alive within 60 days. Accreditation was associated with a reduced LOS through an increase in the standardized risk of being discharged alive and a decrease of in-hospital mortality throughout the hospital stay. We did not observe an association between accreditation and LOS using the naïve approach.

Conclusions: Treating LOS as a time-to-event outcome allows for an estimation of the risk of being discharged alive by specific days after admission while accounting for the competing risk of death.

Keywords: Trauma centers, Accreditation, Verification, Length of Stay, Competing Risks.

INTRODUCTION

Length of stay (LOS) is an important outcome when assessing the impact of hospital interventions(1). In trauma research, LOS is used as a proxy for resources use(2, 3) and is generally assessed when evaluating the impact of interventions such as accreditation(4-7). Accreditation aims to determine whether trauma centers are fulfilling the criteria for optimal care(8, 9). Although it is increasingly recommended that LOS should be considered as a time-to-event outcome i.e., time to discharge(10), a recent systematic review synthesizing evidence of trauma center accreditation on patients' outcomes, including LOS, highlighted that existing studies often modeled LOS as a continuous outcome using linear regression(11). This "naïve" approach may be inappropriate for analysing time-to-event data since linear regression does not incorporate both the event and time aspects in the outcome model(12, 13). These studies also ignore in-hospital mortality as a competing risk, which can bias the results as the relevant times is truncated for decedents(14). In addition to disregarding competing risks of mortality, the literature on hospital accreditation is subject to confounding bias due to changes in patient characteristics over time (e.g., aging population).

There is a vast literature on time-to-event analysis in the presence of competing risks(10, 15-18). The key aspect is that the one-to-one correspondence between the cause-specific hazard and cumulative incidence, between rate and risk, is lost in the presence of competing risks(16). This reinforces the need to clarify the causal contrast of interest. One can consider the competing event as "artificial censoring" and compute the direct effect of the intervention on the event of interest(19, 20). This approach, however, implies a hypothetical intervention capable of completely preventing the competing event(21). An alternative is to estimate the total effect

through all causal pathways between the intervention and the event of interest, including those possibly mediated by the competing event(22). Finally, irrespective of the computed effect (total versus direct) for measuring the impact of interventions, it is preferable to report estimates based directly on the survival function (risk differences and risk ratios) instead of the rate or hazard (cause-specific or subdistribution hazard ratios)(21, 23, 24). The latter are subject to noncollapsibility, and conditioning on previous survival that affect the interpretation of estimate(21, 25).

Our aim is to first illustrate how to estimate the total effect of accreditation on the risk of being discharged alive from the hospital using both pre-post and interrupted time series (ITS) analyses. ITS analyses were performed in addition to the pre-post analyses because the latter cannot account for underlying trends in outcomes(26-29). Second, we will compare results from this approach to the naïve approach.

METHODS

Study sample

We used data from the Quebec trauma registry for trauma patients admitted between April 2008 and March 2017 at an urban level I adult trauma center of the province of Quebec, Canada(30). The registry is subject to extensive validation procedures and contains information on all admissions to trauma centers, including those transferred from another hospital. Patients dead on arrival, and patients aged 65 years or more with isolated orthopedic fractures due to a fall were excluded from the study population. Our analyses are restricted to patients with major

trauma, i.e., an Injury Severity Score ≥12, because they represent the target population for specialized trauma centers(31).

Intervention

The intervention assessed is accreditation, which is mandatory in Quebec and performed by the Institut national d'excellence en santé et en services sociaux. Since the establishment of a trauma system, three cycles of accreditation have been conducted, and a fourth cycle is ongoing. Accreditation generally requires a center to submit a pre-review questionnaire and to complete an on-site visit by an experienced peer review team. Following the visit, a center can have one of the following results: unconditional accreditation, with a certificate of approximately 6 years; accreditation if revisit satisfactory; and accreditation postponed. The latter can result in a downgrading of trauma center designation status(32). We are assessing the third cycle of accreditation conducted in March 2012 for the hospital under consideration, which was successful at maintaining its unconditional accreditation status. We excluded data from the three months preceding the accreditation visit, to capture possible preparation effect.

Outcomes

Our outcome of interest is the total length of stay (LOS) in any hospital unit measured as time to discharge in days after patient admission. In-hospital mortality is the competing event and patients discharged after 60 days were censored.

Covariates

Measured covariates included age, injury severity score, systolic blood pressure, Glasgow coma scale, pulse, number of comorbidities, sex, body region of the most severe injury, mechanism of

injury, transfer-in from another acute care hospital, and the number of hospitalisations in the 12-months prior to injury. Restricted cubic splines with 4 knots were used to model age, injury severity score, pulse and systolic blood pressure(33).

Inverse probability weighting (IPW)

Changes in patient characteristics, if they are correlated with the intervention, could result in bias due to the non-exchangeability of patients over time. IPW was then used to mimic a hypothetical trial where an exchangeable sample of patients is admitted to the hospital each month. When computing the weights (W_{CM}), we modeled the study period (months from April 2008 to March 2017) as a continuous variable rather than a binary indicator (pre versus post accreditation period), and we used the quantile binning method(34). This method consists of splitting the variable into quantiles and computing the probability of being admitted in a given quantile based on measured covariates. This was guided by the rational that weights obtained by modeling time as binary (W_{PP}), although sufficient for a pre-post analysis, could have led to biased estimation of the pre-period outcomes trend for ITS analyses due to residual confounding. Thus, this distinction has important implications for the ITS analyses since the extrapolation of the pre-period serves as the counterfactual. However, as sensitivity analysis, we estimated W_{PP}weights(35). The weights were stabilized, and we assessed the balance of covariates using the standardized mean difference for the pre-post and correlation-based methods for ITS analyses(36). The model specification used is described in the **appendix 4.1**.

Cumulative Incidence function

In the presence of competing risks, the risk function is called the cumulative incidence function, and involves the overall survival function at the previous time point(24). Thus, the cumulative incidence of discharge depends on the cause-specific hazard of death(16). The sum at any time point of the cumulative incidence of discharge, cumulative incidence of death and the overall survival function (remaining alive in the hospital) must be equal to one. To estimate standardized cumulative incidences of discharge and death separately, we assumed that administrative censoring at 60 days is noninformative and used the weighted Aalen-Johansen estimator(24, 37): $\widehat{CIF_{(t,J)}} = \sum_{k \leq t} \frac{E_{kj}^{w}}{n_k^{w}} \prod_{h<k} \left\{1 - \frac{E_h^{w}}{n_h^{w}}\right\}$ **(eq4.1)**, where t is time from patient admission to the event, j is the event type (discharge or death), $\widehat{CIF}$ represents the cumulative incidence density function, E_{kj}^{w} is the weighted number of events j at time k, E_h^{w} is the weighted number of all events at time h regardless of the event type (discharge or death), n_k^{w} is the weighted number of subjects in the risk set at time k, and n_h^{w} the equivalent for time h. As described by Cole et al(23), to allow a simple partition of event types, event times within or between discharge and deaths cannot be tied. Therefore, we randomly added 0.1 day to the LOS of each patient to break ties.

Pre-post analyses

Equation 4.1 was used to compute cumulative incidences separately for the pre- and post-accreditation periods using W_{CM} weights, and risk differences and ratios of discharge and death were computed at 7, 14, 30 and 60-days following admission.

ITS analyses

Two approaches were used. First, we applied **equation 4.1** to compute cumulative incidences for each month (from April 2008 to March 2017) of the study period using W_{CM} weights. We then used piecewise regressions with autocorrelated errors(26) to estimate the impact of accreditation using the value of the cumulative incidence on a specific day (7, 14, 30 and 60): $\hat{Y}_{tm} = \beta_0 + \beta_1 months + \beta_2 Accreditation + \beta_3 Post\_period\_months + R_{tm}$ **(eq4.2)**, with R_{tm}= $\Phi_1 R_{tm-1} + \Phi_p R_{tm-p} + \mathcal{E}_{tm}$. In **equation 4.2**, Y_{tm} is the cumulative incidence of discharge or death for patients admitted in month m on the day t following admission, β_0 is the intercept for the pre-accreditation series, $months$ is coded 1 to 108, and its coefficient $\beta_1$is the slope of the regression line for the pre-accreditation months. The dummy variable $Accreditation$ indicates whether each month occurred before or after the accreditation (0 for every month prior and 1 for months after). The coefficient β_2 is the change in the level of Y due to accreditation. The variable $Post\_period\_months$ represents the number of months since accreditation (0 for all months until the event;1,2,3...for subsequent months), and its coefficient $\beta_3$the change in the slope for the post-accreditation months. R_{tm} is the autoregressive component, comprised of Φ_p which is the autoregressive parameter for lag p, and $\mathcal{E}_{tm}$, the white noise or random error.

In the second ITS approach, we computed cumulative incidences after fitting three weighted stratified Cox models, respectively, for the composite event (death or discharge), discharge and death:(38) h(t|$Z_i, Strata = Accreditation$) = $h_{0Accreditation}$(t) exp [$\beta_1 month + \beta_2 Post\_period\_month$], $Accreditation$ =1,0 **(eq4.3).** In **equation 4.3**, β_1 refers to the slope for the pre-accreditation months, β_2 is the change in the slope for the post-accreditation months, and $h_{0Accreditation}$ is the baseline hazard function which is allowed to vary across strata (pre and

post periods). The β_i coefficients are the same for all strata. Even if the stratified Cox model relaxes the proportional hazard assumption in the two strata, it still assumes that the hazard is proportional within pre- and within the post-accreditation months. After computing the cumulative incidences for both discharge and death, risk differences and ratios of discharge and death were computed at 7, 14, 30 and 60-days following admission for different periods, including the month of accreditation, 6 and 18 months after accreditation.

Naïve approach

Three strategies were taken to handle in-hospital mortality: (1) restrict analyses to survivors; (2) assign the longest recorded LOS, or "worst-LOS", to decedents; and (3), use time until death as the LOS. In each strategy, we used a weighted generalized estimating equations to account for the serial correlation in the data(39).

Multiple imputation with chained equations was used to impute missing data assuming that missingness depends on measured variables(40). Covariates with missing data included the Glasgow coma scale score (16.7%), number of comorbidities (1.2%), systolic blood pressure (0.9%), pulse (0.8%) and age (0.6%). For the pre-post and ITS second approach, standard deviation of 500 bootstrap samples (resampling with equal probability of patients within each month and repeating the analyses including weights computation) was used as an estimate of the standard error when applying Rubin's rules to combine risk estimates across imputed datasets and to obtain 95% confidence intervals(23, 41). All analyses were performed in SAS, version 9.4, software (SAS Institute, Inc., Cary, North Carolina) and the code is available in the **supplement materials**.

RESULTS

There were 10,259 admissions, including 5,300 for major trauma, during the study period. The annual number of admissions remained stable throughout the study period, as well as the proportions of patients transferred from another hospital. However, there was an increase in the mean age of admitted patients, injury severity score, proportion of falls and thoracic-abdominal injuries over time (**Table 4.1**). Among major trauma admissions, 622 (11.7%) died and 4,417 (83.3%) were discharged alive within 60 days during the study period.

There was evidence of imbalances over time in measured covariates in the crude data. Sufficient balance of covariates, however, was achieved when applying W_{CM} weights (**Figure 4.1a** and **b**) and the mean of stabilized weights was closed to one with no extreme values [mean:1.0, range (0.1 to 4.7)](35, 42).

Table 4.1: **Characteristics of trauma admissions during the study period (April 2008 to March 2017)***

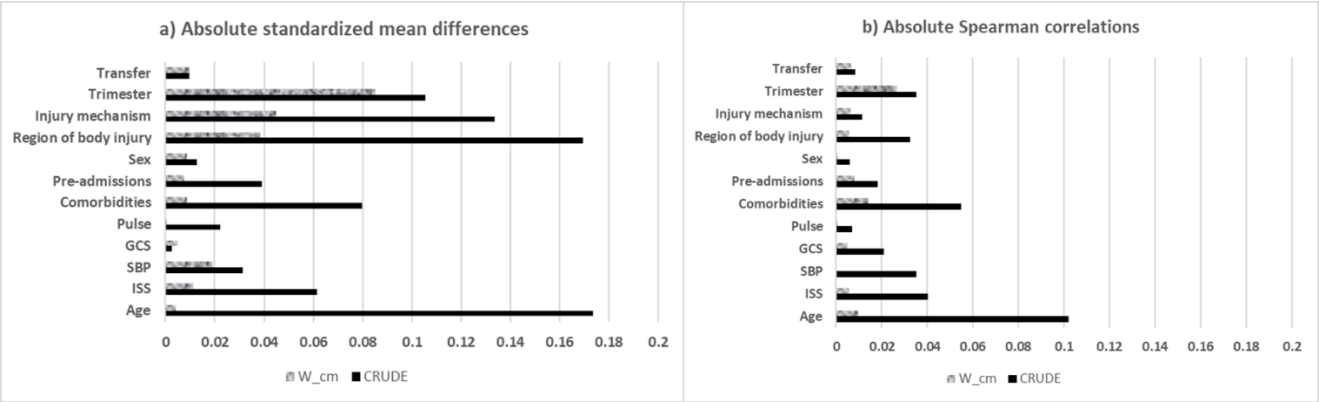
Characteristics	Years					
	2008	2010	2012	2014	2016	Total
Total admissions (n, %)	930 (9.1)	1208 (11.8)	1125 (11)	1075 (10.5)	1113 (10.9)	10259
Major trauma (ISS≥12) (n, %)¥	441 (47.4)	653 (54.1)	603 (53.6)	572 (53.2)	596 (53.2)	5300 (51.7)
Male sex (n, %)	313 (71)	448 (68.6)	429 (71.1)	396 (69.2)	419 (70.8)	3724 (70.3)
Region of the most severe injury (n, %)						
Head	302 (68.5)	443 (67.8)	394 (65.3)	356 (62.2)	341 (57.6)	3362 (63.4)
Thorax and abdomen	81 (18.4)	115 (17.6)	117 (19.4)	147 (25.7)	192 (32.4)	1263 (23.8)
Extremities	26 (5.9)	33 (5.1)	46 (7.6)	22 (3.9)	21 (3.6)	268 (5.1)
Neck and spine	32 (7.3)	62 (9.5)	46 (7.6)	47 (8.2)	38 (6.4)	407 (7.7)
Injury mechanism (n, %)						
MVC	151 (34.2)	205 (31.4)	178 (29.5)	131 (22.9)	158 (26.7)	1583 (29.9)
Fall	195 (44.2)	302 (46.3)	291 (48.3)	317 (55.4)	306 (51.7)	2591 (48.9)
Penetrating	19 (4.3)	29 (4.4)	23 (3.8)	23 (4)	31 (5.2)	271 (5.1)
Others	76 (17.2)	117 (17.9)	111 (18.4)	101 (17.7)	97 (16.4)	855 (16.1)
Transfer from another hospital (n, %)	235 (53.3)	344 (52.7)	320 (53.1)	310 (54.2)	326 (55.1)	2852 (53.8)
Age (mean, SD)	50.4 (21.5)	52.8 (22.3)	55.7 (21.2)	57.9 (20.8)	57.6 (22)	57.8 (22.1)
Systolic blood pressure (mean, SD)	137.1 (26.6)	136.2 (29.8)	138.5 (26.5)	139.9 (29.1)	140 (28.5)	138.4 (28.4)
Pulse (mean, SD)	88.3 (22.1)	85.8 (20.5)	86.6 (21.1)	87.7 (21.6)	87 (22.7)	87.4 (21.5)
Glasgow Coma Scale (n, %)						
3-8	93 (21.1)	138 (21.1)	119 (19.7)	123 (21.5)	122 (20.6)	1064 (20.1)

9-12	39 (8.8)	56 (8.6)	59 (9.8)	51 (8.9)	43 (7.3)	453 (8.6)
13-15	309 (70.1)	459 (70.3)	425 (70.5)	398 (69.6)	427 (72.1)	3783 (71.4)
Number of comorbidities (n, %)						
0	315 (71.4)	471 (72.1)	416 (69)	348 (60.8)	382 (64.5)	3557 (67.1)
1 -2	110 (24.9)	164 (25.1)	153 (25.4)	200 (35.)	184 (31.1)	1229 (28.9)
3+	16 (3.6)	18 (2.8)	34 (5.6)	24 (4.2)	26 (4.4)	214 (4)
Number of hospitalisations in the prior 12 months (n, %)						
0	382 (86.6)	554 (84.8)	514 (85.2)	474 (82.9)	504 (85.1)	4533 (85.5)
1	40 (9.1)	63 (9.7)	48 (8.0)	51 (8.9)	52 (8.8)	447 (8.4)
2+	19 (4.3)	36 (5.5)	41 (6.8)	47 (8.2)	36 (6.1)	320 (6.1)
ISS (Median, IQR)	22 (17 – 26)	22 (17 – 27)	25 (17 – 27)	25 (17 – 28)	25 (17 – 27)	24 (17 – 27)

¥Proportions of severely injured patients in total admissions Only odd years are presented to provide clarity.

*Results from one imputed dataset, other datasets have similar distributions. ISS: Injury Severity Score; MVC: Motor Vehicle Collisions; SD: Standard Deviations.

Figure 4.1: Diagnostics of the balance of covariates after the propensity score model*



*Based on one imputed dataset. Balance of covariates was achieved in all the 20 imputed datasets.

A) relates to the pre-post analyses; B) relates to the interrupted time series analyses.

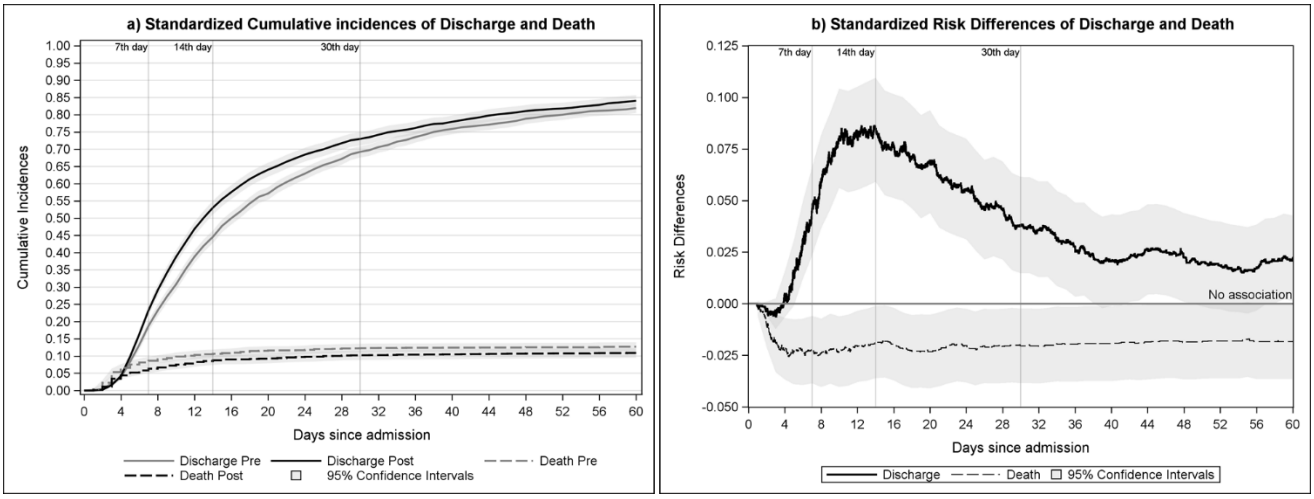
The covariates included in the weights computation were age, injury severity score, systolic blood pressure, Glasgow coma scale, pulse, number of comorbidities, sex, body regions of the most severe injury, mechanism of injury, transfer-in from another acute care hospital, and the number of hospitalisations in the 12-months prior to injury.

Restricted cubic splines with 4 knots were used for age, injury severity score, Glasgow coma scale, pulse and systolic blood pressure. **ISS**: Injury Severity Score; **SBP**: Systolic blood pressure; **GCS**: Glasgow Coma Scale.

Pre-post

The standardized risks of discharge by the 7, 14, 30 and 60th -day since admission were respectively 18.7%, 44.5%, 69.2%, and 81.9% in the pre-period and 23.1%, 53.0%, 73.0%, and 84.0% in the post-period. The standardized risks of death by the 7, 14, 30 and 60th -day were respectively 8.6%, 10.6%, 12.3% and 12.7% in the pre-period and 6.3%, 8.8%, 10.2% and 10.9% in the post-period. **Figure 4.2a** and **b** display the standardized cumulative incidences and risk differences while **Table 4.2** presents the 95% confidence intervals of standardized risk differences and ratios**.** Following accreditation, we observed an increase in the risk of discharge, higher between the 7th and the 30th days since admission, of 4.48 percentage points (95%CI: 2.32 - 6.63) and 2.22 percentage points (0.14 – 4.30) respectively. We also observed a stable decrease in hospital mortality.

Figure 4.2: Pre-Post analyses*



*Average across the 20 imputed datasets, the vertical grey lines represent the 7, 14 and 30th day after hospital admission.

Table 4.2: Standardized risk differences and ratios: pre-post*

Outcome	Risk Difference	95% CI[a]	Risk Ratio	95% CI[a]
Discharged alive				
7-Day	4.48	2.32, 6.63	1.24	1.12, 1.38
14-Day	8.43	5.93, 10.93	1.19	1.13, 1.25
30-Day	3.81	1.47, 6.15	1.06	1.02, 1.09
60-Day	2.22	0.14, 4.30	1.03	1.00, 1.05
Death				
7-Day	-2.23	-3.89, -0.58	0.74	0.60, 0.92
14-Day	-1.85	-3.59, -0.11	0.83	0.69, 0.98
30-Day	-2.03	-4.01, -0.23	0.83	0.71, 0.97
60-Day	-1.82	-3.66, 0.02	0.86	0.74, 0.99

*Rubin's rules were used to combine the estimates from the 20 imputed datasets

[a]The standard deviation of the 500 bootstrap resamples was used as an estimate of the standard error in each imputed dataset.

Interrupted Time Series

The piecewise regression approach (**equation 4.2**), produced similar results as compared to the pre-post design. However, the 95% confidence intervals were wider (**Table 4.3**). In addition to a change in level, we also examined if the intervention led to a change in the slope or trend. **Figures 4.3a** through **f** display the evolution of standardized risks during the 9-year study period. We observed an U-inverted shape of the post-accreditation trend of discharge on the 14th day and a linear increase for the 30-day discharge risk. There was no strong evidence for pre or post-accreditation trends of mortality.

Table 4.3: Standardized risk differences: interrupted time series-piecewise regression (1st approach)*

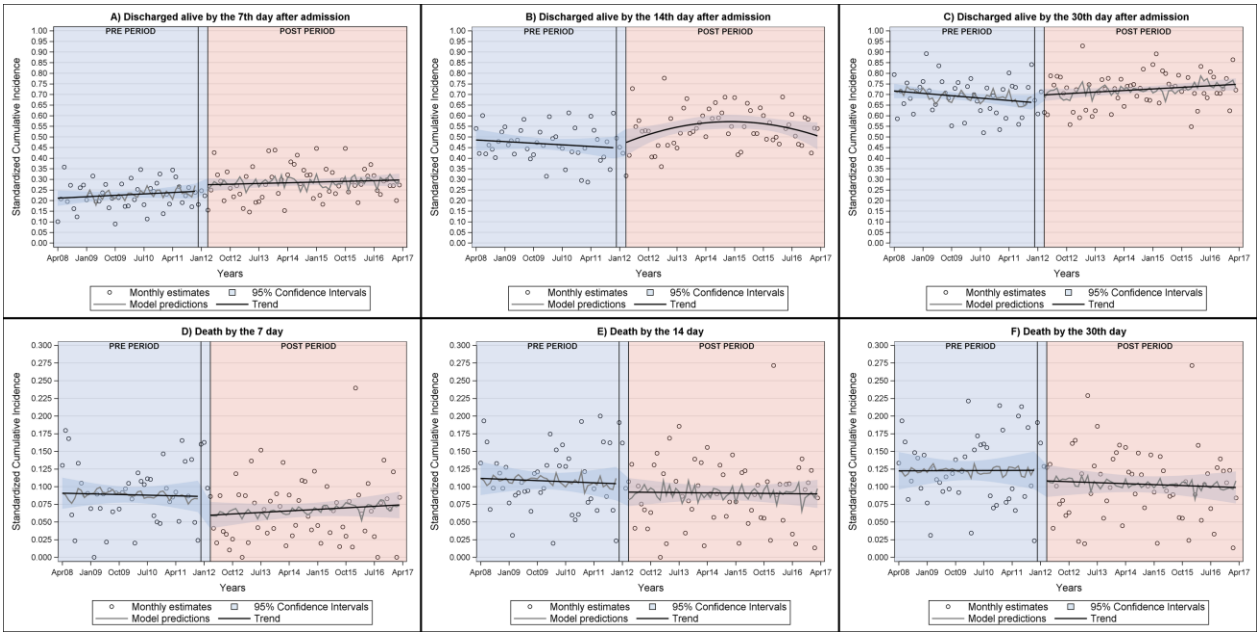
Risks (%)	Intercept		Pre-Period trend		Change in level		Change in trend	
Discharged alive	**Risk**	**95% CI[a]**	**Estimate**	**95% CI[a]**	**RD**	**95% CI[a]**	**RD**	**95% CI[a]**
7-Day	21.25	17.52, 24.98	0.07	-0.08, 0.22	2.93	-2.30, 8.17	-0.03	-0.20, 0.13
14-Day	48.92	44.13, 53.71	-0.10	-0.28, 0.09	5.96	-0.95, 12.87	¥	-
30-Day	71.67	67.93, 75.42	-0.12	-0.26, 0.03	3.69	-1.42, 8.81	0.20	0.03, 0.38
60-Day	81.09	77.55, 84.63	0.00	-0.13, 0.14	0.84	-3.88, 5.55	0.02	-0.14, 0.18
Death								
7-Day	9.23	6.94, 11.52	-0.02	-0.10, 0.07	-2.59	-5.73, 0.55	0.04	-0.07, 0.14
14-Day	11.10	8.74, 13.45	-0.02	-0.11, 0.08	-1.04	-4.32, 2.20	0.00	-0.10, 0.11
30-Day	12.19	9.48, 14.90	0.00	-0.10, 0.10	-1.44	-5.16, 2.28	-0.02	-0.14, 0.10
60-Day	12.80	10.09, 15.21	0.00	-0.11, 0.10	-1.16	-4.89, 2.56	0.00	-0.13, 0.12

*Rubin's rules were used to combine the estimates from the 20 imputed datasets

[a]Obtained through a piecewise regression with autoregressive errors

¥The post trend was modeled using quadratic terms. The two terms estimates were 0.37 (95% CI: 0.08, 0.65), and-0.01 (95% CI:-0.02, 0.00). RD: Risk differences.

Figure 4.3: Interrupted time series analyses, standardized risks: piecewise regression (1st approach)



Figures 4.4a and **d** shows the standardized cumulative incidences and risk differences of discharge and death, and **Table 4.4** shows the corresponding estimates and 95% confidence intervals in the first month following accreditation**,** based on the stratified Cox models (**equation 4.3**). Magnitudes of risk differences one month following accreditation were similar to those (level changes) obtained through the piecewise-regression approach, except for the 14-day discharge because pre-and post-accreditation trend were modeled linearly. Nevertheless, the pattern was the same, with accreditation being associated with an increase in the risk of discharge after admission and an imprecise reduction in mortality. Compared to the first approach, the assessment for any changes in the outcome trends is harder. Therefore, estimates for the 6- and 18-months following accreditation were computed to provide some indication **(Figures 4.4b,c, e** and **f,** and **Table 4.4)**.

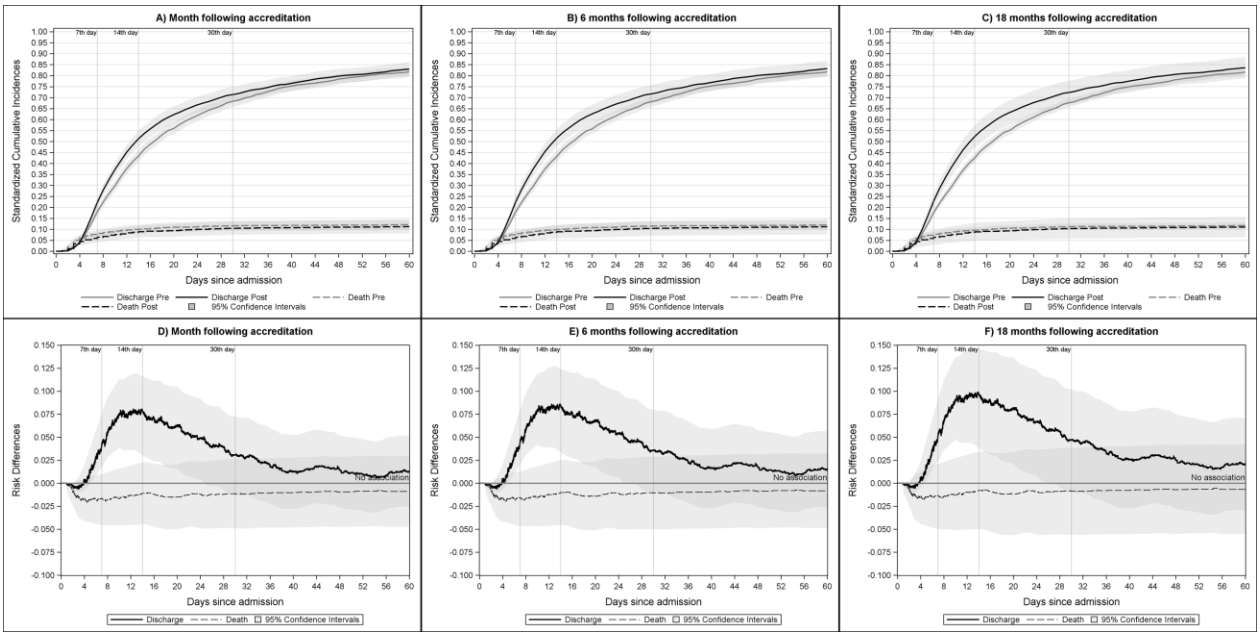
Naïve approach

The results were highly sensitive to how we handled in-hospital mortality. In analyses restricted to survivors, there was no association between accreditation and [LOS 0.23 day (95% CI: -2.99, 3,44)], whereas assigning the "worst-LOS" was associated with an imprecise increase in the mean LOS of 3.47 days (95% CI: -2.07, 9.01) (**Table 4.5**). In addition, using time until death as the LOS for decedents, we observed a 0.8 day increase in the mean LOS (95% CI: -2.22, 3.77).

Using W_{PP} weights in sensitivity analyses yielded very similar result for the pre-post design (**eTable 4.1, eFigure 4.2** in the **supplement materials)**. For the ITS design, however, estimated changes in level due to accreditation were greater in magnitude than the ones obtained with the W_{CM} weights (**eTables 4.2** and **3, eFigures 4.3** and **4.4** in the **supplement materials**). We also

observed some evidence for a change in outcome trends (increase in the monthly discharge and decrease in the monthly mortality risks) following accreditation.

Figure 4.4: Interrupted time series analyses: stratified Cox models (2nd approach)*



*Average across the 20 imputed datasets

Table 4.4: Standardized risk differences and ratios: interrupted Time Series-stratified Cox models (2nd approach)*

Outcome Discharged alive after	Risk Difference (%)	95% CI[a]	Risk Ratio	95% CI[a]
MONTH FOLLOWING ACCREDITATION				
7-Day	4.04	1.24, 6.84	1.23	1.06, 1.42
14-Day	7.87	3.65, 11.96	1.18	1.08, 1.30
30-Day	3.05	-1.13, 7.24	1.05	0.98, 1.11
60-Day	1.41	-2.39, 5.21	1.02	0.97, 1.07
6 MONTHS FOLLOWING ACCREDITATION				
7-Day	4.34	1.45, 7.24	1.25	1.07, 1.46
14-Day	8.34	3.94, 12.74	1.19	1.08, 1.32
30-Day	3.52	-0.96, 7.98	1.05	0.98, 1.13
60-Day	1.63	-2.39, 5.66	1.02	0.97, 1.07
18 MONTHS FOLLOWING ACCREDITATION				

7-Day	5.06	1.84, 8.30	1.29	1.08, 1.55
14-Day	9.60	4.37, 14.84	1.23	1.08, 1.39
30-Day	4.64	-0.83, 10.10	1.07	0.98, 1.16
60-Day	2.18	-2.68, 7.05	1.03	0.97, 1.09
Death				
MONTH FOLLOWING ACCREDITATION				
7-Day	-1.65	-4.43, 1.12	0.79	0.56, 1.14
14-Day	-1.10	-4.48, 2.26	0.89	0.63, 1.25
30-Day	-1.16	-4.88, 2.56	0.90	0.65, 1.25
60-Day	-0.89	-4.73, 2.93	0.93	0.68, 1.27
6 MONTHS FOLLOWING ACCREDITATION				
7-Day	-1.56	-4.48, 1.36	0.80	0.55, 1.17
14-Day	-1.00	-4.53, 2.51	0.90	0.63, 1.28
30-Day	-1.08	-4.99, 2.83	0.91	0.65, 1.28
60-Day	-0.83	-4.83, 3.17	0.93	0.67, 1.30
18 MONTHS FOLLOWING ACCREDITATION				
7-Day	-1.35	-4.83, 2.13	0.83	0.53, 1.29
14-Day	-0.79	-4.96, 3.39	0.92	0.60, 1.41
30-Day	-0.89	-5.59, 3.37	0.92	0.61, 1.39
60-Day	-0.68	-5.46, 4.09	0.94	0.64, 1.40

*Rubin's rules were used to combine the estimates from the 20 imputed datasets

[a]The standard deviation of the bootstrap resamples was used as an estimate of the standard error in each imputed dataset.

Table 4.5: Change in mean length of stay following accreditation: naïve approach.*

	Difference in days	95% CI[a]	Geometric mean Ratio	95% CI[a]
Pre-Post				
Only survivors[λ]	-2.01	-3.51, -0.50	0.89	0.84, 0.94
Worst LOS[¥]	-3.31	-5.88, -0.74	0.87	0.82, 0.93
All[§]	-1.60	-3.15, -0.06	0.95	0.89, 1.00
ITS				
Only survivors[λ]	0.23	-2.99, 3.44	0.94	0.84, 1.06
Worst LOS[¥]	3.47	-2.07, 9.01	0.96	0.84. 1.09
All[§]	0.77	-2.22, 3.77	1.00	0.89, 1.12

LOS: Length of stay

*Rubin's rules were used to combine the estimates from the 20 imputed datasets

[a]Robust standard errors were used in each imputation.

[λ]Analyses are restricted to patients discharged alive.

¥Decedents were assigned the longest recorded LOS during the month corresponding to their admission.
§The time until death was used as the LOS for decedents.

DISCUSSION

Main findings

Our study found that accreditation led to an increase risk of being discharged alive from hospital in severely injured patients, mostly between the 7th and 30th days after admission both in pre-post and ITS analyses. These risk difference estimates represent the total effect of accreditation on discharges through all causal pathways, including those possibly mediated by in-hospital mortality. We also examined the effect of accreditation on in-hospital mortality, given that the increase observed in discharge could have been driven by an increase in mortality. Analyses provided modest evidence of a reduction in in-hospital mortality following accreditation, which suggests that accreditation decreases LOS by increasing the risk of being discharged alive. We also showed that using linear regressions with mean LOS as the outcome (naïve approach) can lead to misleading conclusions depending on how we handled decedents. This is because restricting analyses to survivors or assigning the worst LOS to decedents is a form of conditioning on the future (i.e., explain what happens tomorrow based on knowledge to be collected in a more distant future)(43).

Previous studies looking at the impact of accreditation on LOS did not find an association(4-6) or observed an imprecise effect, including a reduction(44, 45) or increase(46, 47). These results should be interpreted cautiously, because they applied the naïve approach, and rarely adjusted for change in case-mix(11).

Limitations

Our study has some caveats that should be considered when interpreting our results. First, we assumed that our set of measured covariates is sufficient and that the propensity scores used to estimate inverse probability weights W_{CM} were correctly specified to assure conditional exchangeability between pre- and post-accreditation periods for the pre-post and between each month of the study period for ITS analyses(48). In addition, a change in coding practices may have led to errors in the measurement of covariates. Second, we should assume that accreditation is a well-defined intervention and that the consistency assumption holds(49). Among accredited centers there are those that fulfilled almost all the criteria and others which barely crossed the threshold for accreditation. In a single center setting, however, where the pre-accreditation period serves as the control, the consistency assumption might hold. Third, we assumed positivity, in the sense that the probability of a patient at any level of measured covariates to be admitted in the pre- and post-accreditation periods (pre-post design) or at any month of the study period (ITS design) is greater than zero(35, 50). Given the distribution of W_{CM} weights, this assumption probably holds in our study.

There are other issues in relation to patients admitted through transfer, and the imputation model. One half of patients were admitted through transfer from other acute care hospitals, which could lead to left truncation. However, this might not be problematic in our study given the distribution of the delay in hours from the first hospital to the study center [mean: 0.96; median:0.62 and IQR range (0.36 to 1.10)] in the pre-period and [mean: 0.96; median:0.63 and IQR range (0.35 to 1.10)] in the post-period. Concerning multiple imputation for survival analysis, there are many ways to specify the survival outcome in the imputation model(51). We used the

log transformation of the survival time and an indicator specifying the event of interest treated as a factor. Recent simulations have shown this method to be optimal for handling missing covariate values on missing at random data in the context of competing risks(40). Finally, information on the time in the intensive care unit and its contribution to the overall time to discharge was not consistently collected during our study period and therefore not included in our analyses.

Acknowledging the potential limitations mentioned above, our results support the hypothesis that accreditation improves patient outcomes. This might be due to accreditation improving the standardisation of the human and material resources and/or better adherence to evidence-based clinical processes of care(52-54). There is a full range of potential beneficial outcomes that might accrue from accreditation beyond mortality and LOS. However, our focus was to highlight the issue of competing risk when analysing LOS and to illustrate how to address that issue specifically within the framework of an ITS analysis, where there is little guidance.

As mentioned in the introduction, in-hospital mortality could have been considered as “artificial censoring” and censoring weights used to estimate the direct effect of accreditation on the mean LOS or the risk of being discharged alive(19, 20). Although it might be of interest to estimate the direct effect of accreditation, such an estimate is not sufficiently well-defined, because it is difficult to think about an intervention that would eliminate in-hospital mortality(21, 55). In addition, when treating LOS as a continuous outcome, it is impossible to assess the impact of the intervention after specific hospital stay. The survivor average causal effect (SACE), which is the effect of accreditation restricted to patients that will not die in the hospital either before or after the accreditation, could have been estimated(56). However, the SACE requires strong

assumptions, it is impossible to identify those patients and the time point for defining always-survivorship is not implicit(55, 57). For instance, we may be interested in the effect of accreditation on being discharged alive on the 14^{th} days among patients who would survive either in the pre or post-accreditation periods at 7, 14 or 60 days. Examining such quantities across different values of time to discharge and death can serve different inferential purposes(57). Recent developments in methods to address competing risks has proposed estimating separable effects, which consist of isolating effects of the intervention through event-specific pathways(55). However, to estimate the separate direct effect of accreditation on discharge and death, we must assume that accreditation has a component which acts on death and another component acting on discharge. More importantly, the component acting on death must not directly impact hospital discharge and the one acting on discharge do not directly affect death.

Finally, other multi-state models could have been used, and we refer to the articles of Putter et al. and Rosthoj et al. for additional details(58, 59). The approaches presented here can be adapted if a control center is used, assuming the control group has been carefully selected(60). They can possibly also account for left truncation and loss to follow-up using censoring weights(22, 23).

CONCLUSIONS

We presented different approaches to estimate the impact of a hospital intervention on length of stay in presence of competing risks. Assessing differences in cumulative incidences of being discharged alive provide more useful information to hospital managers than the differences in the average length stay.

Appendix 4.1

The quantile binning approach was used to compute W_{CM} weights. We ranked the study period (108 months) in 10 quantiles. Generalised logit model was used to compute the denominator i.e., the predicted probabilities for being admitted in a given quantile j based on measured covariates : $\Pr(Q = Q_j)|\ C = c$; with C representing the vectors of measured covariates. A generalized logit model was used instead of a conditional cumulative logistic model because the proportional odds assumption was not verified. The numerator was simply the marginal probability of falling into a given quantile (which is 1/10).

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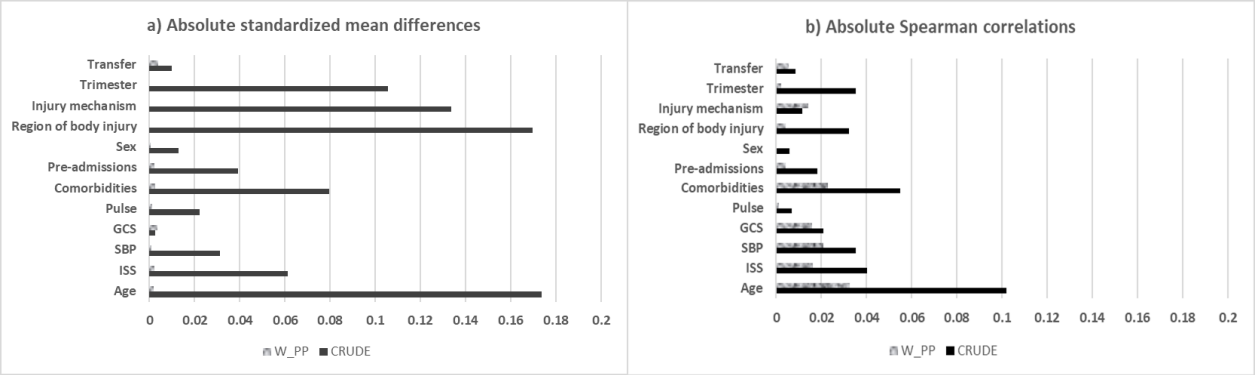
4.3 Supplemental material: Manuscript 2

eFigure 4.1: Diagnostics of the balance of covariates after the propensity score model*



*Based on one imputed dataset. Balance of covariate was achieved in all the 20 imputed datasets.

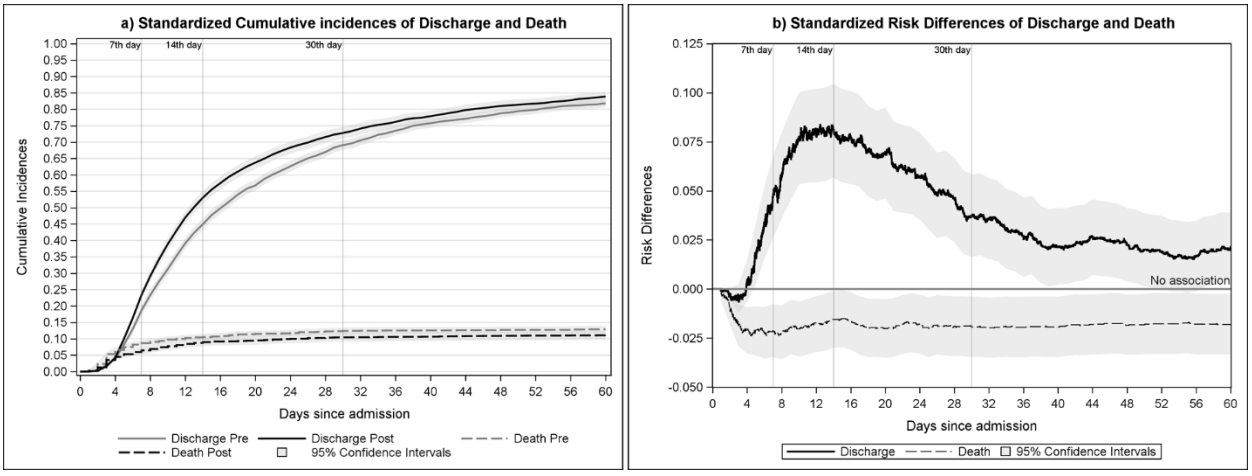
A) relates to the pre-post analyses; B) relates to the interrupted time series analyses.

Covariates included in the weights computation were age, injury severity score, systolic blood pressure, Glasgow coma scale, pulse, number of comorbidities, sex, body regions of the most severe injury, mechanism of injury, transfer-in from another acute care hospital, the number of hospitalisations in the 12-months prior to injury and the month and trimester of the year.

Restricted cubic splines with 4 knots were used for age, injury severity score, Glasgow coma scale, pulse and systolic blood pressure.

ISS: Injury Severity Score; **SBP**: Systolic blood pressure; **GCS**: Glasgow Coma Scale.

eFigure4.2: Pre-Post Design*



* Average across the 20 imputed datasets.

eTable 4.1: Standardized Risk differences and ratios: Pre-Post*

Outcome	Risk Difference (%)	95% CI[a]	Risk Ratio	95% CI[a]
Discharged alive				
7-Day	4.70	2.63, 6.77	1.25	1.13, 1.38
14-Day	8.07	5.70, 10.43	1.18	1.12, 1.24
30-Day	3.75	1.65, 5.85	1.05	1.02, 1.09
60-Day	2.14	0.36, 3.92	1.03	1.00, 1.05
Death				
7-Day	-2.13	-3.47, -0.79	0.75	0.63, 0.90
14-Day	-1.54	-2.98, -0.10	0.85	0.74, 0.99
30-Day	-1.92	-3.45, -0.39	0.84	0.74, 0.96
60-Day	-1.79	-3.35, -0.24	0.86	0.76, 0.98

*Rubin's rule was used to combine the estimates from the 20 imputed datasets

[a]The standard deviation of the 500 bootstrap resamples was used as an estimate of the standard error in each imputed dataset.

eTable 4.2: Standardized Risk differences ITS: 1st approach*

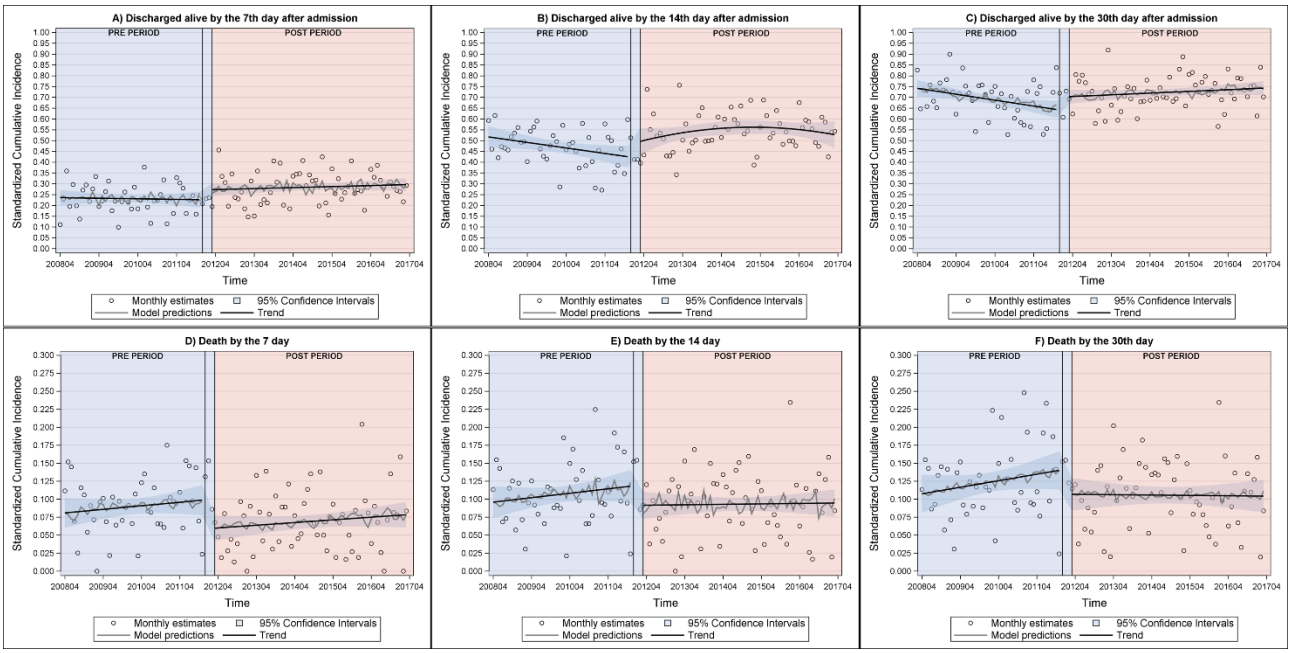
Risks (%)	Intercept		Pre-Period trend		Change in level		Change in slope	
Discharge	**Risk**	**95% CI[a]**	**Estimate**	**95% CI[a]**	**RD**	**95% CI[a]**	**RD**	**95% CI[a]**
7-Day	23.62	19.99, 27.24	-0.02	-0.17, 0.12	4.67	-0.40, 9.75	0.06	-0.10, 0.22
14-Day	51.91	47.27, 56.55	-0.22	-0.40, -0.04	9.86	3.17, 16.55	[¥]	
30-Day	74.25	70.16, 78.33	-0.22	-0.38, -0.06	6.69	1.07, 12.31	0.29	0.10, 0.48
60-Day	83.12	79.44, 86.79	-0.09	-0.23, 0.05	3.92	-0.86, 8.69	0.10	-0.07, 0.27
Death								
7-Day	8.06	5.94, 10.18	0.04	-0.04, 0.12	-4.05	-6.96, -1.13	0.00	-0.11, 0.09
14-Day	9.51	7.23, 11.78	0.05	-0.04, 0.14	-2.85	-6.03, 0.31	-0.05	-0.15, 0.05
30-Day	10.64	7.94, 13.34	0.08	-0.03, 0.18	-3.65	-7.38, 0.08	-0.08	-0.20, 0.04
60-Day	11.38	8.66, 14.10	0.06	-0.04, 0.17	-3.29	-7.04, 0.45	-0.06	-0.19, 0.06

*Rubin's rules were used to combine the estimates from the 20 imputed datasets

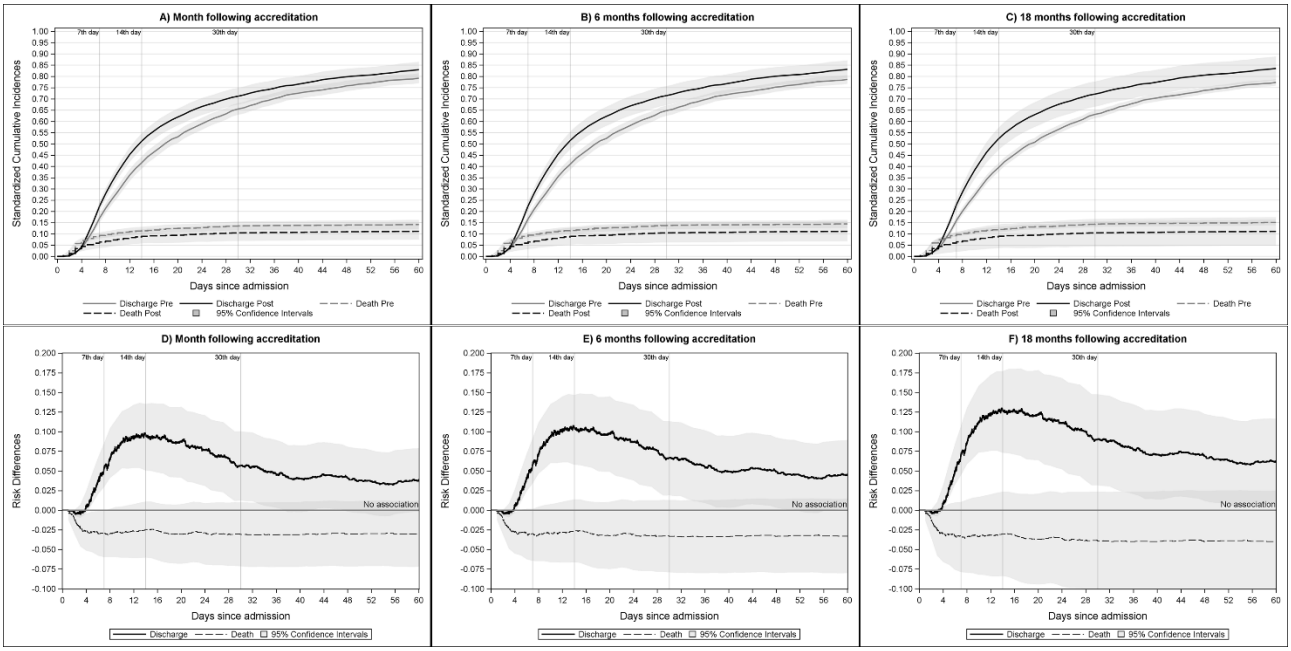
[a]Obtained Through a segmented regression with autoregressive errors

[¥]The post trend was modeled using quadratic terms. The two terms estimates were 0.40 (95% CI: 0.12, 0.67), and-0.005 (95% CI:-0.012, 0.002).

eFigure 4.3: Interrupted Time Series Design, standardized risks: 1st approach*



eFigure 4.4: Interrupted Time Series Design: 2nd approach*



* Average across the 20 imputed datasets

eTable 4.3: Standardized Risk differences and ratios: ITS: 2nd approach*

Outcome	Risk Difference (%)	95% CI[a]	Risk Ratio	95% CI[a]
Discharged alive				
MONTH FOLLOWING ACCREDITATION				
7-Day	5.29	2.55, 8.02	1.31	1.13, 1.52
14-Day	9.57	5.37, 13.77	1.23	1.12, 1.35
30-Day	5.71	1.32, 10.10	1.09	1.02, 1.16
60-Day	3.89	-0.16, 7.94	1.05	1.00, 1.10
6 MONTHS FOLLOWING ACCREDITATION				
7-Day	5.78	2.99, 8.57	1.35	1.16, 1.57
14-Day	10.51	6.09, 14.93	1.26	1.13, 1.39
30-Day	6.70	1.98, 11.42	1.10	1.03, 1.19
60-Day	4.59	0.20, 8.98	1.06	1.00, 1.12
18 MONTHS FOLLOWING ACCREDITATION				
7-Day	6.96	3.92, 10.00	1.44	1.20, 1.72
14-Day	12.74	7.57, 17.92	1.32	1.16, 1.50
30-Day	9.05	3.26, 14.85	1.14	1.04, 1.25
60-Day	6.29	0.85, 11.73	1.08	1.01, 1.16
Death				
MONTH FOLLOWING ACCREDITATION				
7-Day	-2.86	-5.79, 0.06	0.69	0.49, 0.98
14-Day	-2.45	-6.03, 1.12	0.78	0.56, 1.10
30-Day	-3.07	-7.16, 1.02	0.77	0.56, 1.07
60-Day	-3.02	-7.20, 1.17	0.79	0.57, 1.08
6 MONTHS FOLLOWING ACCREDITATION				
7-Day	-2.97	-6.27, 0.33	0.68	0.47, 0.99
14-Day	-2.61	-6.64, 1.42	0.77	0.54, 1.11
30-Day	-3.31	-7.92, 1.31	0.76	0.54, 1.08
60-Day	-3.29	-8.02, 1.43	0.77	0.55, 1.09
18 MONTHS FOLLOWING ACCREDITATION				
7-Day	-3.24	-7.67, 1.19	0.66	0.42, 1.05
14-Day	-2.99	-8.41, 2.44	0.75	0.48, 1.16
30-Day	-3.89	-10.15, 2.38	0.73	0.47, 1.12
60-Day	-3.98	-10.39,10.00	0.73	0.48, 1.12

*Rubin's rule was used to combine the estimates from the 20 imputed datasets

[a]The standard deviation of the bootstrap resamples was used as an estimate of the standard error in each imputed dataset. ITS=Interrupted time series.

Optional: Distribution of weights*

Weights		
	Mean	**Min – Max**
$\mathbf{W_{PP}}$	1.00	0.61 – 2.42
$\mathbf{W_{CM}}$	1.00	0.13 – 4.72

*Based on one imputed dataset but was similar in all the 20 imputed datasets.

$\mathbf{W_{PP}}$ = Obtained by dichotomizing the study period; $\mathbf{W_{CM}}$ = Obtained through the quantile binning approach.

The SAS Code is available here: https://tinyurl.com/y8zm49r8.

CHAPTER 5. Impact of trauma center accreditation on mortality and complications in a Canadian trauma system: An interrupted time series analysis

5.1 Preface: Manuscript 3

This manuscript fills one of the gaps identified in the literature, which was the fact that all available studies evaluating the impact of trauma center accreditation were from the United States, where accreditation is mostly voluntary. In the province of Quebec, accreditation is mandatory, and a negative result may lead a center to lose its designation.

This study was the first to assess the impact of accreditation in the Quebec trauma system and used the ITS framework detailed in Chapter 3 to provide robust estimates of the impact of accreditation on patient outcome. It was presented as an oral presentation at the Quebec trauma congress (February 2020). The manuscript is accepted for publication to *BMJ Quality & Safety*.

5.2 Manuscript 3

Title: Impact of trauma center accreditation on mortality and complications in a Canadian trauma system: An interrupted time series analysis.

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Funding

Funds for this project are covered by the Fonds de recherche du Québec – Santé (FRQS) PhD scholarship (BB) and a Canadian Institute of health Research (CIHR) Foundation grant (FRN 353374 for LM and FRN 148467 for AN).

Acknowledgments

The authors would like to thank Melanie Berube PhD, Amina Belcaid and Xavier Neveu for their help in the design and interpretation of this study.

Abstract

Background: Trauma systems have led to important reductions in injury mortality in many high-income countries. Periodic external accreditation visits aiming to determine whether trauma centers are fulfilling the criteria for optimal care are part of most trauma systems. However, despite the growing trend towards accreditation of trauma centers, its impact on patients' outcomes remains unclear. In addition, a recent systematic review found inconsistent results on the association between accreditation and patient outcomes, mostly due to the lack of robust controls. We aim to address these gaps by assessing the impact of trauma center accreditation on patient outcomes, specifically in-hospital mortality and complications, using a quasi-experimental design.

Methods: Data are from admissions to all level I and II trauma centers in Quebec, Canada between 2008 and 2017. We first obtained monthly estimates of the proportions of in-hospital mortality and complications accounting for changes in patient case-mix using prognostic scores. We then used piecewise regressions with autocorrelated errors to estimate changes in levels and trends in both outcomes due to accreditation.

Results: Globally, we did not observe an association between accreditation and patient outcomes. However, associations were heterogenous across centers. Among centers with worsening pre-accreditation outcomes, accreditation led to decreases in levels and/or trends of mortality and complications.

Conclusion: Using a quasi-experimental design while accounting for changes in patient case-mix, our results indicate that accreditation was beneficial for centers that were experiencing a decrease in performance in the months preceding the accreditation.

Keywords: Trauma centers, Accreditation, Verification, Mortality, Complications, Trauma care.

INTRODUCTION

Trauma systems, which are an organized and multidisciplinary response to injury along the continuum from pre-hospital care to rehabilitation, have led to important reductions in injury mortality in many high-income countries(1, 2). Essential to trauma systems are trauma centers, which are designated by states or provinces according to levels of care (levels I – V for adults and I or II for pediatric centers)(3). Trauma centers are acute care hospitals where resources are prioritized to ensure that injured patients receive appropriate and timely care(4, 5). Injury organizations, including the American College of Surgeons (ACS) and the Trauma Association of Canada, have established trauma facility standards(3). These criteria have been used to develop a trauma center accreditation process, which aims to determine whether trauma centers are fulfilling the criteria for optimal care.

Accreditation covers broad aspects of trauma care including a center's organization chart, transfer agreements, emergency and operating room protocols, intensive care unit and medical imaging(6). It generally requires a center to submit a prereview questionnaire and to complete an on-site visit by an experienced peer review team(3). Advocates of accreditation believe that it allows for standardization of personnel, equipment as well as stronger hospital commitment to

trauma care(7). Opponents, however, highlight the required mobilization of human and financial resources and the possibility that improvements in care are transitory(8-10). A recent systematic review synthesizing the evidence of trauma centers accreditation found that it was imprecisely associated with reductions in mortality and the occurrence of complications(11). That review, however, highlighted methodological concerns that might bias observed associations, including the inappropriate selection of control centers in cross-sectional studies, inadequate control for underlying trends in outcomes in pre-post studies and the lack of adjustment for center and patient level potential confounders. In addition, the external validity was limited, with all published studies from the United States, where accreditation is mostly voluntary.

The accreditation process has become common practice in North America, under the rationale that it verifies trauma centers' abilities to deliver appropriate levels of care(5, 12, 13). Accordingly, we hypothesized that accreditation should lead to an improvement in patient outcomes. This study aims to fill important gaps in the current literature by using an interrupted time-series (ITS) approach, which can account for underlying trends in outcomes, to assess the impact of trauma center accreditation on in-hospital mortality and major complications.

METHODS

Study sample

Our population consisted of major trauma patients, defined as those with an Injury Severity Score (ISS) ≥12 admitted between April 2008 and March 2017 in all level I and II adult and pediatric trauma centers of the province of Quebec, Canada(14). The focus on major trauma patients is

because they are the primary target of trauma systems, and if accreditation leads to better patient outcomes, that effect will be stronger for these patients.

We used data from the Quebec trauma registry, which is subject to validation procedures and contains information on all patients admitted to trauma centers, including those transferred from another hospital(15). Patients dead on arrival, and patients aged 65 years or more with isolated orthopedic fractures due to a fall were excluded from the study population(16). These patients were excluded because their injury is oftentimes the result of chronic conditions (e.g. osteoporosis) that do not require treatment in designated trauma centers.

Intervention

The Quebec Trauma system consists of three adult level I, two pediatric level I, five adult level II and 49 lower level centers(17). Accreditation is mandatory in Quebec, in contrary to other Canadian provinces and United States where it is voluntary. In Quebec, accreditation is performed by the Institut National d'Excellence en Sante et Service Sociaux (INESSS), while Accreditation Canada and the ACS are the accreditation bodies for the rest of Canada and the United States, respectively(3, 18).

Since the establishment of a trauma system in 1991, four cycles of accreditation have been conducted. During the accreditation visit, a committee of external experts verify adherence to criteria based on recommendations from the American College of Surgeons-Committee on Trauma(3, 19). Each center is evaluated according to its level of designation. Following the accreditation visit, a center can have one of the following results: unconditional accreditation, in which case the certificate lasts approximately 5 years; provisional accreditation, in which case a

new site visit would be performed within 18 months; and accreditation postponed. The latter can result in a downgrading of trauma center designation status(17). Due to data availability, we assessed the third cycle of accreditation, which was conducted between January 2012 and March 2015(17). In addition to the accreditation, some centers also experienced co-interventions. Specifically, they were visited to maintain their status as specialized centers for spinal cord injury or neurotrauma. One level II center was excluded from the analysis because we lack information on the chronology of different co-interventions. All included centers (three adult level I, two pediatric level I and four adult level II) obtained unconditional accreditation following the visit.

Outcomes

Our outcomes of interest were in-hospital mortality, defined as any death occurring between arrival in the emergency department and discharge, and major complications, defined as the occurrence of any of the following during the hospitalization: acquired respiratory distress syndrome, cardiac arrest, myocardial infarction, pneumonia, pulmonary emboli, renal failure, respiratory failure, sepsis, stroke and death(20-22). Death is generally considered as a complication in the trauma literature, and it is a competing risk for non-fatal complications. Covariates comprised physiological variables including, age, sex, number of comorbidities, systolic blood pressure, Glasgow coma scale and pulse measured on arrival at the emergency department. The body region of the most severe injury, mechanism of injury, injury severity score and transfer-in from another acute care hospital was also retrieved from the registry. We accounted for changes in the Abbreviated Injury Scale version used to record injury severity throughout the study period by using published conversion tools(23, 24).

Statistical methods

A two-step approach was used. First, we used the prognostic score methodology to obtain standardized monthly or quarterly proportions of mortality and major complications(25). These proportions represent, for each center, the probability of each health outcome if all patients in that hospital were admitted at each time point (months or quarters). Secondly, piecewise regression with autocorrelated errors was used to estimate changes in levels and trends due to accreditation while taking serial correlation into account(26). Seasonality and non-linearity in trends were investigated and modeled by incorporating autocorrelated error terms at a given seasonal lag and splines(26). We used the Ljung-Box test to verify to what extent the residuals of each model approximated a white-noise process and the tolerance statistic to assess the collinearity between changes in levels and trends(27, 28). Details of the model specifications of each statistical approach are presented in **appendix 5.1.**

Our focus was on the accreditation process per se, rather than just having the certificate. Therefore, data from the three months preceding the accreditation visit were excluded from our analyses, to capture the preparation effect. All analyses were performed by center because of the variation in center performance, difference in accreditation visit dates and the presence of specific co-interventions in some centers(9, 17, 29). However, to assess the impact of accreditation across all centers stratified by level, we used a weighted generalized estimating equations(GEE) model with robust standard errors(30). Weights were obtained by the inverse of the estimated outcome variance, to account for the fact that some centers have a higher volume of patients than others(31).

It is not unusual for a center to be asked to improve its recording of data on comorbidities or complications following an accreditation visit(17). In sensitivity analyses, we therefore investigated potential biases introduced, for example, by an increase in reporting of complications (which could lead to differential measurement error in the outcome)(32) and comorbidities (residual confounding)(33) due to changes that may have occurred in coding practices following accreditation. The formulas used for these analyses are described in **appendix 5.2.**

Piecewise regressions are unable to model changes in variation and/or correlation of outcomes following an intervention. In addition, the time at which accreditation initially affects the outcomes may occur earlier than three months before the visit (due to the preparation for the accreditation visit). We applied a robust interrupted time series (robust-ITS) that overcomes these limitations(34, 35), in order to investigate the possibility that accreditation may have lead to change in variability and dependency of studied outcomes. However, only center 2 was used, because the software application currently available for Robust-ITS only allows for monthly time-series and cannot handle co-interventions(36).

Multiple imputation with chained equations was used to impute missing data(37). Covariates with missing data included the Glasgow coma scale score (11.6%), number of comorbidities (2.2%), systolic blood pressure (2.2%), pulse (2.2%) and age (0.6%). Rubin's rules were used to combine estimates across imputed datasets and to obtain 95% confidence intervals(38). Analysis were conducted using SAS software, version 9.4 and a RShiny toolbox(36).

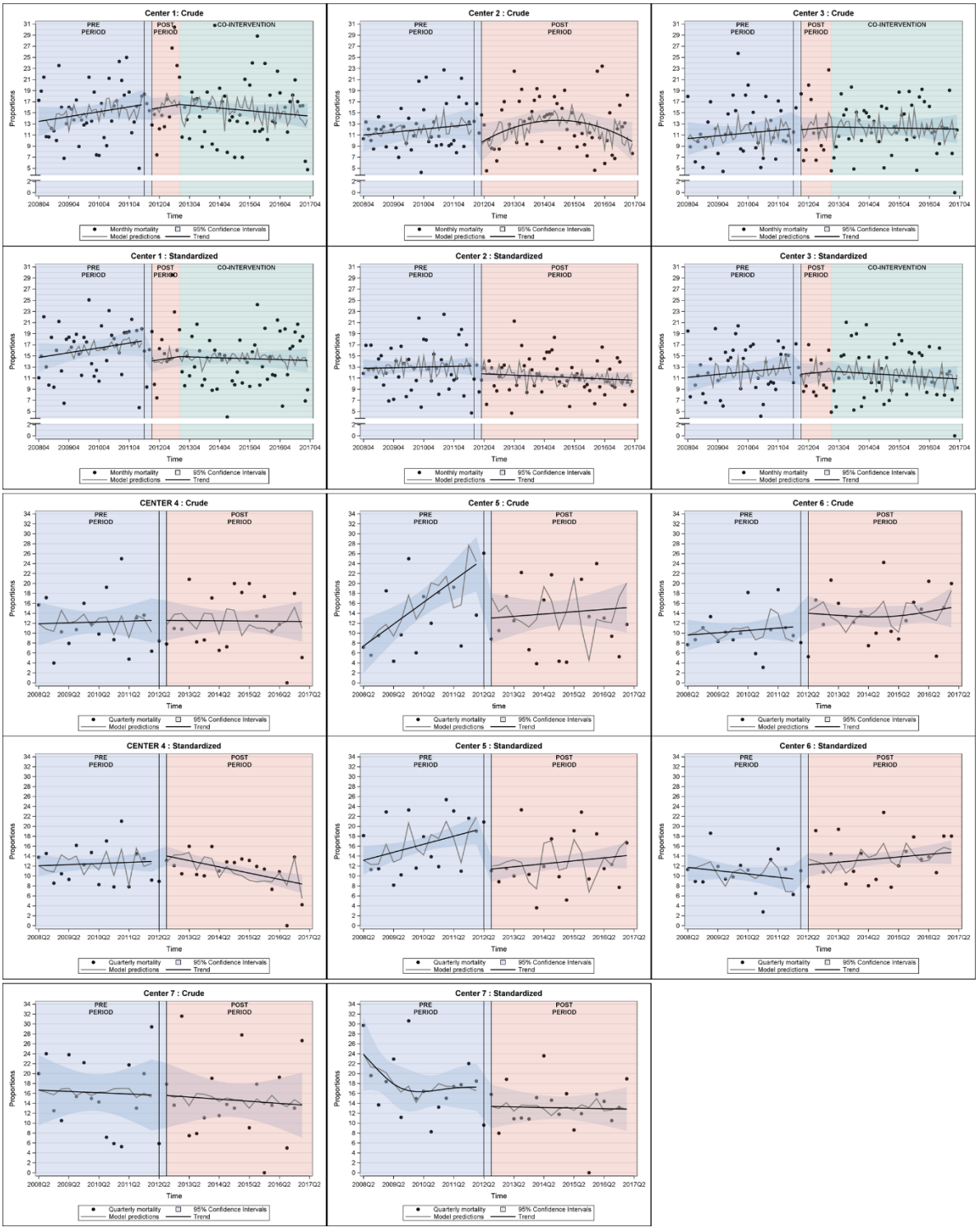
RESULTS

There were 51,035 admissions, including 20,165 for major trauma during the study period. The number of major trauma admissions remained stable throughout the study period, with an annual average of 539, 40 and 137 admissions respectively for adult Level I, pediatric Level I and adult level II centers. The proportion of patients transferred from another hospital was stable. However, there was an increase in the mean age of admitted patients, comorbidities, the proportion of falls and thoracic-abdominal injuries in all centers (**supplemental materials - eTable 5.1**). Among the major trauma patients, 12.90%, 5.73% and 12.77% experienced in-hospital death and 28.46%, 11.19% and 21.33% experienced major complications, respectively, for adult Level I, pediatric Level I and adult level II centers.

In-Hospital Mortality

Figure 5.1 displays the crude and standardized monthly probabilities of mortality for the three adult level I centers. In each center, we observed a decrease in the mean level and monthly trends of mortality following accreditation. However, the 95% confidence intervals were wide, and we lacked the precision to conclude that accreditation had a consistent beneficial impact on patient outcomes. Combining the three centers led to similar results (**Table 5.1**).

Figure 5.1: Monthly and quarterly proportions of in-hospital mortality in level I and II centers*



*Co-interventions represent visits for certification of centers as reference sites for spinal cord injury.

The time axis shows the year and the month for level I (1, 2 and 3) and year and quarters for level II centers (4 to 7).

Table 5.1: Change in trends and levels of the proportion in-hospital mortality following accreditation of level I & II centers*

Centers	Intercept		Pre-Period trend		Change in level		Change in trend	
	(%)	95% CI	Estimate	95% CI	RD	95% CI	RD	95% CI
Level I								
Center 1¥								
Crude	13.35	10.55, 16.15	0.07	-0.04, 0.19	-1.09	-5.46, 3.28	-0.11	-0.25, 0.03
Standardized	14.66	11.92, 17.41	0.07	-0.04, 0.18	-3.77	-8.14, 0.61	-0.08	-0.21, 0.06
Center 2								
Crude	10.89	7.94, 13.84	0.05	-0.07, 0.16	-2.00	-5.91, 1.91	-[a]	-[a]
Standardized	12.91	11.28, 14.54	0.00	-0.06, 0.07	-1.27	-3.50, 0.96	-0.02	-0.10, 0.05
Center 3¥								
Crude	10.33	7.28, 13.39	0.04	-0.08, 0.17	-0.47	-5.45, 4.51	-0.05	-0.20, 0.11
Standardized	11.20	8.68, 13.73	0.04	-0.06, 0.14	-1.30	-5.39, 2.79	-0.07	-0.19, 0.06
All$^{\lambda}$								
Crude	11.57	9.27, 13.87	0.01	-0.08, 0.10	0.93	-2.45, 4.31	-0.03	-0.14, 0.08
Standardized	13.11	11.35, 14.87	0.02	-0.06, 0.10	-1.00	-3.93, 1.93	-0.04	-0.13, 0.05
Level II								
Center 4								
Crude	11.78	7.47, 16.09	0.05	-0.41, 0.52	-0.47	-6.71, 5.77	-0.03	-0.58, 0.52
Standardized	11.73	9.41, 14.06	0.08	-0.16, 0.33	0.77	-2.39, 3.93	-0.41	-0.71, -0.10
Center 5								
Crude	6.29	0.34, 12.24	1.10	0.47, 1.73	-13.07	-21.17, -4.96	-0.98	-1.78, -0.19
Standardized	12.17	9.02, 15.32	0.47	0.13, 0.80	-9.08	-13.29, -4.87	-0.34	-0.76, 0.08
Center 6								
Crude	9.57	7.04, 12.10	0.11	-0.18, 0.40	3.10	-0.64, 6.84	-[b]	-[b]
Standardized	12.20	9.61, 14.80	-0.18	-0.47, 0.11	3.05	-0.33, 6.44	0.31	-0.03, 0.65
Center 7								
Crude	16.71	8.96, 24.47	-0.07	-0.88, 0.75	0.03	-10.74, 10.80	-0.04	-1.05, 0.97
Standardized$^{\varepsilon}$	28.80	19.16, 38.44	-[b]	-[b]	-4.71	-11.97, 2.56		
All$^{\lambda}$								
Crude	11.08	7.57, 14.58	0.05	-0.26, 0.37	0.56	-4.07, 5.18	-0.33	-0.69, 0.03
Standardized	12.29	10.02, 14.54	-0.12	-0.34, 0.11	1.03	-2.79, 4.86	-0.05	-0.44, 0.35
Pediatric centers§								
Center 8 & 9								
Crude	6.92	3.48, 10.37	-0.39	-0.89, 0.12	1.57	-1.71, 4.84	0.53	-0.12, 1.19
Standardized	8.70	3.22, 14.19	-0.33	-1.20, 0.53	0.83	-1.90, 3.57	0.39	-0.66, 1.43

*RD: differences in in-hospital mortality proportions; Risk differences and 95% confidence intervals are obtained though piecewise regressions with autocorrelated errors; Rubin's rule was used to combine the estimates from the 20 imputed datasets.

[¥]Due to collinearity, we modeled the change in the trend following the co-intervention.

[a]Non-linear trend modeled using quadratic terms; [b]Non-linear trend modeled using restricted cubic splines.

[λ]Risk differences and 95% confidence intervals were obtained from a weighted generalized estimated equation, with robust standard errors. Weights were obtained by the inverse of the squared standard errors of each monthly probability, to account for the fact that some centers have a higher volume of patients than others. Fixed effects for each center were also added to account for unmeasured characteristic between centers which are constant over the study period.

[ε]Due to collinearity, we only modeled the change in level following accreditation

[§]Risk differences and 95% confidence intervals were obtained from a weighted generalized estimated equation, with robust standard errors. Weights were obtained by the inverse of the squared standard errors of each monthly probability, to account for the fact that some centers have a higher volume of patients than others. The time unit was semester due to the small sample size, and we only standardized for age, sex, body region of the most severe injury, injury severity and mechanism.

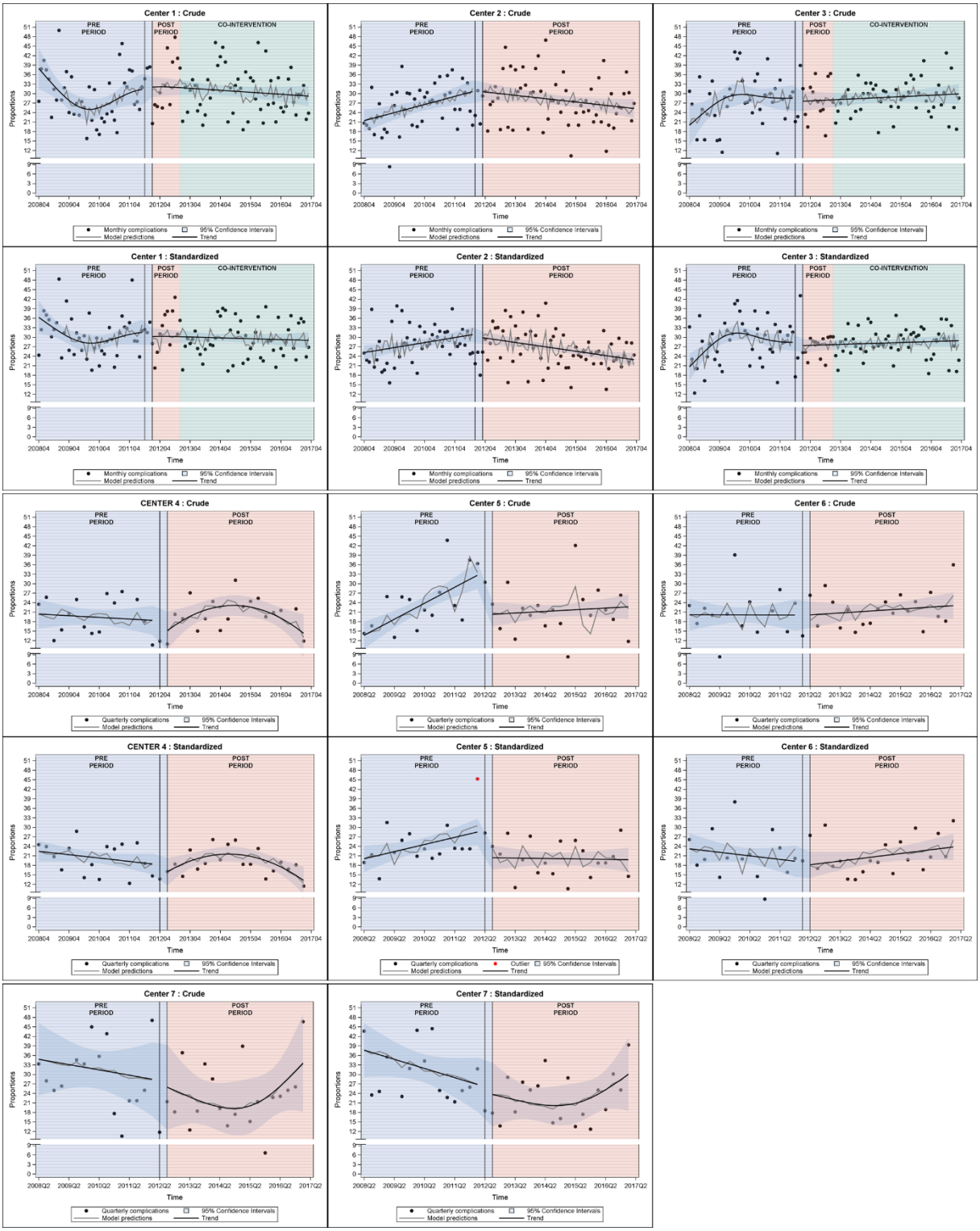
In adult level II centers, data were aggregated by quarter due to the smaller sample sizes. Across centers, we observed substantial variation in performance (**Figure 5.1**). For center 5, which exhibited a strong pre-accreditation increase in mortality, accreditation was associated with a 9.08 percentage point reduction (95% CI: -13.29, -4.87) in mortality. We also observed a 0.41 percentage point reduction (95% CI: -0.71, -0.10) in the quarterly trend in center 4. Combining all level II centers, observed associations were no longer present, given that centers 5 and 7 had a smaller volume of patients (around 800 admissions for each center during the study period) compared to centers 4 and 6, which each recorded more than 1,300 admissions (**Table 5.1**).

Due to the low number of deaths in pediatrics centers (n=41), we used a weighted GEE model combining the two centers. Results do not show an association between accreditation and in-hospital mortality (**Table 5.1**).

Complications

Figure 5.2 displays the crude and standardized monthly probabilities of major complications in adult level I centers. Trend in complications were non-linear. Accreditation was associated with a 0.25 percentage point decrease (95% CI: -0.35, -0.15) in the monthly trend for center 2. When combining the three centers together, accreditation was associated with a decrease in the monthly trend of complications (**Table 5.2**).

Figure 5.2: Monthly and quarterly proportions of major complications in level I and II centers*



*Co-interventions represent visits of certification of centers as reference site for spinal cord injury. Major complications included the following: acquired respiratory distress syndrome, pneumonia, pulmonal emboli,

respiratory failure, cardiac arrest, sepsis, renal failure, stroke, myocardial infarction and in-hospital mortality. The time axis shows the year and the month for level I (1, 2 and 3) and year and quarters for level II centers (4 to 7).

Table 5.2: Change in trends and levels of major complications following accreditation of level I & II centers*

Centers	Intercept		Pre-Period trend		Change in level		Change in trend	
	(%)	95% CI	Estimate	95% CI	RD	95% CI	RD	95% CI
Level I								
Center 1¥								
Crude	38.85	31.66, 46.04	-[a]	-[a]	0.32	-6.78, 7.42	-	-
Standardized	36.99	31.38, 42.98	-[a]	-[a]	-1.49	-7.00, 4.03	-	-
Center 2								
Crude	21.21	17.45, 24.97	0.21	0.07, 0.36	-0.87	-6.05, 4.30	-0.30	-0.47, -0.13
Standardized	24.98	22.78, 27.18	0.13	0.05, 0.22	-1.37	-4.42, 1.68	-0.25	-0.35, -0.15
Center 3¥								
Crude	19.25	11.99, 26.50	-[a]	-[a]	-1.03	-6.77, 4.71	-	-
Standardized	19.76	15.13, 24.39	-[a]	-[a]	-1.15	-4.74, 2.44	-	-
All[λ]								
Crude	25.42	23.04, 27.80	0.10	0.01, 0.19	-0.34	-3.97, 3.29	-0.14	-0.25, -0.03
Standardized	27.75	25.70, 29.79	0.07	0.00, 0.14	-2.03	-4.79, 0.73	-0.12	-0.20, -0.03
Level II								
Center 4								
Crude	20.52	15.53, 25.50	-0.13	-0.65, 0.39	-0.19	-7.32, 6.94	-[b]	-[b]
Standardized	22.17	18.65, 25.69	-0.21	-0.58, 0.16	-0.16	-5.19, 4.87	-[b]	-[b]
Center 5								
Crude	12.43	7.82, 17.05	1.26	0.78, 1.75	-14.85	-21.10, -8.61	-1.13	-1.75, -0.51
Standardized	19.18	14.68, 23.68	0.60	0.12, 1.08	-9.60	-15.77, -3.43	-0.63	-1.24, -0.02
Center 6								
Crude	20.26	15.16, 25.37	-0.01	-0.59, 0.57	0.03	-7.07, 7.12	0.16	-0.49, 0.82
Standardized	24.24	18.79, 29.68	-0.34	-0.95, 0.28	-0.34	-7.90, 7.23	0.63	-0.07, 1.32
Center 7								
Crude	35.17	22.69, 47.65	-0.42	-1.72, 0.88	-1.70	-20.83, 17.44	-[a]	-[a]
Standardized	38.61	29.82, 47.41	-0.77	-1.68, 0.14	-1.01	-14.46, 12.43	-[a]	-[a]
All[λ]								
Crude	20.75	16.86, 24.64	-0.04	-0.45, 0.36	-1.00	-6.91, 4.91	0.09	-0.34, 0.52
Standardized	22.77	19.93, 25.61	-0.20	-0.49, 0.10	-1.02	-5.29, 3.25	0.21	-0.17, 0.60
Pediatric centers[§]								
Center 8 & 9								
Crude	17.16	10.46, 23.86	-0.86	-1.87, 0.16	-1.86	-8.01, 4.29	1.92	0.14, 3.69

Standardized	18.01	9.36, 26.67	-0.82	-2.25, 0.61	0.83	-3.72, 5.40	0.84	-0.80, 2.47

*Risk difference and 95% confidence intervals are obtained though a piecewise regression with Autocorrelated errors; Rubin's rule was used to combine the estimates from the 20 imputed datasets.

¥Due to collinearity, we only modeled a change in level after accreditation for center 1 and center 3.

[a]Non-linear trend modeled using restricted cubic splines; [b]Non-linear trend was modeled adding quadratic terms.

λRisk differences and 95% confidence intervals were obtained from a weighted generalized estimated equation, with robust standard errors. Weights were obtained by the inverse of the squared standard errors of each monthly probability, to account for the fact that some centers have a higher volume of patients than others. Fixed effects for each center were also added to account for unmeasured characteristic between centers which are constant over the study period.

§Risk differences and 95% confidence intervals were obtained from a weighted generalized estimated equation, with robust standard errors. Weights were obtained by the inverse of the squared standard errors of each monthly probability, to account for the fact that some centers have a higher volume of patients than others. The time unit was semester due to the small sample size, and we only standardize for age, sex, body region of the most severe injury, injury severity and mechanism.

Among adult level II centers, center 5, which experienced a 0.60 (95% CI: 0.12, 1.08) percentage point increase in the quarterly pre-accreditation trend, accreditation was associated with a 9.60 percentage point reduction (95% CI: -15.77, -3.43) in the level and a 0.63 percentage point reduction (-1.24, -0.02) for the quarterly trend in complications (**Figure 5.2**). We further adjust for the outlier point two quarters before the accreditation visits in that centers and observed a smaller reduction, 5.68 percentage point reduction (95% CI: -11.64, 0.28). We do not observe an association between accreditation and complications when combining all level II centers together (**Table 5.2**).

Accreditation was not associated either with a change in levels or trends of complications in pediatric centers, after combining the two pediatric centers due to the low number of major complications (n=80) (**Table 5.2**).

Sensitivity analysis

Table 5.3 presents corrected estimates and 95% confidence intervals for the average change in outcomes following accreditation in center 5 (center for which accreditation had the greatest observed association), over a range of different values of sensitivity parameters (RR_{UY} and RR_{AU}). The columns represent the inverse of the largest relative risk of the effect of one or more unmeasured confounders U on the outcome (RR_{UY}) and the rows the inverse of the largest relative risk of accreditation and U (RR_{AU}). For example, if following accreditation, there is a 40% increase in reports of comorbidities due to changes in coding practices, then RR_{AU} =0.7 (1/1.4); and if patients who were more susceptible of having their comorbidities underreported in the pre-accreditation area (mostly older patients) are 25% more likely to die than other patients then RR_{UY}=0.8 (1/1.25). Therefore, the corrected reduction in in-hospital mortality due to accreditation is -7.88 percentage points (95%CI: -12.15, -3.61). **Table 5.3** also indicates that if RR_{AU} =0.7, patients who were more likely to have their comorbidities underreported should have at least twice more risk of death compared to other patients (RR_{UY}=0.5) to explain away the observed associations.

Table 5.3: Change in levels corrected for unmeasured confounder (U); Columns correspond to decreasing strength of the risk ratio of U on the outcome; Rows correspond to decreasing strength of risk ratio relating accreditation and U.*

	Center 5				
	In-hospital mortality				
	0.5	**0.6**	**0.7**	**0.8**	**0.9**
0.5	(,)	11.42 (2.82 , 20.01)	-1.41 (-7.00 , 4.17)	-5.69 (-10.38 , -1.00)	-7.83 (-12.1 , -3.55)
0.6	11.42 (2.82 , 20.01)	-0.9 (-6.60 , 4.8)	-5.01 (-9.83 , -0.18)	-7.06 (-11.48 , -2.64)	-8.29 (-12.48 , -4.1)
0.7	-1.41 (-7.00 , 4.17)	-5.01 (-9.83 , -0.18)	-6.8 (-11.27 , -2.33)	-7.88 (-12.15 , -3.61)	-8.6 (-12.73 , -4.46)
0.8	-5.69 (-10.38 , -1.00)	-7.06 (-11.48 , -2.64)	-7.88 (-12.15 , -3.61)	-8.43 (-12.59 , -4.26)	-8.82 (-12.92 , -4.72)
0.9	-7.83 (-12.10 , -3.55)	-8.29 (-12.48 , -4.10)	-8.6 (-12.73 , -4.46)	-8.82 (-12.92 , -4.72)	-8.98 (-13.05 , -4.91)

Major complications					
	0.5	**0.6**	**0.7**	**0.8**	**0.9**
0.5	(,)	8.57 (5.31 , 11.83)	1.98 (-1.68 , 5.64)	-2.96 (-7.01 , 1.10)	-6.8 (-11.2 , -2.40)
0.6	8.57 (5.31 , 11.83)	2.42 (-1.21 , 6.05)	-1.97 (-5.94 , 2.00)	-5.26 (-9.52 , -1.00)	-7.82 (-12.32 , -3.32)
0.7	1.98 (-1.68 , 5.64)	-1.97 (-5.94 , 2.00)	-4.79 (-9.01 , -0.57)	-6.91 (-11.32 , -2.5)	-8.55 (-13.12 , -3.99)
0.8	-2.96 (-7.01 , 1.10)	-5.26 (-9.52 , -1.00)	-6.91 (-11.32 , -2.5)	-8.14 (-12.67 , -3.61)	-9.1 (-13.72 , -4.48)
0.9	-6.8 (-11.2 , -2.4)	-7.82 (-12.32 , -3.32)	-8.55 (-13.12, -3.99)	-9.1 (-13.72 , -4.48)	-9.53 (-14.19 , -4.87)

*The columns represent the inverse of the largest relative risk of the effect of any unmeasured confounders U on the outcome (RR_{UY}) and the rows the inverse of the largest relative risk of accreditation and U (RR_{AU}). If following accreditation, there is for example a 40% increase in reports of comorbidities only due to changes in coding practices, then RR_{AU} =0.7 (1/1.4); then patients who were more susceptible to have their comorbidities underreported should have at least twice more risk of death compared to other patients (RR_{UY}=0.5) to explain away the observed association. In the case of complications, if RR_{AU} =0.7, then patients who were more susceptible to have their comorbidities underreported should have at least a 65% higher risk of complications compared to other patients (RR_{UY}=0.6) to explain away the observed association.

The average change in level correspond to the accreditation average marginal effect for all the post period time points.

Applying a sensitivity analysis formula for differential measurement errors in continuous outcomes (**appendix 5.2**)(32), we estimated that an increase in the reporting of complications following accreditation could only amplify the observed associations, while a decrease in the report of complications would reduce the observed association. The former is more plausible, and therefore our results are likely an underestimate of any true effect.

Finally, applying robust-ITS to assess the impact of accreditation yielded similar results (**supplemental materials - eTable 5.2**). In the case of in-hospital mortality, a 2.34 percentage point reduction (95%CI -4.96, 0.18) in level and a 0.04 percentage point reduction (95%CI: -0.13, 0.04) in the monthly trend were observed. In addition, robust-ITS models identified that the change point in the series (time at which accreditation initially affects the outcomes) occurred five months before the visit. A change in data dependency following accreditation was also

observed, there was a negative first order autocorrelation in the pre-period suggesting that outcomes taken close together in time are likely to be dissimilar, while in the post-accreditation period there was less evidence for the presence of autocorrelation.

DISCUSSION

Main findings

After accounting for changes in patient's case-mix and secular trend in studied outcomes, our study did not find consistent evidence of a beneficial impact of accreditation on in-hospital mortality or complications in severely injured patients. However, for centers (2 and 5) with a pre-accreditation increase in the levels of these outcomes, accreditation was associated with a decrease in levels (due to the preparation for the visit) and/or trends. These associations were robust to moderate levels of residual confounding and differential measurement error, potentially due to changes in coding practices following accreditation.

Previous studies looking at the impact of accreditation on mortality and complications found inconsistent results(11). Accreditation was imprecisely associated with decreased mortality, except among critically injured patients (Injury Severity Score>24) [OR: 1.17 (95% CI: 1.05 - 1.30)](29, 39-43). Some studies suggested an association between accreditation and reductions in the occurrence of complications, which was stronger among older adults [OR: 0.40 (95% CI: 0.27 - 0.60)] and pediatric critically injured patients [OR: 0.23 (95% CI: 0.12 - 0.47)](40, 41). Other studies did not observe any association between accreditation and patient outcomes(44, 45). However, all these studies were either cross-sectional or pre-post and conducted in the United States where accreditation is mostly voluntary. Cross-sectional studies do not distinguish centers

that failed during the accreditation process from those that never applied among their control centers. This may have led to a bias given that high-performing centers might be more willing to seek accreditation than low-performing centers. Although pre-post studies are less vulnerable to the bias mentioned above, they cannot account for the underlying trend in the measured outcomes before accreditation, which can bias estimates in either direction(26).

Limitations

Our study has some caveats that should be considered when interpreting our results. Other events capable of influencing studied outcomes may have occurred at the same time as the accreditation, introducing bias. In addition, changes in coding practices following accreditation may also have biased our results by introducing errors in the measurement of patient characteristics and outcomes. However, our sensitivity analyses suggested that the magnitude of these errors would have to be strong to completely explain our observed effects. In addition, we adjusted for other major co-interventions that occurred at the center level. We also adjusted for seasonality which can bias the results if the accreditation occurs around a seasonal changing point. The Ljung-Box test of each ITS model indicated that residuals could be considered as white noise and thus our models were correctly accounting for trends, seasonality and any other cycles present in the series(28).

In sensitivity analyses, we also applied a robust interrupted time series (robust-ITS) model that overcomes limitations of piecewise regressions, i.e., inability to model changes in variation and/or correlation of outcomes following accreditation(34, 35). In addition, the change point (time at which accreditation initially affects the outcomes) may have occurred earlier than three months

before the visit, due to possible improvements in patient outcomes during the preparation for the visit(46-48). Using robust-ITS, we observed slightly higher estimates of change in level and trends compared to our main analysis, mostly because the change point in the series was identified as occurring five months before the visit. In addition, there was a negative autocorrelation in the pre-period suggesting that outcomes taken close together in time are likely to be dissimilar, while in the post-accreditation period there was less evidence for presence of autocorrelations(49).

Our study might be underpowered, even with several time points. Recent simulations demonstrated that in addition to the number of time points, other factors such as the sample size per time point, expected effect size, location of intervention in the time series, and pre-intervention trends need to be considered to denote an ITS analysis as sufficiently powered(50). However, there was no way to increase our sample size, given that we include all trauma patients satisfying inclusion criteria. Finally, our outcomes were percentages and restricted to lie between 0 and 100. This has important consequences given that ceiling or floor effects can bias results(34, 51).

Estimates of accreditation impact stratified by levels are weighted average, with weights being a function of both center size and variances. Given that the accreditation visit dates were different by center, these estimates might be a poor summary of the average center-specific effects(52). In addition, with heterogeneous treatment effects, linear regressions with period and group fixed effects can yield a negative average effect while all specific effect are positive(53).These caveats considered, our results do not consistently support the hypothesis that accreditation decreases

in-hospital mortality and major complications. Our hypothesis was based on the fact that accreditation aims to ensure the standardization of the human and material resources within the center and/or better adherence to evidence-based clinical processes of care. However, its impacts on patient outcomes in a mature trauma system might be less evident if centers have already achieved a plateau in their performance(46, 54, 55). This is supported by the fact that we do observe some associations within centers experiencing a deterioration in their performance before the accreditation visit. While a changing trend from positive to negative or flat can be considered a successful outcome of accreditation, the lack of deviation from an already flat trend does not necessary constitute a failure given that other outcomes such as organizational culture and patient reported outcome measures could also be impacted.

CONCLUSIONS

We presented a comprehensive assessment of mandatory trauma center accreditation in a mature trauma system. Our study fills a gap in the literature given that previous studies were limited in their internal validity, since they lacked a design to identify the effect of accreditation, and their external validity, since the prior literature was derived from the United States where accreditation is mostly voluntary. Accreditation seems to be beneficial for centers experiencing a decrease in performance in the months preceding the visit. However, further studies looking at clinical processes of care and other outcomes such as patient or health staff satisfaction are needed to improve our understanding of the impact of accreditation.

Appendix 5.1

Prognostic score

To obtain monthly or quarterly estimate of outcomes for level I and level II centers, respectively, we first estimated the risk of the respective outcome (in-hospital mortality or major complications) in a sample of patients admitted during the pre-accreditation area to avoid overfitting, using a pooled logistic regression: $logit\, Y_{ic} = \beta_0 + \beta_z Z_{ic}$ **(eq 5.1)**, with Y_{ic} representing the outcome of interest of a patient i in the center c; Z being the vector of patient risk factors including age, sex, number of comorbidities, systolic blood pressure, Glasgow coma scale, pulse, body region of the most severe injury, mechanism of injury, injury severity score and transfer-in from another acute care hospital. β_z coefficients from model **(eq 5.1)** were then used to estimate the probability of the respective outcome ($Score_{ic}$) for all patients during the study period based on their observed covariates Z_{ic}.

Secondly, we ran a second logistic model $logit\, Y_{ic} = \beta_0 + \beta_1 Unit + \beta_2 Center + \beta_3 Unit * Center + \beta_4\, logit(Score_{ic})$ **(eq 5.2)**, with $Unit$ being months for level I and trimesters for level II adult centers, modeled as factors. Marginal predictions from equation **(eq 5.2)** were aggregated at the unit level to obtain for each center, a time series of 108 monthly or 36 quarterly proportions of mortality or complications. **Note:** Restricted cubic splines with 4 knots were used for age, injury severity score, pulse and systolic blood pressure.

Piecewise regression

After verifying that each series of marginal proportions were trend stationary using correlogram and the Augmented Dickey-fuller test, we performed our interrupted time-series analysis using equation**(eq 5.3)**: $Y_u = \beta_0 + \beta_1 time + \beta_2 Accreditation + \beta_3 Post\_period\_time + R_u$, with $R_u = \Phi_1 R_{u-1} + \Phi_p R_{u-p} + \varepsilon_u$. Y_u is the monthly or quarterly proportion of the studied outcome in a given time unit u, β_0 is the intercept for the pre-accreditation series, $time$ is coded 1 to 108 for level I or 1 to 36 for level II centers, and its coefficient $\beta_1$is the trend of the regression line for the pre-accreditation period. The dummy variable $Accreditation$ indicates whether each time point occurred before or after the accreditation (0 for all time prior and 1 for all time after). The coefficient β_2 is the change in the level of Y_u due to the preparation for accreditation. The variable $Post\_period\_time$ represents the number of months or quarters since accreditation (0 for all time until the event;1,2,3...for subsequent time points), and its coefficient $\beta_3$the change in the trend of the post-accreditation months. R_u is the autoregressive component, comprised of Φ_p which is the autoregressive parameter for lag p, and ε_u, the white noise or random error.

Appendix 5.2

Bounding factor for Risk Difference Using Sensitivity Parameters on the Relative Risk Scale

Applying the formula described by Ding et al, for an apparently preventive exposure we have(33) : $RD_{true} \leq P_1 \times BF_U - P_0$, with P_1 and P_0 are probabilities of the outcome in the pre and post accreditation period, adjusted for the pre-trend; BF_U is the bounding factor defined as $BF_U = RR_{AU} \times RR_{UY} / (RR_{AU} + RR_{UY} - 1)$. RR_{UY} represents the inverse of the largest relative risk of the effect of one

or more unmeasured confounders U on the outcome (columns in **Table 5.3**) and RR_{AU} the inverse of the largest relative risk of accreditation and U (rows in **Table 5.3**).

Differential measurement error of continuous outcomes

Applying the formula proposed by VanderWeele et al, we have(32):

(1) $Y_{MISS} = \gamma_0 + \gamma_1 Accreditation + \gamma_2 Y_{GOOD} + \gamma_3 time$

(2) $Y_{MISS} = \beta_0 + \beta_1 Accreditation + \beta_2 time$

(3) $\beta_{1\_GOOD} = (\beta_1 - \gamma_1)/\gamma_2$

With Y_{MISS} representing the monthly or quarterly proportions of major complications which is subject to a differential error; Y_{GOOD} is the correct or true measure of major complications and β_{1_GOOD} is the corrected estimate of the change in level of monthly or quarterly complications following accreditation.

If the effect of Y_{GOOD} on Y_{MISS} (γ_2)=1 so that Y_{MISS} scales with Y_{GOOD}, then we have $\beta_{1\_GOOD} = (\beta_1 - \gamma_1)$. Therefore, to obtain the corrected estimate of the change in level of monthly or quarterly complications following accreditation, we only subtract γ_1 (differential measurement error direct effect of accreditation on Y_{MISS} not through Y_{GOOD}) to the observed β_1 obtained with our analysis.

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5.3 Supplemental material: Manuscript 3

eTable 5.1: Characteristics of the 20,165 severely injured admissions during the study period (April 2008 to March 2017)*

Characteristics	Years					
	2008	2010	2012	2014	2016	Total
Total admissions (n, %)	5,064 (9.93)	5,855 (11.47)	5,606 (10.98)	5,237 (10.26)	5,423 (10.63)	51,035
Major trauma (ISS≥12) (n, %)	1,693 (8.40)	2,274 (11.28)	2,267 (11.24)	2,174 (10.78)	2,269 (11.25)	20,165
Center Level (%)						
Level I	72.42	72.21	70.62	71.76	72.98	72.06
Level II	23.69	23.66	25.54	24.93	24.33	24.39
Pediatrics	3.90	4.13	3.84	3.31	2.69	3.55
Male sex (%)	71.77	69.00	69.43	71.7	70.52	70.38
Body region of the most severe injury (%)						
Head	60.96	60.64	61.23	57.41	55.49	58.98
Thorax and abdomen	20.14	19.70	19.94	24.89	27.37	23.00
Extremities	6.85	6.38	6.97	5.47	5.42	6.00
Neck and spine	12.05	13.28	11.87	12.24	11.72	12.03
Injury mechanism (%)						
MVC	44.65	42.13	39.13	32.93	33.98	38.23
Fall	38.57	40.77	44.16	48.44	49.23	44.73
Penetrating	2.01	2.42	2.07	2.62	2.78	2.69
Others	14.77	14.69	14.64	16.01	14.01	14.35
Transfer from another hospital (%)						
Level I	63.30	58.71	57.28	59.04	58.27	59.20
Level II	42.39	35.32	35.75	38.93	40.04	37.75
Pediatrics	71.21	74.47	68.97	75.00	75.41	76.78
Shock (SBP<90) (%)						
Level I	3.43	4.08	4.31	4.17	3.80	3.77
Level II	3.49	4.09	5.01	3.32	2.90	4.47
Pediatrics	9.09	6.38	10.34	6.94	6.56	9.65

Glasgow Coma Scale (%)						
3-8	23.57	22.43	20.11	19.92	18.20	20.17
9-12	7.50	6.90	7.85	6.85	6.35	7.16
13-15	68.93	70.67	72.03	73.23	75.45	72.67
Number of comorbidities (%)						
0	81.33	74.45	71.02	68.08	66.64	71.31
1 -2	16.72	22.69	24.93	27.92	28.08	25.11
3+	1.95	2.86	4.06	4.00	5.29	3.57
Age (mean, SD)						
Level I	49.80 (21.96)	51.93 (22.45)	53.93 (22.59)	56.97 (21.60)	57.66 (21.46)	54.36 (22.16)
Level II	50.56 (23.49)	52.78 (23.76)	54.60 (22.88)	56.74 (22.66)	57.10 (22.54)	54.72 (23.00)
Pediatrics	8.71 (5.56)	8.47 (5.52)	7.43 (5.84)	9.29 (5.13)	8.70 (5.76)	8.43 (5.73)
ISS (Median, IQR)						
Level I	21 (16 – 26)	21 (16 – 26)	22 (16 – 26)	22 (17 – 26)	22 (17 – 26)	22 (16 – 26)
Level II	18 (16 – 25)	18 (14 – 25)	18 (14 – 25)	19 (16 – 25)	18 (14 – 25)	18 (14 – 25)
Pediatrics	19 (14 – 26)	17 (16 – 25)	17 (16 – 25)	20 (16 – 26)	18 (16 – 26)	18 (16 – 26)

*Results from one imputed dataset, other datasets have similar distributions. Only even years are presented for parsimony.

ISS: Injury Severity Score; MVC: Motor Vehicle Collisions; SBP: Systolic Blood Pressure; SD: Standard Deviations.

eTable 5.2: Robust Interrupted time series*

	Change in level		Change in trend		AR(1) pre-period		AR(1) post-period	
	(%)	**95% CI**	**Estimate**	**95% CI**	**RD**	**95% CI**	**RD**	**95% CI**
Center 2								
In-hospital mortality	-2.34	-4.96, 0.18	-0.04	-0.13, 0.04	-0.25	-0.51, 0.05	0.02	-0.24, 0.27
Major complications	-2.84	-6.19, 0.51	-0.22	-0.33, -0.11	-0.32	-0.57, -0.03	-0.18	-0.42, 0.08

*Rubin's rule was used to combine the estimates from the imputed datasets, while applying appropriate transformation for autocorrelation coefficients.

AR(1)=First order autocorrelations.

5.4. Accreditation and hospital length of stay for Quebec trauma centers

Hospital length of stay (LOS) was not included in manuscript 3 to provide clarity. Given that the analyses were performed per center, presenting LOS results in manuscript 3 would have led to a very dense paper.

5.4.1. Brief overview of the statistical methods

The same study sample and covariates as in manuscript 3 were used and the same accreditation cycle (3rd) was evaluated. The outcome of interest was the total length of stay (LOS) measured as time to discharge in days. In-hospital mortality was the competing event. Patients with LOS exceeding 60 days were censored.

The statistical approaches used were described in Chapter 4 (manuscript 2). Briefly, inverse probability weighting (IPW) was used to account for changes in patient case-mix over the study period, and the weighted Aalen-Johansen estimator was used to compute standardized cumulative incidences of discharge for the pre- and post-accreditation periods for descriptive analyses.(195-197). However, to account for possible underlying trends, monthly or quarterly estimates of the risk of being discharged alive by specific days (7, 14 and 30) after admission were computed and piecewise regressions with autocorrelated errors **(eq3.4)** were used to assess the impact of accreditation(143). The regression based ITS approach was selected because the outcomes series were trend stationary.

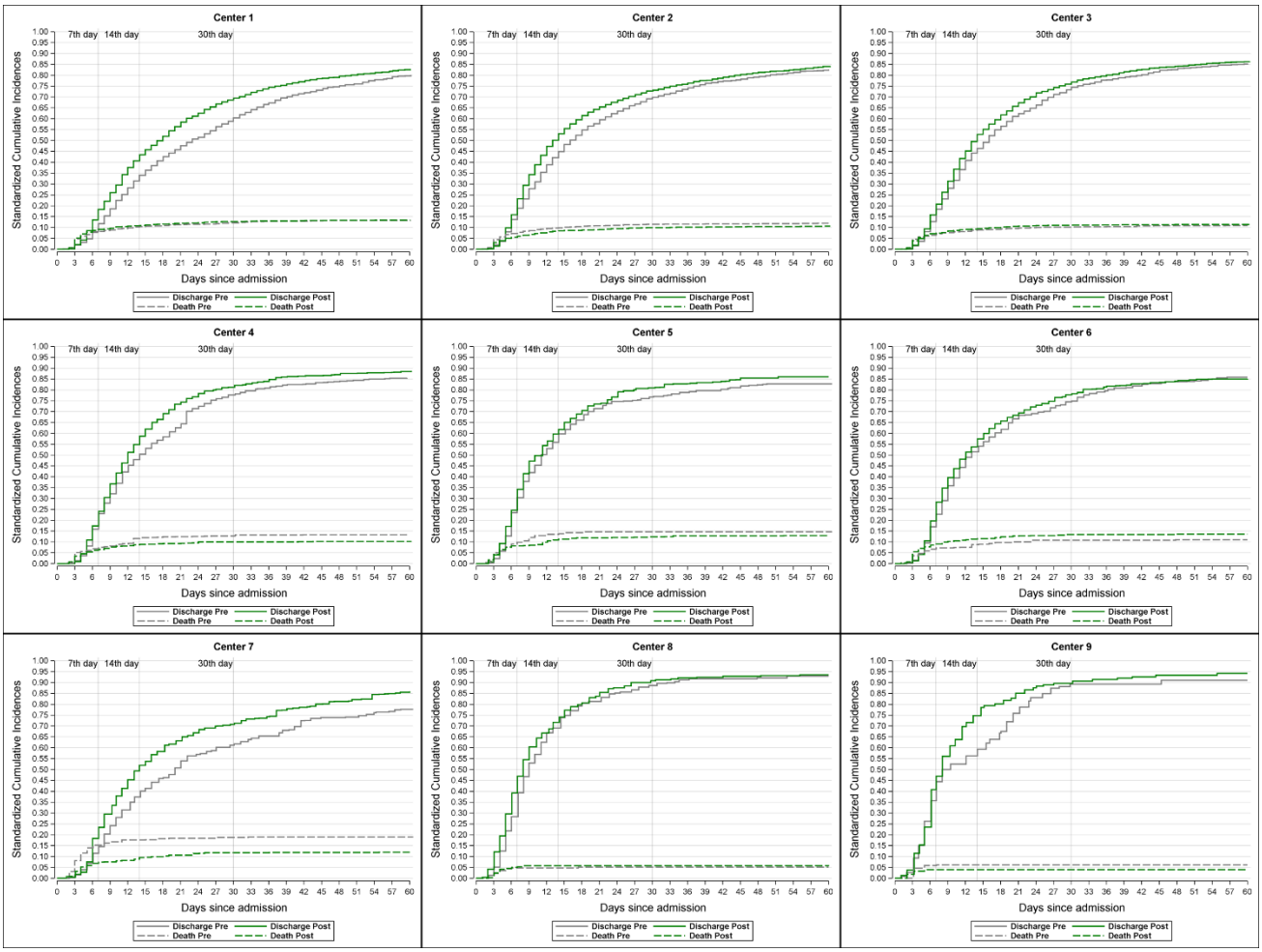
Assessing the impact of accreditation on risks of discharge by specific days provides more useful information to hospital managers than the differences in the average length stay, which do not account for the competing risk of death. An increase in the discharge risk indicates a decrease in

the LOS. Multiple imputation with chained equations was used to impute missing data(198). All analyses were performed in SAS, version 9.4, software (SAS Institute, Inc., Cary, North Carolina).

5.4.2. Results

Figure 5.3 displays the standardized cumulative incidences (risks) of being discharged alive in the pre- and post-accreditation periods. In all centers, around 95% of patients were either dead or discharged alive 60 days after admission. In level I centers (centers 1 to 3), the risk of being discharged alive were higher in the post-accreditation period, mostly between the 7^{th} and 30^{th} days following admission. At the same time, there was no increase in in-hospital mortality. In fact, there was some indication of a reduction in center 2, in line with the results observed in **manuscript 3**. Similar results were observed for level II centers (particularly for centers 4 to 7), with a higher risk of being discharged alive in the post-accreditation periods compared to the pre-period. There was also an indication of a lower risk of in-hospital mortality in the post-accreditation period except for center 6, in line with the results described in **manuscript 3**. For pediatric centers (8 and 9), there was a stronger indication of an increase in discharge risks in center 9 than in center 8.

Figure 5.3: Standardized cumulative incidences of being discharged alive*



*Standardized weights were obtained by inverse probability weighting.

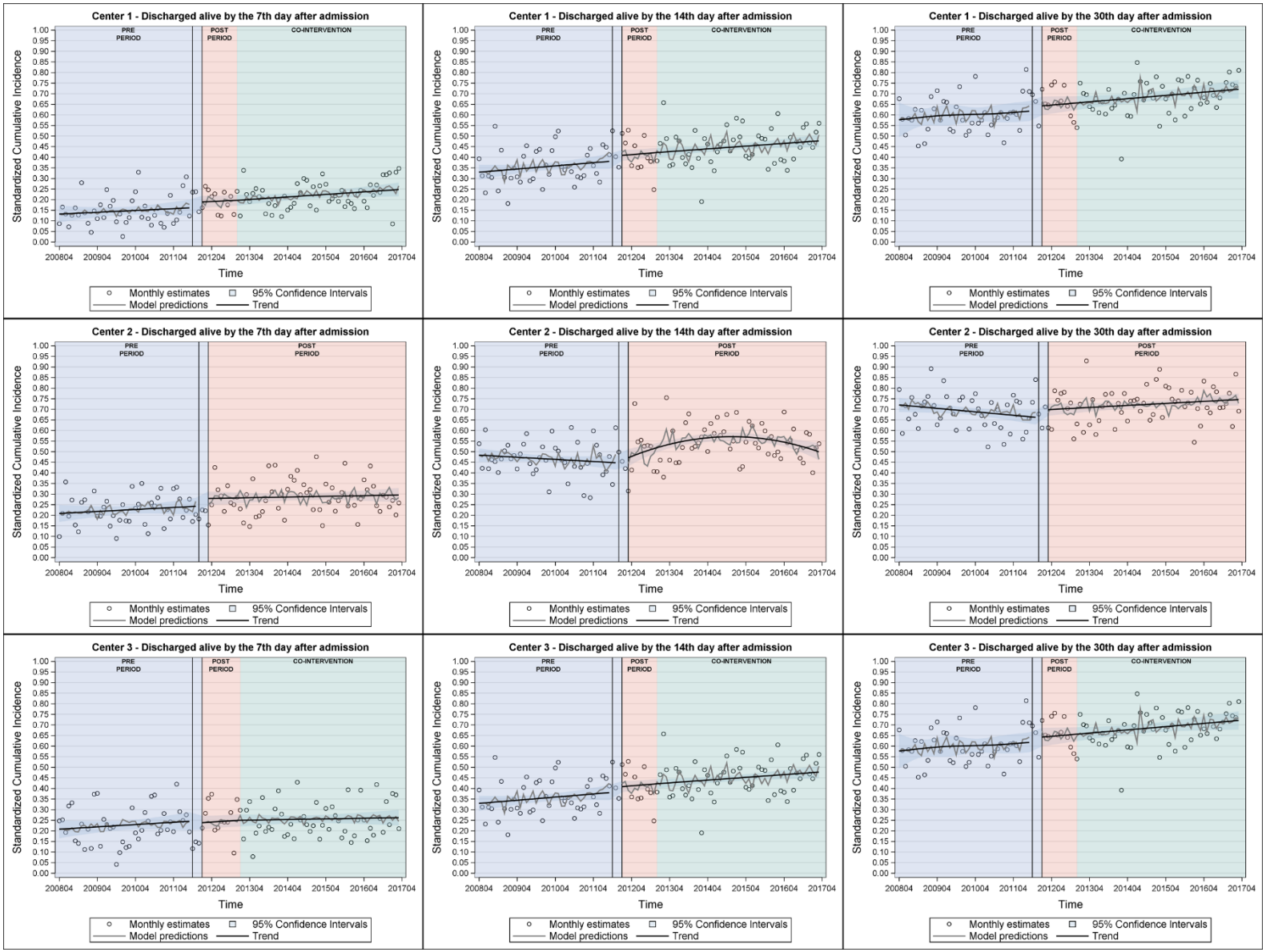
To estimate the impact of accreditation on the risk of being discharged alive, monthly (for level I) or quarterly (for level II) estimates for specific days were used in a segmented regression to account for possible underlying trends in outcomes**.** Standardized cumulative incidences of being discharged alive by given specific days since admission throughout the study period are shown in **Figure 5.4,** and the corresponding change in level and trend estimates following accreditation with 95% confidence intervals in **Table 5.4**. For level I centers, the apparent increases in the risk of being discharged alive following accreditation observed in **Figure 5.4** were no longer present

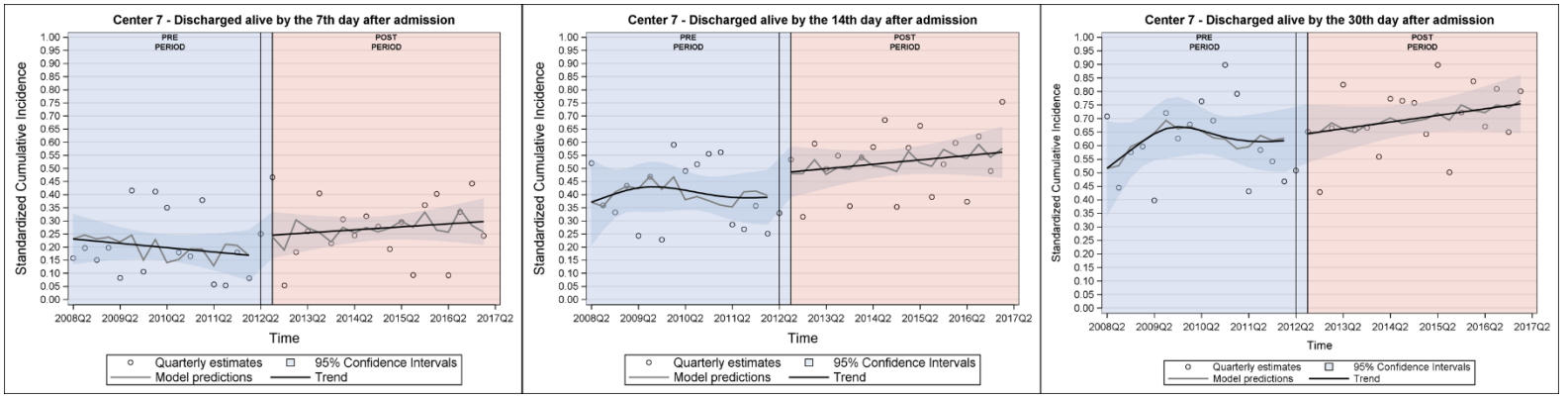
in centers 1 and 3, after accounting for the underlying trend in discharge risks. For center 2, which experienced a decrease in pre-accreditation trends, we observed a 5.19 percentage point increase (95% CI: -0.04, 10.43) in the level of discharge by the 14th day after admission, a 3.86 percentage point increase (95% CI: -1.13, 8.05) in the level of discharge by the 30th day, and a 0.21 percentage point increase (95% CI: 0.05, 0.38) in the trend of the monthly discharge by the 30th day.

Similar patterns were observed for level II centers, where accreditation seemed to increase the risk of being discharged alive in centers with a downward pre-accreditation trend of discharge, specifically centers 5 and 7 (**Table 5.4**).

Only pre-post analyses were conducted for pediatric centers due to the small sample size (**Figure 5.5**). The increase in discharge risk following accreditation was higher between the 7th and 30th day (**Table 5.4).** However, the 95% confidence intervals were wide, limiting inference concerning the impact of accreditation on the risk of being discharged alive.

Figure 5.4: Risk of being discharged alive on given specific days*





*The time axis shows the year and the month for level I (1, 2 and 3) and year and quarters for level II centers (4 to 7).

Table 5.4: Change in trends and levels of the risk of being discharged alive following accreditation of level I & II centers*

Discharged alive	Intercept		Pre-Period trend		Change in level		Change in trend	
	(%)	95% CI	Estimate	95% CI	RD	95% CI	RD	95% CI
				Level I				
Center 1¥								
By the 7th day	12.83	8.97, 16.69	0.08	-0.08, 0.24	2.29	-3.89, 8.47	0.02	-0.17, 0.21
By the 14th day	32.30	28.67, 35.94	0.14	-0.01, 0.29	1.98	-3.77, 7.73	-0.02	-0.20, 0.16
By the 30th day	56.43	48.43, 64.44	-[a]	-[a]	2.57	-3.30, 8.43	0.12[c]	0.03, 0.21
Center 2								
By the 7th day	20.95	16.81, 25.09	0.07	-0.09, 0.24	3.50	-2.30, 9.31	-0.05	-0.23, 0.14
By the 14th day	48.66	45.04, 52.27	-0.09	-0.23, 0.05	5.19	-0.04, 10.43	-[b]	-[b]
By the 30th day	72.11	68.46, 75.77	-0.13	-0.27, 0.01	3.86	-1.13, 8.85	0.21	0.05, 0.38
Center 3¥								
By the 7th day	20.51	16.33, 24.68	0.09	-0.08, 0.26	-0.89	-7.48, 5.70	-0.07	-0.28, 0.14
By the 14th day	45.48	42.84, 48.12	0.11	-0.01, 0.23	2.29	-2.12, 6.70	-0.12	-0.25, 0.01
By the 30th day	74.88	72.02, 77.75	-[a]	-[a]	-4.68	-15.71, 6.35	-[¥]	-[¥]
				Level II				
Center 4								
By the 7th day	26.51	20.02, 32.99	0.29	-0.39, 0.97	-4.32	-13.40, 4.77	-0.04	-0.86, 0.79
By the 14th day	47.52	39.50, 55.53	0.84	0.02, 1.66	-8.03	-18.67, 2.61	-0.16	-1.19, 0.87
By the 30th day	78.45	74.56, 82.35	-0.04	-0.44, 0.36	2.94	-2.10, 7.98	0.03	-0.46, 0.53
Center 5								
By the 7th day	23.29	6.14, 40.44	-[a]	-[a]	-0.03	-12.42, 12.36	1.03[c]	0.25, 1.81
By the 14th day	50.54	39.60, 61.48	-[a]	-[a]	6.29	-0.37, 12.96	0.53[c]	0.00, 1.06
By the 30th day	72.82	59.22, 86.42	-[a]	-[a]	8.62	-1.29, 18.54	-0.18[c]	-0.84, 0.48
Center 6								
By the 7th day	27.23	18.51, 35.96	0.10	-0.89, 1.08	2.36	-9.78, 14.50	0.09	-1.01, 1.19
By the 14th day	51.17	45.06, 57.28	0.44	-0.23, 1.11	-2.01	-10.22, 6.20	-0.24	-1.03, 0.55
By the 30th day	77.35	74.37, 80.34	-0.33	-0.66, 0.00	6.24	2.61, 9.86	0.24	-0.14, 0.62
Center 7								
By the 7th day	24.37	13.54, 35.21	-0.43	-1.55, 0.70	8.75	-6.02, 23.52	0.63	-0.80, 2.05
By the 14th day	33.59	12.70, 54.49	-[a]	-[a]	10.74	-4.71, 26.20	0.37[c]	-0.38, 1.12
By the 30th day	48.19	27.94, 68.44	-[a]	-[a]	5.20	-11.57, 21.97	0.52[c]	-0.53, 1.56
				Pediatric centers				
Center 8ε								
By the 7th day					8.02	0.28, 15.76		
By the 14th day					0.81	-5.16, 6.79		
By the 30th day					2.14	-2.03, 6.31		

Center 9 [ε]		
By the 7th day	3.30	-8.39, 14.99
By the 14th day	18.05	8.03, 28.07
By the 30th day	0.49	-6.10, 7.08

*RD: differences in hospital discharge risks; risk differences and 95% confidence intervals are obtained through piecewise regressions with autocorrelated errors. Rubin's rule was used to combine the estimates from the 20 imputed datasets.

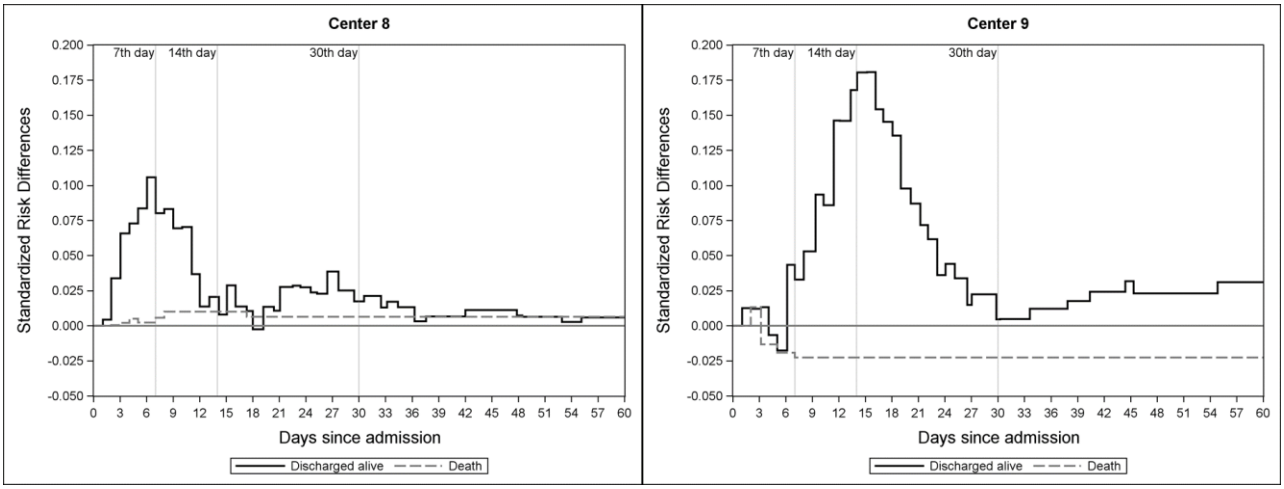
[¥]Due to collinearity, we modeled the change in the trend following the co-intervention, except for the risk of being discharge alive by the 30th day where only a change in level was assessed.

[a]Non-linear trend modeled using restricted cubic splines; [b]Non-linear trend modeled using quadratic terms.

[c]Estimates represent the trend in the post period.

[ε]Due to the small sample size, estimates are obtained by subtracting the cumulative incidences from pre-post analyses and the standard errors were obtained using bootstrapping.

Figure 5.5: Risk of being discharged alive at given specific days for pediatric centers (pre-post)*



*Average across the 20 imputed datasets, the vertical grey lines represent the 7th, 14th and 30th day after hospital admission.

5.4.3. Discussions

While pre-post results suggest a higher risk of being discharged alive following accreditation, overall, there was weak evidence of an impact of accreditation on the risk of discharge after

accounting for underlying trends. However, for centers experiencing downward pre-accreditation trends, specifically centers 2 and 5, accreditation led to a shorter LOS through an increase in the risk of being discharged alive, higher on the 14th day following admission. Nevertheless, observed estimates were too imprecise to confidently conclude that accreditation reduced LOS.

Previous studies on the impact of accreditation on LOS found mixed and inconsistent results. Two studies found an increase in mean LOS following accreditation of 6.10 days (95%CI: 1.63, 10.57) in major trauma patients with thoracic vascular injuries(199), and 4.05 days (95%CI: -0.02, 8.12) for patients with head injuries(200). Two other studies including all trauma patients found a decrease of 0.48 days (95%CI: -0.76, -0.20)(201), and -0.78 days (confidence intervals not provided) for pediatric patients(201, 202). Other studies did not find an association(31, 165, 203). These studies, however, applied linear regressions with mean LOS as the outcome, without considering the competing risks of in-hospital mortality, rarely adjusted for change in case-mix and were all performed in a context where accreditation is voluntary.

LOS should be considered as a time to event outcome and estimating the probability that a patient will be discharged alive by a given day is an important indicator of quality of care and a proxy for hospital costs(190). Given that in all adult centers, more than 10% (range from 11.6 % in center 4 to 14.4% in center 1) of patients died during the study period, disregarding the competing risks of in-hospital mortality would have led to an overestimation of the discharge risks. Finally, the associations observed between accreditation and higher risks of being discharged alive (shorter LOS) in centers 2, 5, 7 and 9 cannot be explained by an increase in in-hospital mortality since

accreditation was also associated either with a reduction of the level or trends of mortality proportions in these centers (**manuscript 3**).

The results presented above are subject to the same limitations detailed in **manuscript 3,** including potential change in coding practices which may have led to errors in the measurement of patient characteristics, and the possibility that co-occurring events around accreditation visits, which may have influenced mortality and discharge risks. It is impossible to predict the directions of the resulting bias this would induce.

5.4.4. Conclusions

As with in-hospital mortality and major complications, accreditation seems to be beneficial for centers experiencing a decrease in performance in the months preceding the visit. However, the observed estimates were too imprecise to conclude that accreditation reduced LOS through an increase of the risk of being discharged alive.

CHAPTER 6. Trauma system accreditation and patient outcomes in British Columbia: An interrupted time series analysis

6.1 Preface: Manuscript 4

This thesis has identified gaps and limitations in the literature on the impact of trauma accreditation with patient outcomes (chapter 2) and potential mitigation strategies to address them (chapters 3 and 4). In Chapter 5, I incorporated these approaches to assess the impact of accreditation in a mandatory context, whereas this chapter examines the impact of accreditation in a voluntary context (manuscript 4). In addition, this manuscript evaluates if change in the accreditation body has an impact on investigated outcomes.

This study uses the ITS framework detailed in Chapter 3 and is was accepted for a poster presentation at the 79th Annual Meeting of the American Association for the Surgery of Trauma and Clinical Congress of Acute Care Surgery to be held in Waikoloa, Hawaii on September 9-12, 2020.[9] It is now accepted for publication to the *International Society for Quality in Health Care*.

[9] The meeting will be in a virtual format due to the COVID-19 pandemic

6.2 Manuscript 4

Title: Trauma system accreditation and patient outcomes in British Columbia: An interrupted time series analysis.

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Funding

Funds for this project are covered by the Fonds de recherche du Québec – Santé (FRQS) PhD scholarship (BB) and a Canadian Institute of health Research (CIHR) Foundation grant (FRN 353374 for LM and FRN 148467 for AN).

Acknowledgement

The authors will like to thank Recep Gezer from the British Columbia Trauma services and Xavier Neveu from the Population Health and Optimal Health Practices Research Unit, Trauma –

Emergency – Critical Care Medicine, Centre de Recherche du CHU de Québec for their help in the analyses and design stage of this study.

Conflict of Interest

NY was a former president of the Trauma Canada Association and JT is part of the Data, Evaluation & Analytics team of the British Columbia Trauma services.

Abstract

Objectives: Periodic external accreditation visits aiming to determine whether trauma systems and centers are fulfilling the criteria for optimal care are now common in Canada. However, their impact remains unclear. A recent systematic review found inconsistent results on the association between accreditation and patient outcomes, with the lack of robust controls cited as a major limitation to extant research. We aim to address these gaps using a quasi-experimental design to assess the impact of several accreditation cycles on patient outcomes, specifically in-hospital mortality, complications and hospital length of stay.

Design: Interrupted time-series.

Setting: British Columbia, Canada.

Subjects: Trauma patients admitted to all level I and II trauma centers between January 2008 and March 2018.

Intervention: Accreditation.

Measurements: We first computed quarterly estimates of the proportions of in-hospital mortality, complications and survival to discharge standardized for change in patient case-mix using prognostic scores and the Aalen-Johansen estimator of the cumulative incidence function. Piecewise regressions were then used to estimate the change in levels and trends for patient outcomes following accreditation.

Main results: For in-hospital mortality and major complications, the impact of accreditation seems to be associated with short- and long-term reductions after the first cycle and only short-

term reductions for subsequent cycles. However, the 95% confidence intervals for these estimates were wide, and we lacked the precision to consistently conclude that accreditation is beneficial.

Conclusions: Applying a quasi-experimental design to time series accounting for changes in patient case-mix, our results indicate that accreditation might reduce in-hospital mortality and major complications. Further studies looking at clinical processes of care and other outcomes such as patient or health staff satisfaction are needed.

Keywords: Trauma centers, Trauma systems, Accreditation, Verification, Mortality, Complications, Length of stay.

INTRODUCTION

Trauma systems, which are organized and multidisciplinary responses to injury along the continuum from pre-hospital care to rehabilitation, have led to important reductions in injury mortality(1, 2). Essential to the development of a trauma system is the role of the regional designating authority (state/provincial)(3), which is responsible for the determination and designation of trauma centers according to levels of care (levels I – and II for adult- and pediatric specific centers; levels III-V for all ages), based on regional needs and available resources(3). Trauma centers are acute care hospitals where resources are prioritized to ensure that injured patients receive appropriate and timely care(4). Many North American organizations such as the American College of Surgeons Committee on trauma(ACS-COT), Trauma Association of Canada (TAC) and Accreditation Canada (AC) have established trauma system and center standards(3-5).

These standards have been used to develop trauma center accreditation processes, which aims to determine whether trauma centers and systems are fulfilling the criteria for optimal care. Accreditation generally requires a center to submit a prereview questionnaire, provide data on some performance indicators and to complete an on-site visit by an experienced peer review team(3, 6, 7). In Canada (except the province of Quebec), accreditation is voluntary and was sought by individual trauma centers until 2005. Thereafter, the focus of accreditation shifted from trauma centers to regional trauma systems, although still required that each center in the system be evaluated. Prior to 2014, the accreditation process was performed by the TAC and resulted in one of three outcomes for individual trauma centers: 1) successful, with a certificate valid for 5 years; 2) provisional, which confers a certificate valid for one year, during which the center or organization must correct of deficiencies identified in the review, and a full accreditation may be granted; and 3) unsuccessful, in which case a new application for a full review is required(4). From 2014, the process of accreditation of both regional systems and their included trauma centers was taken over by AC, thereafter, resulting in success or failure, with a certificate valid for four years(8). Since AC took the reins, only British Columbia (BC) and the Alberta regional trauma systems have undergone accreditation to date.

Proponents of accreditation argue that it enhances stakeholder engagement, strengthens collaboration through elements of the continuum of care and improves adherence to evidenced-based protocols, all of which improve patient outcomes(9). Criticisms of accreditation include the mobilization of resources and the possibility that improvements in care are only transitory(10-12). A recent systematic review synthesizing the evidence on hospital accreditation found that it was imprecisely associated with longer length of stay and reductions in mortality and occurrence

of complications(13). That review, however, highlighted methodological concerns that might bias observed associations, including the inappropriate selection of control centers in cross-sectional studies, inadequate control for underlying trends in outcomes in pre-post studies and the lack of adjustment for potential center and patient level confounders.

This study aims to fill important gaps in the current literature by using an interrupted time-series (ITS) design to assess the impact of the first and subsequent trauma center accreditation cycles on in-hospital mortality, major complications and hospital length of stay in British Columbia.

METHODS

Context

British Columbia trauma services can be described as a collaboration of five regional trauma systems, which consists of two adult level I, one pediatric level I, three adult level II and 68 lower level centers(14).

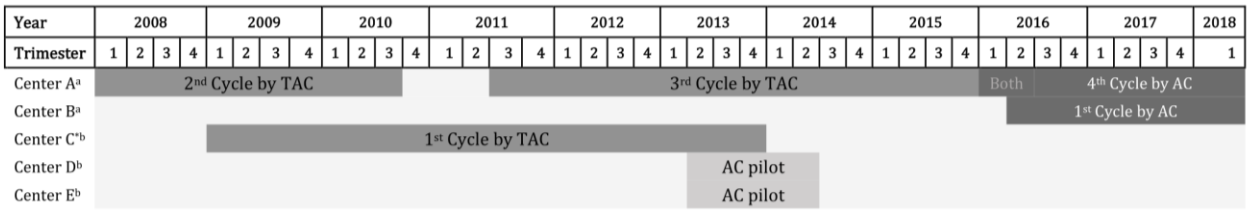
Study Sample

Our population consisted of trauma patients admitted to all level I and II adult trauma centers in British Columbia between 2008 and 2018. We used data from the British Columbia trauma registry, which is subject to rigorous data quality checks to ensure a high level of data integrity and consistency(14). Patients dead on arrival and patients aged 65 years or more with isolated orthopedic fractures due to a fall were excluded from the study population(15). Given our hypothesis that accreditation leads to better patient outcomes and that the effect is stronger for

severely injured patients, our analyses are restricted to patients with major trauma defined as having an Injury Severity Score (ISS) ≥12(16).

Since the establishment of a trauma service in 1990, three centers, including two Level I (center A and B) and one level II (center C), successfully completed at least one accreditation cycle during our study period (**Figure 6.1**). The other level II centers (D and E) did not seek accreditation during the study period. Due to data availability, we assessed the third and fourth cycles of accreditation in center A and the first cycle in center B. We did not evaluate the impact of accreditation in center C because the shorter pre-intervention period was inadequate to properly account for underlying secular trends in studied outcomes.

Figure 6.1 : Accreditation cycles in British Columbia Figure 6.1



AC: Accreditation Canada; TAC: Trauma association of Canada.
Accreditation Canada launched a pilot program in September 2013 before formally taking over Trauma Association of Canada accreditation program.
*Center C was accredited by Accreditation Canada in April 2018.
a: Level I center; b: level II center.

Measures

Our outcomes of interest included 1) in-hospital mortality defined as any death occurring between arrival in the emergency department and discharge; 2) major complications defined as the occurrence of any of the following during the hospitalization: acquired respiratory distress syndrome, cardiac arrest, myocardial infarction, pneumonia, pulmonary emboli, renal failure,

respiratory failure, sepsis, stroke or death(17-19); 3) total length of stay (LOS) measured as survival to discharge in days since admission(20). We presented risk of being discharge alive by given specific days rather than differences in the average length stay because the former provides more useful information to hospital managers and the latter cannot account for the competing risk of death. An increase in the proportion of patients discharged alive indicates a reduction in the LOS.

Covariates included age, sex, systolic blood pressure, Glasgow coma scale, pulse, body region of the most severe injury, mechanism of injury, ISS and transfer-in from another acute care hospital. Physiological variables were based on the first measurement taken on arrival in the emergency department. Patient comorbidities were not included due to substantial changes in the list of recorded comorbidities in the registry over the study period. To account for changes over times of the Abbreviated Injury Scale (AIS90 to AIS2005 in April 2012) used to compute ISS, published conversion tools were applied(21, 22).

Statistical methods

The analytical methods are described in detail in **appendix 6.1**. Briefly, a two-step approach was used. First, we used prognostic scores to obtain standardized quarterly proportions of mortality and major complications for each center(23, 24). For LOS, we accounted for the competing risk of in-hospital mortality by combining inverse probability weighting and the Aalen-Johansen estimator of the cumulative incidence function to obtain quarterly estimates of hospital discharges at specific weeks after admission(25, 26). Second, to estimate the impact of accreditation cycles on changes in levels (abrupt or short-term effects) and trends (long term

effects) in these proportions, we used a piecewise regression with autocorrelated errors to take serial correlation into account(27, 28). Seasonality and non-linearity in trends were investigated and modeled by incorporating autocorrelated error terms at a given seasonal lag and splines, respectively(29). Because centers prepare for accreditation, and it might take a longer time to prepare for the first cycle than subsequent ones, we excluded data from the twelve months preceding the first accreditation cycle and the three months preceding subsequent accreditation cycles to capture that possible preparation effect(30).

Sensitivity analyses

To assess the robustness of our results to possible co-interventions which may have coincided with accreditation visits, comparative interrupted time series (CITS) was applied when suitable controls could be found among level II centers, in particular if the outcome trends for the accredited and the non-accredited centers were parallel(27, 31). Otherwise, a propensity score based CITS where the control centers are weighted to represent the average outcome that the accredited center would have exhibited in the absence of accreditation was applied(32).

Multiple imputation with chained equations was used to impute missing data on the Glasgow coma scale score (22%), pulse (3.3%) and systolic blood pressure (2.9%)(33). Rubin's rules were used to combine estimates across 25 imputed datasets and to obtain 95% confidence intervals(25, 34). All analyses were conducted using SAS software, version 9.4.

RESULTS

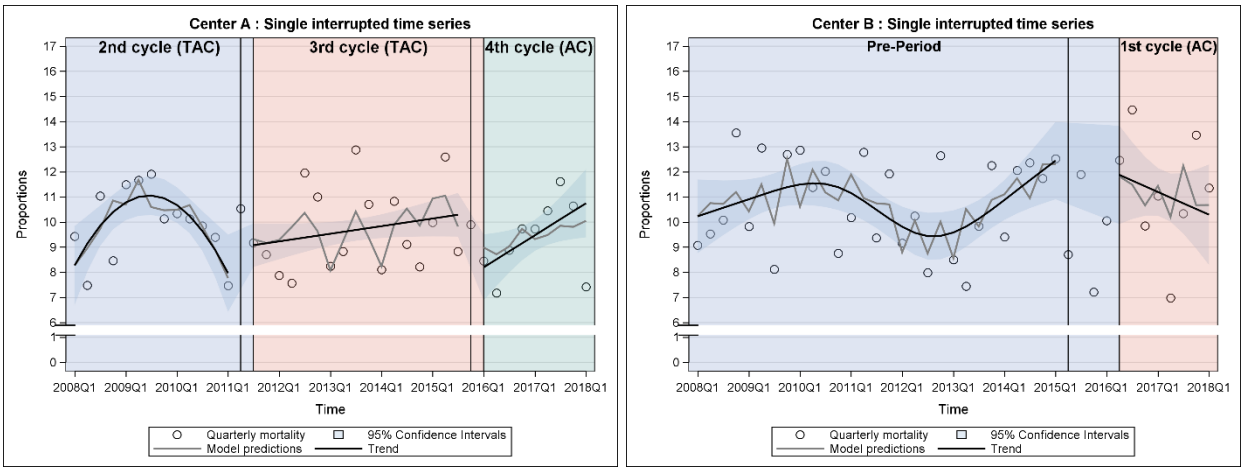
Overall, there were 17,606 admissions for major trauma during the study period. The number of admissions increased slightly during the study period. There were on average 624, 457 and 213 annual admissions, respectively, for center A, center B and adult level II centers. There was an increase in the mean age and the proportion of falls of admitted patients (**supplemental materials eTable 6.1**).

In-hospital mortality

Level I centers had similar levels of mortality: 9.84% (95%CI: 9.25 – 10.44) for center A and 10.34% (95% CI: 9.66 – 11.02) for center B. There was more variability in mortality among level II centers: 11.34% (95%CI: 10.46 – 12.21), 10.24% (95%CI: 9.03 – 11.45) and 11.91% (95%CI: 10.70 – 13.13) for centers C, D and E respectively.

Figure 6.2 displays the quarterly proportions of in-hospital mortality for the two level I centers. The 3rd cycle of accreditation in center A was associated with a 0.87 percentage point reduction (95% CI: -2.60, 0.87) in the level of mortality, while the 4th cycle performed by AC was associated with a 3.28 percentage point reduction (95% CI: -6.18, -0.38). However, those reductions were temporary or abrupt, and followed by an increase in the quarterly trend of mortality after each cycle (**Table 6.1**). Center B, which only underwent one cycle of accreditation during the study period, also experienced a 2.13 percentage point reduction (95% CI: -5.95, 1.69) in the mortality level. That apparent decrease seemed to be sustained, as we also observed a 0.50 percentage point reduction (95% CI: -1.11, 0.11) in the quarterly trend (**Table 6.1**). However, we lacked the precision to conclude that accreditation had a beneficial impact in center B.

Figure 6.2: Quarterly proportions of in-hospital mortality*



* The time axis shows the year and the trimester.

AC: Accreditation Canada; TAC: Trauma association of Canada.

Major Complications

Due to changes in the list of complications included in the registry during the study period, we excluded data before April 2012 to ensure consistency in the type of complications reported over time. Subsequently, 25.53% (95% CI: 24.39 – 26.68), 20.25% (95%CI: 19.02 – 21.48), 22.12% (95% CI: 20.54 – 23.71), 20.03% (95%CI: 18.05 – 22.01) and 20.42% (95%CI: 18.44 – 22.40) of patients experienced major complications, respectively, for centers A, B, C, D and E.

Figure 6.3 displays the quarterly proportions of major complications in adult level I centers. The 4th cycle of accreditation was associated with a 6.29 percentage point reduction (95% CI: -13.36, 0.77) in the level of complications. For center B, results suggested a decrease in the level and trend of major complications following accreditation (**Table 6.1**). However, we still lacked the precision to conclude that accreditation had a consistent beneficial impact.

Table 6.1: Change in trends and levels of the proportion of in-hospital mortality, major complications and hospital discharges following accreditation cycles*

Center A¥	Intercept		Pre- period		3rd cycle (TAC)				4th cycle (AC)			
			Trend		Change in level		Change in trend		Change in level		Change in trend	
	%	95% CI	Estimate	95% CI	RD	95% CI	RD	95% CI	RD	95% CI	RD	95% CI
Mortality	8.27	6.71, 9.84	-[a]	-[a]	-0.87	-2.60, 0.87	0.27	0.04, 0.50	-3.28	-6.18, -0.38	0.16	-0.19, 0.52
Complications[λ]	29.00	24.43, 33.56	-0.08	-0.53, 0.38	-		-		-6.29	-13.36, 0.77	0.58	-0.57, 1.73
Discharged alive												
Two weeks	53.03	47.21, 58.89	0.27	-0.47, 1.01	1.10	-6.63, 8.34	-0.66	-1.55, 0.23	6.91	-6.13, 19.96	0.14	-1.24, 1.51
One month	69.37	66.05, 72.69	0.54	0.12, 0.96	-1.29	-5.59, 3.02	-0.74	-1.24, -0.23	-1.68	-9.04, 5.69	0.81	-0.03, 1.65

Center B	Intercept		Pre- period		1st cycle (AC)							
			Trend		Change in level		Change in trend					
	%	95% CI	Estimate	95% CI	RD	95% CI	RD	95% CI	-		-	
Mortality	10.06	8.16, 11.97	-[b]	-[b]	-2.13	-5.95, 1.69	-0.50	-1.11, 0.11				
Complications[λ]	17.11	11.06, 23.16	0.50	-0.12, 1.11	-2.93	-10.23, 4.37	-0.72	-2.02, 0.58	-		-	
Discharged alive												
Two weeks	58.33	53.08, 63.58	0.01	-0.29, 0.32	1.57	-10.26, 13.40	1.32	-0.73, 3.37	-		-	
One month	77.28	74.35, 80.21	-0.06	-0.23, 0.10	0.69	-4.83, 6.20	0.96	0.05, 1.87	-		-	

AC: Accreditation Canada; RD: differences in outcomes proportions; TAC: Trauma association of Canada.

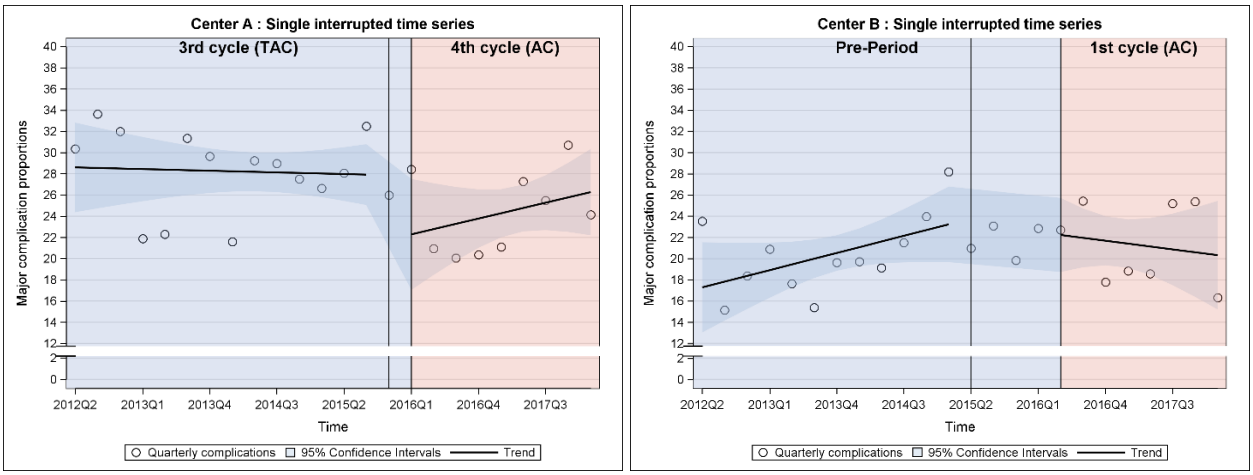
*Risk differences and 95% confidence intervals are obtained though piecewise regressions with autocorrelated errors; Rubin's rule was used to combine the estimates from the 25 imputed datasets.

¥ The pre-period in center 1 corresponds to the second cycle of accreditation performed by Trauma Association of Canada for mortality and discharges, and to the third cycle for complication.

[a]Non-linear trend modeled adding quadratic terms; [b]non-linear trend fitted using restricted cubic splines.

[λ]Data before April 2012 were excluded due to inconsistencies in the recording of complications; risk differences and 95% confidence intervals are obtained from generalized estimated equations, with robust standard errors.

Figure 6.3: Quarterly proportions of major complications*



AC: Accreditation Canada; TAC: Trauma association of Canada.

* The time axis shows the year and the trimester, and data before April 2013 were excluded due to inconsistencies in the recording of complications.

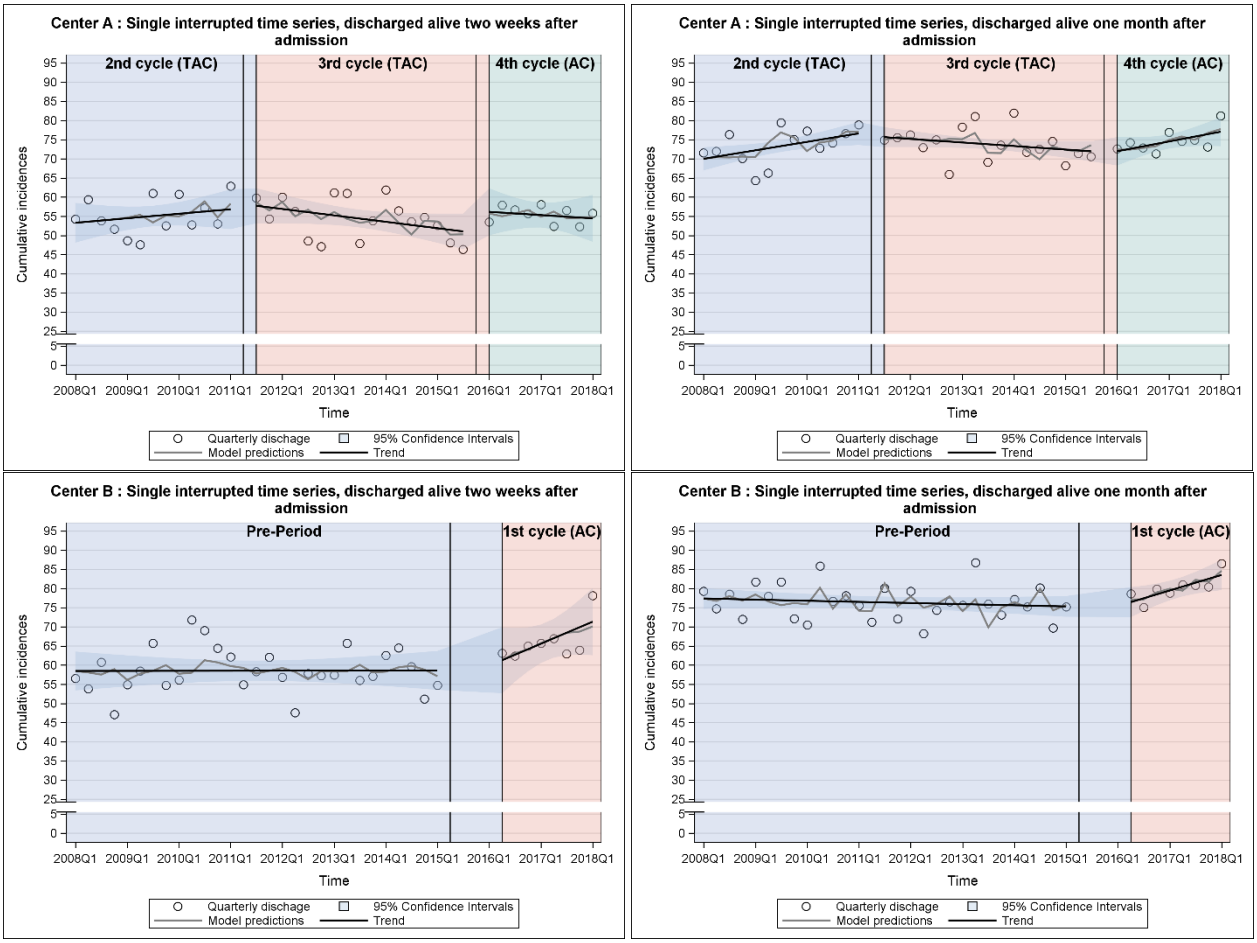
Major complications included the following: acquired respiratory distress syndrome, pneumonia, pulmonal emboli, respiratory failure, cardiac arrest, sepsis, renal failure, stroke, myocardial infarction and in-hospital mortality.

Hospital length of Stay

The cumulative incidence of being discharged alive between accreditation cycles in centers A and B suggest higher discharge risks following accreditation only for center B (**supplemental materials eFigure 6.1).** However, to account for possible underlying trends in outcomes, the risk of discharge at two weeks and at one month after patient admissions were used in ITS models (**Figure 6.4**). In center A, there was a 0.54 percentage point increase (0.12, 0.96) in the quarterly trend of being discharged alive by the 30th day after admission before the 3rd cycle of accreditation. While subsequent accreditation cycles were not associated with changes in levels in center A, there was a decrease in quarterly trends following the 3rd cycle and an increase after

the fourth cycle. In center B, accreditation was only associated with an increase in the quarterly trend, notably a 0.96 percentage point increase (95% CI: 0.05, 1.87) for the risk of being discharged alive by the 30th day (**Table 6.1** and **Figure 6.4**).

Figure 6.4: Cumulative incidences of being discharged alive and home respectively after two weeks and one month following admission*



AC: Accreditation Canada; TAC: Trauma association of Canada.

*The time axis shows the year and the trimester. Discharged alive comprised discharge at home, to rehab, to other long or acute care hospital.

Sensitivity Analysis

To assess the robustness of our results to possible co-interventions which may have occurred around accreditation visits, we applied a CITS analysis for major complications in center A (which satisfied the assumption of parallel trends). The results were similar to those obtained with single ITS, with a 7.94 percentage point reduction (95% CI: -15.84, -0.04) in the level of complications, relative to the change for the control group. We also attempted to use a propensity score-based weighting model for time series data, when it was not possible to perform a CITS analysis. However, due to the small number of potential control centers, the weights were too large or did not achieve good balance on the outcomes investigated in the pre-accreditation quarters. Nevertheless, reasonable balance was obtained for in-hospital mortality in center A and the results were similar to those obtained with single ITS for the 3rd accreditation cycle (**supplemental materials eFigure 6.2 and eTable 6.2**).

DISCUSSION

Main findings

In this multicenter cohort study, we observed results suggestive of a beneficial impact of accreditation on patient's outcomes for major trauma, after accounting for changes in patient case-mix and underlying trends in outcomes. For in-hospital mortality and major complications, accreditation seemed to be associated with a reduction in levels and trends after the first cycle (sustained effect) and only change in levels due to preparation for subsequent cycles (short term effect). The apparent decrease in levels might be due to the preparation for the accreditation visit. The change in the accreditation organization did not appear to modify observed

associations, except for LOS where we only observed an association (increase in the trend of the proportion of patients discharged alive by the 30th day after patient admission) for accreditation cycles performed by AC.

Previous studies on the impact of accreditation in a voluntary context found mixed and inconsistent results(13). Grossman et al.(35) observed increased in-hospital mortality among critically injured patients (Injury Severity Score>24; OR=1.17, 95% CI: 1.05 - 1.30), while other studies found a small reduction for all patients admitted to level I centers (combined OR=0.95, 95% CI: 0.91 - 1.00)(11, 13, 36, 37). Associations between accreditation and reductions in the occurrence of complications, stronger among older adults (OR=0.40, 95% CI: 0.27 - 0.60) and pediatric critically injured patients (OR=0.23, 95% CI: 0.12 - 0.47), have also been observed by some studies(35, 36), but not by others(38, 39). Concerning LOS, results are mixed, with previous studies observing no association(39-41), a reduction(38, 42) or an increase following accreditation(43, 44). These results should be interpreted cautiously because linear regressions with mean LOS as the outcome was applied, without accounting for the competing risks of death and change in case-mix was rarely considered(13).

In addition, these studies were either cross-sectional or pre-post studies and conducted in the United States. Cross-sectional studies lack a strategy for identifying the causal effect of accreditation and depend on robust adjustment for potential patient and center level confounders. Additionally, they, do not distinguish centers that failed during the accreditation process from those that never applied among their control centers. Although pre-post studies are less vulnerable to the bias mentioned above, since they account for time-fixed characteristics,

they cannot account for the underlying trend in the measured outcomes before accreditation, which can bias estimates in either direction(29). A study using ITS to assess accreditation impact in Quebec, Canada but in a mandatory context, observed heterogenous associations across centers. However, among centers with worsening pre-accreditation outcomes, accreditation led to decreases in levels and/or trends of mortality and complications(45). The authors concluded that the impact of accreditation on patient outcomes in a mature trauma system might be less evident if centers have already achieved a plateau in their performance.

The terms designation and accreditation (or verification, as it is known as in the United States context) are sometimes used interchangeably despite having different meanings and referring to different processes(9, 36, 39, 46). Accreditation aims to ensure the standardization of the human and material resources and better adherence to recommended clinical practices(47-49). Although many of the original accreditation criteria were based on expert opinion, they are regularly updated, to account for evidence-based research findings(48, 50, 51). This study was an attempt to assess the impact of first and subsequent accreditation cycles using quasi-experimental designs. Associations observed, particularly reductions in in-hospital mortality and major complications, might support the hypothesis that compliance to accreditation programs is important for achieving appropriate standards of care. The temporary effect observed for subsequent accreditation cycles might be partially explained by the fact that an accredited center is already adhering to most of the criteria for optimal care.

Limitations

Some caveats should be considered when interpreting our results. For example, changes in coding practices following accreditation may have led to errors in the measurement of patient characteristics and outcomes(28). In addition, ITS relies on extrapolation and thus on functional form assumptions, making model specification of pre- and post-intervention time series crucial(27). Nevertheless, sensitivity analyses using CITS or propensity score based weighted CITS to strengthen our inference suggested that our results were largely unaffected and seemingly robust to these biases. While these sensitivity analyses cannot rule out the presence any co-occurring events at the center level, they might have helped by excluding those at the provincial or regional trauma system level. Furthermore, an increase in the reporting of complications following accreditation due to changes in coding practice following accreditation could only lead to an underestimation of any true effect(52). We adjusted for seasonality (which can bias the results if the accreditation occurs around a seasonal changing point) and accounted for non-linear trends using splines or quadratic terms. The short length of our series may have limited our ability to estimate the pre-accreditation trends and worsen problems associated with extrapolation when evaluating subsequent accreditation cycles. In addition, it may have also led to collinearity problems when estimating change in outcome trends. However, except for LOS analyses, the tolerance statistic did not suggest multicollinearity issues between changes in levels and trends.

To capture the possible improvements in patient outcomes during the preparation for the visit, we removed data from the twelve and the three months preceding accreditation for the first and subsequent cycles, respectively(30, 49, 53, 54). However, the time at which the accreditation process could potentially start affecting outcomes may occur earlier. It also plausible for outcome

variability and dependency to change because of the accreditation. Unfortunately, our models were unable to assess changes in outcomes variation and/or correlation following accreditation. Ceiling and floor effects may have also bias observed associations since our outcomes were percentages, so restricted to lie between 0 and 100(55, 56). Finally, our study might be underpowered to detect small effect size, as illustrated by wide 95% confidence intervals in some analyses. However, there was no way to increase our sample size as we included all trauma patients satisfying inclusion criteria(57).

CONCLUSIONS

Our study helps to address a gap in the literature, given that previous studies had important limitations to their internal validity, since they lacked a strategy for accounting for unmeasured confounding. Accreditation seemed to be associated with a sustained effect on patients' outcomes for the first cycle, and a temporary effect during subsequent ones. Further studies are needed to confirm these findings. Investigating other relevant outcomes such as patient or health staff satisfaction are also warranted.

Appendix 6.1

Prognostic score

To obtain quarterly estimate of outcomes, we first estimated the risk of the respective outcome (in-hospital mortality or major complications) in a sample of patients admitted during the pre-accreditation area to avoid overfitting, using a pooled logistic regression: $logit\ Y_{ic} = \beta_0 + \beta_z Z_{ic}$

(6.1), with Y_{ic} representing the outcome of interest of a patient i in the center c; Z being the vector of patient covariates. β_z coefficients from model **(6.1)** were then used to estimate the probability of the respective outcome ($Score_i$) for all patients during the study period based on their observed covariates Z_{ic}.

Secondly, we ran a second logistic model $logit\, Y_{ic} = \beta_0 + \beta_1 Unit + \beta_2 Center + \beta_3 Unit * Center + \beta_4\, logit(Score_i)$ **(6.2)**, with $Unit$ being trimesters, modeled as factors. Marginal predictions from equation **(6.2)** were aggregated at the unit level to obtain for each center, a time series of 41 quarterly proportions of mortality or complications.

Cumulative incidences function

To estimate standardized cumulative incidences of being discharged alive while accounting for the competing risk of death, we assumed that administrative censoring at 60 days is noninformative and used the weighted Aalen-Johansen estimator(26): $\widehat{CIF^q_{(t,J)}} = \sum_{k \le t} \frac{E^w_{kj}}{n^w_k} \prod_{h<k} \left\{1 - \frac{E^w_h}{n^w_h}\right\}$, where t is time from patient admission to the event, j is the event type (discharge alive or home), $\widehat{CIF^q}$ represents the cumulative incidence density function for the trimester q, E^w_{kj} is the weighted number of events j at time k, n^w_k is the weighted number of subjects in the risk set at time k, and E^w_h is the weighted number of all events at time h regardless of the event type (discharge or death).

Single ITS

We used the following equation for center A:

$Y_Q = \beta_0 + \beta_1 time + \beta_2 TAC + \beta_3 Post_{TAC} + \beta_4 AC + \beta_5 Post_{AC} + R_Q$, with $R_{CQ} = \Phi_1 R_{Q-1} + \Phi_p R_{Q-p} + \mathcal{E}_Q$. Y_Q is the quarterly proportion of the investigated outcome in a given time unit q, β_0 is the intercept for the pre-accreditation series, $time$ is coded 1 to 41, and its coefficient $\beta_1$is the trend of the regression line for the pre-accreditation period. The dummy variables TAC and AC indicates whether each trimester occurred before or after the TAC or AC accreditation respectively (0 for all trimester prior and 1 for all trimester after). β_2 and β_4 coefficients are the change in the level of Y_Q respectively due to the preparation for the TAC or AC accreditation. The variables $Post_{TAC}$ and $Post_{AC}$ represent the number of trimesters since accreditation (0 for all quarters prior; 1,2,3...for subsequent trimesters), and their coefficients β_3 and β_5 the change in the trend of Y_{CQ} following accreditation. R_Q is the autoregressive component, comprised of Φ_p which is the autoregressive parameter for lag p, and $\mathcal{E}_Q$, the white noise or random error. For center B, all TAC regressor terms were removed.

ITS with control centers (CITS)

We performed linear regression models using generalized estimating equations, regressing the outcome Y_{CQ} on the centered time variable (T – $taccr$), the intervention indicator Post (0 if t < $taccr$, otherwise 1), the group indicator G (G = 1 for the treatment group and G = 0 for the control group), and the corresponding two-way and three-way interactions:

$$Y_{CQ} = \beta_0 + \beta_1(T - taccr) + \beta_2 Post + \beta_3 G + \beta_4 Post * (T - taccr) + \beta_5 Post * G + \beta_6 G * (T - taccr) + \beta_7 Post * G * (T - taccr) + \beta_8 Center$$

Y_{CQ} is the marginal quarterly proportion of the investigated outcomes, β_5 estimates the difference between accredited and control centers in the level of the studied outcomes immediately after the onset of the intervention (due to preparation for the visit) and β_7 the

difference between accredited and control centers in the change in trend of the outcome variables. β_8 represent fixed effects for centers, to adjust for unmeasured characteristic between centers which are constant over the study period. Robust standard errors were used to account for data dependency structures.

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6.3 Supplemental material: Manuscript 4

eTable 6.1: Characteristics of the severely injured (ISS≥12) admissions during the study period (January 2008 to March 2018)*

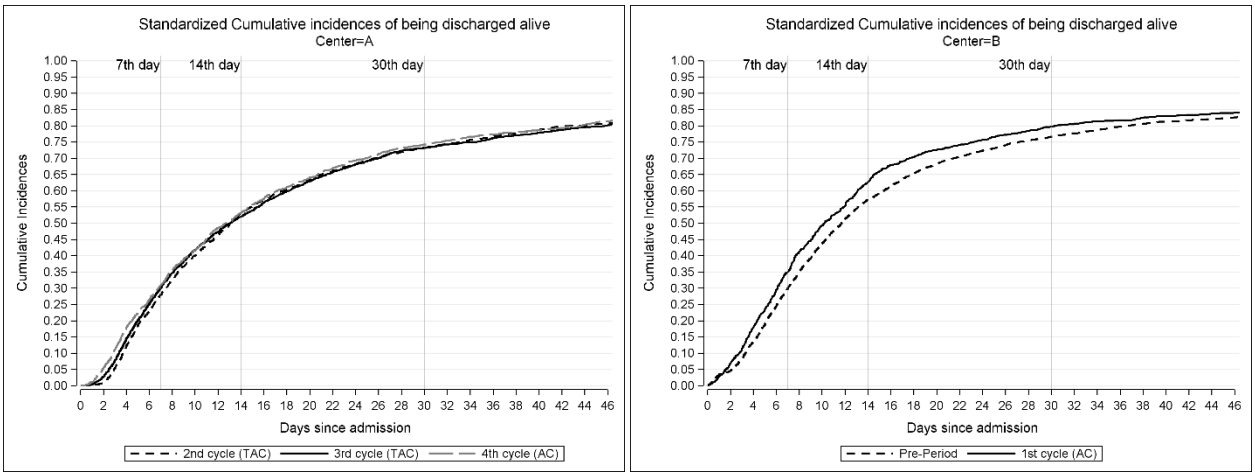
Characteristics	Years					
	2009	2011	2013	2015	2017	Total
Total admissions (n, %)	1,610 (9.14)	1,605 (9.12)	1,589 (9.03)	1,890 (10.73)	1,925 (10.93)	17,606
Center A	610 (37.89)	611 (38.07)	579 (36.44)	677 (35.82)	697 (36.21)	6.383 (36.25)
Center B	437 (27.14)	398 (24.80)	422 (26.56)	513 (27.14)	506 (26.29)	4.681 (26.59)
Center C	237 (14.72)	257 (16.01)	270 (16.99)	309 (16.35)	303 (15.74)	2.807 (15.94)
Center D	203 (12.61)	176 (10.97)	175 (11.01)	190 (10.05)	209 (10.86)	1.962 (11.64)
Center E	123 (7.64)	163 (9.19)	143 (9.00)	201 (10.63)	210 (10.91)	1.773 (10.07)
Male sex (%)	71.06	69.53	71.19	71.38	71.01	70.65
Body region of the most severe injury (%)						
Head	49.94	51.78	46.19	49.37	46.70	48.77
Thorax and abdomen	26.40	25.98	28.89	27.83	27.79	27.34
Extremities	11.30	9.41	9.94	8.41	10.91	10.03
Neck and spine	12.36	12.83	14.98	14.39	14.60	13.86
Injury mechanism (%)						
MVC	51.74	46.29	48.84	45.87	49.56	48.73
Fall	35.59	41.00	39.46	41.38	39.74	38.42
Penetrating	9.75	9.03	7.49	8.89	7.64	9.20
Others	2.92	3.68	4.22	3.86	3.06	3.65
Transfer from another hospital (%)	38.32	35.45	39.71	36.35	38.13	37.04
Center A	40.66	38.46	46.11	43.43	42.32	42.38
Center B	33.18	30.15	35.07	28.46	31.82	30.68
Center C	35.44	35.41	37.78	32.36	35.64	34.81
Center D	45.32	36.36	37.14	42.63	38.76	39.35
Center E	39.02	36.20	37.04	32.23	56.10	35.98
Shock (SBP<90) (%)	5.34	4.80	4.28	3.76	4.36	4.69
Center A	4.43	4.58	5.18	1.92	4.16	4.28
Center B	7.55	6.03	4.98	4.87	3.95	5.30
Center C	2.95	5.84	2.96	3.88	4.95	5.02
Center D	6.40	2.27	1.14	4.74	3.83	4.13
Center E	4.88	3.68	4.90	5.97	5.71	4.68
Glasgow Coma Scale (%)						

3-8	13.60	14.27	11.20	12.54	13.87	13.55
9-12	7.08	8.85	6.86	7.78	8.16	7.85
13-15	79.32	76.88	81.94	79.68	77.97	78.60
Age (mean, SD)	48.60 (22.28)	51.38 (22.23)	51.76 (22.18)	53.59 (21.65)	53.60 (21.73)	51.24 (22.10)
Center A	50.07 (21.90)	51.05 (21.16)	51.01 (22.54)	53.53 (21.57)	52.80 (21.67)	50.73 (21.69)
Center B	46.78 (22.19)	50.35 (22.60)	52.40 (21.68)	50.99 (21.18)	53.41 (20.95)	50.52 (22.01)
Center C	52.36 (24.40)	55.67 (24.11)	55.61 (22.84)	58.56 (21.66)	57.79 (22.91)	53.40 (23.35)
Center D	46.57 (20.56)	46.28 (20.83)	48.00 (20.76)	52.00 (22.09)	52.38 (22.14)	49.17 (21.25)
Center E	43.94 (21.46)	53.91 (22.42)	50.27 (21.68)	54.32 (21.55)	51.90 (21.03)	50.72 (21.97)
ISS (Median, IQR)	20 (16 – 26)	20 (16 – 26)	18 (16 – 26)	19 (16 – 26)	19 (16 – 26)	19 (16 – 26)
Center A	20 (16 – 26)	20 (16 – 26)	20 (16 – 26)	21 (16 – 27)	21 (16 – 27)	20 (16 – 27)
Center B	22 (16 – 27)	21 (16 – 26)	19 (16 – 25)	21 (14 – 26)	21 (16 – 26)	21 (16 – 26)
Center C	19 (16 – 26)	19 (16 – 26)	18 (14 – 25)	18 (14 – 25)	18 (16 – 25)	19 (16 – 26)
Center D	18 (17 – 25)	18 (14 – 25)	17 (14 – 24)	17 (14 – 25)	18 (16 – 25)	18 (16 – 25)
Center E	17 (14 – 25)	19 (16 – 25)	18 (14 – 25)	17 (14 – 25)	17 (14 – 25)	18 (14 – 25)

*Results from one imputed dataset, other datasets have similar distributions. Only even years are presented to have a cleaner table.

ISS: Injury Severity Score; MVC: Motor Vehicle Collisions; SBP: Systolic Blood Pressure; SD: Standard Deviations.

eFigure 6.1: Cumulative incidences of being discharged alive and home*

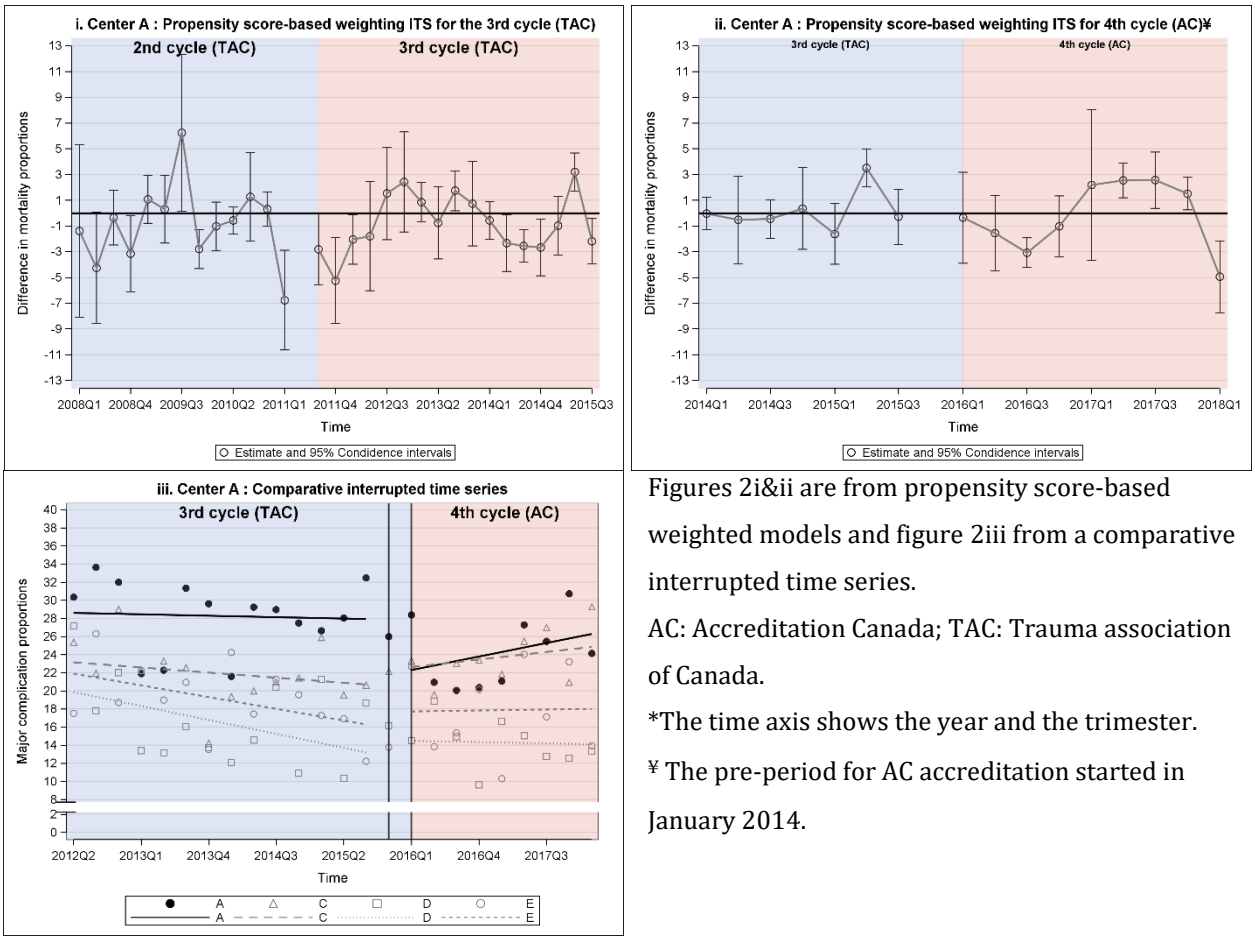


*The vertical grey lines represent the 7th, 14th and 30th day since admission.

AC: Accreditation Canada; RD: differences in major complication proportions; TAC: Trauma association of Canada.

Inverse probability weighting was used to standardize patients' case-mix over time. Covariates included in the weights computation were age, injury severity score, systolic blood pressure, Glasgow coma scale, pulse, sex, body regions of the most severe injury, mechanism of injury, and transfer-in from another acute care.

eFigure 6.2: Propensity score-based weighted and Comparative Interrupted time-series*



Figures 2i&ii are from propensity score-based weighted models and figure 2iii from a comparative interrupted time series.

AC: Accreditation Canada; TAC: Trauma association of Canada.

*The time axis shows the year and the trimester.

¥ The pre-period for AC accreditation started in January 2014.

eTable 6.2: Sensitivity analysis using propensity score-based weighting ITS*

CENTER A - DIFFERENCE IN MORTALITY (%)	RD	95% CI
3RD CYCLE (TAC)	-2.81	-5.56, -0.06
3 MONTHS AFTER THE 3RD CYCLE (TAC)	-5.24	-8.59, -1.89
6 MONTHS AFTER THE 3RD CYCLE (TAC)	-2.04	-3.97, -0.11
12 MONTHS AFTER THE 3RD CYCLE (TAC)	1.53	-2.07, 5.12
18 MONTHS AFTER THE 3RD CYCLE (TAC)	0.86	-0.67, 2.39
AVERAGE ACROSS THE POST 3RD CYCLE (TAC) PERIOD	-0.79	-1.31, -0.26
4TH CYCLE (AC)	-0.36	-3.90, 3.19
3 MONTHS AFTER THE 4TH CYCLE (AC)	-1.55	-4.49, 1.39
6 MONTHS AFTER THE 4TH CYCLE (AC)	-3.07	-4.21, -1.92
12 MONTHS AFTER THE 4TH CYCLE (AC)	2.18	-3.67, 8.04
18 MONTHS AFTER THE 4TH CYCLE (AC)	2.56	0.37, 4.75
AVERAGE ACROSS THE POST 4TH CYCLE (AC) PERIOD	-0.24	-1.02, 0.54

AC: Accreditation Canada; ITS: Interrupted time series; RD: differences in mortality complication proportions; TAC: Trauma association of Canada.

*Risk differences and 95% confidence intervals are obtained from generalized estimated equations, with robust standard errors; Rubin's rule was used to combine the estimates from the 25 imputed datasets.

CHAPTER 7. General discussion

7.1 Summary of Findings

The collective findings of this thesis provide a detailed picture of the impact of trauma center accreditation on patient outcomes, including in-hospital mortality, major complications and hospital length of stay in both mandatory and voluntary contexts. First, chapter 2 (manuscript 1) highlights that the current state of knowledge provided little clarity or guidance, given that previous studies were limited in their internal validity and their external validity. They did not have an appropriate design to assess the causal effect of accreditation and were all based on data derived from the United States where there is a high proportion of intentional injury and penetrating trauma and a multi-payer heavily private system(204, 205). Second, using interrupted time series analyses, chapter 5 (manuscript 3) suggests that in a mandatory context, accreditation may be beneficial for centers experiencing decreases in performance in the months preceding the visit. Third, chapter 6 (manuscript 4) indicates that in a voluntary context, accreditation seems to be associated with short- and long-term reductions in in-hospital mortality and major complications after the first cycle; and only short-term reductions for subsequent cycles. Chapter 6 also suggests that the change in the accreditation body has not modified observed estimates. Overall, these measured estimates were imprecise, mostly for level II centers, which tempers the inference that can be made about the beneficial impact of accreditation on studied outcomes.

7.2 Limitations and Mitigation Strategies

Caution is required before making any causal interpretations of the results described in this thesis, given that several assumptions must be verified. I will describe these assumptions in the following paragraphs and the efforts that have been made to satisfy them.

7.2.1. Consistency Assumption

This assumption requires two conditions: 1) that the values of treatment under comparison correspond to well-defined interventions; 2) observed outcome for every accredited center equals its outcome if it had received accreditation and that the observed outcome for every non-accredited center equals its outcome if it had remained non-accredited(206, 207). Since they are many variants of the accreditation process (different accreditation organizations, different criteria and different threshold for success or not), accreditation is probably not a well-defined intervention. In addition, among accredited centers there are those that fulfilled almost all the criteria and others that barely crossed the threshold for accreditation. This variation in performance according to accreditation criteria is also true for non-accredited centers. Therefore, the second condition could also be violated if we compared a group of accredited centers to a group of non-accredited centers. However, the fact that analyses were performed separately by settings (mandatory versus voluntary) and by center (a single model for each center) using an ITS design may have helped to relax these two consistency conditions. For the consistency assumption to be verified in this thesis, the two conditions described above only need to hold within each center, which is more realistic.

7.2.2. Assumption of exchangeability

Exchangeability is an essential requirement for any causal statement. It means that the risks of the studied outcome in the treated group would have been the same as the risk of outcome in the control group had individuals in the treated group not received the treatment (206). For this thesis, it means that patients admitted in the post-accreditation periods would have the same risk of mortality, major complications, and being discharged alive as those admitted in pre-accreditation periods in ITS analyses, had they been admitted in the pre-period; or for ITS with control centers, that patients admitted in accredited centers would have had the same risk of outcomes as those admitted in non-accredited centers, had they been admitted in non-accredited centers.

Change in patient case-mix was a potential threat to the exchangeability assumption. Fortunately, the Quebec and British Columbia trauma registries have details on several center and patient characteristics commonly considered in the trauma care literature as risk factors for the studied outcomes. In addition, the statistical approaches (prognostic score and inverse probability weighting) used to account for changes in patient case-mix over the study period are validated strategies to ensure exchangeability over measured characteristics i.e., conditional exchangeability(138, 195).

Co-occurring events are a major source of non-exchangeability in ITS design(143, 144, 150). Adding a control center in a CITS design can discriminate between the accreditation effect and the effects of co-occurring events, if the co-occurring events affect the accredited and control center to the same extent(208). However, control groups were not available in the mandatory

context since all centers underwent the accreditation process. Although the use of other outcomes as controls (for example, in-hospital mortality due to non-trauma conditions) was considered, these data were not available and there was the possibility that such outcomes might be influenced by other interventions during the study period. In a voluntary context, CITS was used as sensitivity analyses when suitable control centers were found to reinforce the design validity. Several others sensitivity analyses were performed to assess the robustness of results from single ITS, including deriving bounding factors that an unmeasured confounder must satisfy to explain away the observed association; and propensity score-based weighted ITS model(177, 178). They generally indicated that observed associations were robust to co-occurrent events, such as a moderate change in coding practice of patient characteristics (**Section 5.2 and 6.2**).

ITS and CITS rely heavily on the extrapolation of the pre-intervention period(208). While in the case of monthly series, there were sufficient preintervention measures to capture periodic variations, and therefore reliably estimate the functional form, quarterly series may have limited the ability to estimate pre-accreditation trends when evaluating several accreditation cycles.

Missing data, in addition to reducing the precision (loss of power) of estimates can also be a source of non-exchangeability by creating selection bias(181, 209). To account for that, multiple imputation with chained equations was used to impute missing data assuming that missingness depends on measured variables(198). Studies have suggested that this assumption is reasonable for missing data on physiological parameters such as the Glasgow Coma Scale in trauma registries, when data on injury severity and age are available. Therefore, when implemented with care, multiple imputation leads to valid frequency distributions and preserves associations with

mortality(210-213). While using data-specific imputation models allowed for the inclusion of variables that predicted missingness but were not considered in the analysis, eased replication, and ensured that data was consistent for different analyses, it may have led to residual confounding(183). This is because the coefficients of non-linear terms not included in the imputation model, but used to represent the relation between some risk factors and studied outcomes in the prognostic score estimations are likely underestimated(182). Given that LOS was analyzed as a time to event outcome, special attention was given to the imputation model specification. Log transformation of the time to discharge and death was applied and an indicator specifying the event of interest (dead or discharge) modeled as a factor was included in the imputation model in addition to other covariates detailed in **section 3.6**. Recent simulations have shown this procedure to be optimal for handling missing covariate values on missing at random or not at random data in the context of competing risks(198).

Finally, the study population consisted of major trauma patients defined as patients with an Injury severity score (ISS) ≥12 treated in designated trauma centers. The ISS is computed using the Abbreviated Injury Scale (AIS), and there was a change in the AIS version (AIS 1990 update 1998 versus AIS 2005 Update 2008) used during the study period (April 2013 in Quebec and April 2012 in British Columbia). Published conversion tools were applied to account for that change, in order to use a single AIS version (AIS 2005 Update 2008) throughout the study period(130, 131). However, in the case where this conversion was not sufficient, it may have resulted in bias toward the null. Indeed, when coding injuries using AIS 2005 Update 2008, many injuries, particularly head injuries had a lower score than those assigned using AIS 1990 update 1998 to account for improvement in prognosis over time(117).

7.2.3. Positivity Assumption

This assumption simply means that the probability of receiving every value of the intervention conditional on potential confounders is greater than zero(206). While easy to understand, the concept of positivity is ambiguous for crossover or ITS designs, given that the unit of analysis is the center which is compared against itself. To illustrate a source of non-positivity in this thesis, let us consider a scenario where the confinement measures taken by all Canadian provinces to fight against the COVID-19 pandemic in March 2020 were enacted just after some centers got accredited. These measures would have dramatically reduced the probability of a trauma patient being admitted due to a motor vehicle collision in the post-accreditation period.

Although there was an increase in falls as a cause of trauma due to the aging of the population, this increase might not be enough to violate the positivity assumption. In addition, the distribution of weights obtained through inverse probability weighting do not indicate non-positivity (Manuscript 2 - **section 4.3**).

7.2.4. Measurement error

Following accreditation some centers are asked to improve their coding practices of patient characteristics such as comorbidities, and outcomes such as complications. Measurement errors of patient case-mix covariates was discussed under the exchangeability section. In fact, bias due to mismeasured potential confounders could be seen as a form of unmeasured confounding(206), and therefore sensitivity analyses for unmeasured confounder (deriving bounding factor) were conducted. Concerning complications, if the change in coding practice led to a better recording, there were differential measurement errors for the outcome(179). Results from sensitivity analysis for differential measurement error suggest that change in coding practice for studied

outcomes would likely lead to an underestimation of the observed associations, i.e., results are likely an underestimate of any true effect (**Manuscript 3**). This is because the measurement error in the recording of complications probably led to an underestimation the number of cases in the pre-period.

7.2.5. Statistical Inference

Despite the fact that several time points were available, other factors such as the sample size per time point, expected effect size, location of intervention in the time series, and pre-intervention trends need to be considered to denote an ITS analysis as sufficiently powered(214-216). While this thesis is certainly underpowered to detect small effect sizes, it was not possible to increase the sample size. In each setting (Quebec and British Columbia), all major trauma admissions to level I and II centers fulfilling inclusion criteria were included in the analyses. In addition, since the accreditation status is valid for a pre-determined period of time, there is a limit on the number of possible time points.

Investigated outcomes were aggregated at the month or quarter time scale in this thesis. However, the uncertainty around these monthly or quarterly proportions were not considered when conducting piecewise regression with autocorrelated errors. Sensitivity analyses (data not shown) using weighted generalized estimating equations with robust standard errors, with weights representing the inverse of the variance of each monthly or quarterly estimate were performed(217, 218). While the change in levels and trends estimates were similar, the 95% confidence intervals were slightly larger or smaller for some centers when compared to the results presented throughout this thesis. Nevertheless, the pattern was the same and all statistically significant associations remained. Aggregating individual data to complete ITS

analyses is very common in health care research. Further methodological research is needed to establish how to better estimate the uncertainty around estimates based on ITS from aggregated individual data; or to combine the strengths of time-series analysis with the strengths of generalized linear models used for individual data, typically in the form of serial cross-sections (i.e., panel data)(153, 219, 220).

Finally, while performing analyses by center may have helped satisfying the consistency assumption, it potentially induced inferential problems due to multiple testing.

7.2.6. Other issues

As discussed in manuscripts 3 and 4, piecewise regression cannot assess change in data dependency or variability. This is an important limitation since complex interventions such as accreditation could also change the dependency (autocorrelation) or reduce the variability (creating a more consistent outcome) in the outcome series. Robust-ITS has been proposed as an alternative, however, its actual implementation is limited (difficulties with multiple interventions, and only assumed a first-order correlation in both the pre and post-period)(221-223). However, when possible, it was used as a sensitivity analysis and results suggest that accreditation also affected the data dependency by reducing the level of negative correlation, i.e., reducing the dissimilarity of outcomes taken close together in time (**Manuscript 3**).[10] Further developments of the Robust-ITS methodology might allow for a better assessment of accreditation impact.

In addition, effects computed in this work might not be transportable to other trauma centers and systems if they had different patient case-mix distributions(206). This is because the effect of

[10] A negative autocorrelation suggests that outcomes taken close together in time are likely to be dissimilar.

accreditation might vary by level of some characteristics such as injury mechanism, injury type and transfer from another hospital.. While computing accreditation effects in each stratum of potential risk factors of the studied outcome would have produced more transportable results (improved external validity), it would also have led to multiple testing issues, loss of power and positivity violations.

Change in patient case-mix was considered as a potential source of non-exchangeability in this thesis given the possible correlation with accreditation. However, even in the case where that change was only driven by underlying secular trends, accounting for patient case-mix has probably increased the precision of observed estimates (as illustrated in **manuscript 3** in **chapter 5**), given that patient characteristics are risk factors of investigated outcomes.

Finally, I did not assess the associations between accreditation and patient outcomes in the United States. This is because the ITS framework could not be applied using the National Trauma Data Bank (NTDB) which do not contain precise details (month or trimester) on the accreditation visit. The results observed in this thesis might not be transportable to the United States context. This is because, in addition to the differences in patients' case-mix compared to Canadian centers (high proportion of intentional injury and penetrating trauma), the multi-payer heavily private system in place in the United States might also play an important role in access to trauma care.

7.3 Opportunities for future research

In Quebec, the last accreditation cycle was conducted during the second semester of 2017 and was the first not to include site visits. In addition to the pre-review questionnaire, centers had to submit data which were used to compute the average performance of each center on clinical

outcomes and process indicators for the three preceding years(224). The accreditation body then asked centers to comment on their results and to provide a plan to maintain or improve their performances, specifically when the performance of a center on a specific indicator was below the provincial average of centers with the same level of designation. This thesis suggests that in addition to comparing centers to their peers, within center performance over time should also be considered for this new format of accreditation. It would be interesting to assess the impact of this new accreditation process when more post-accreditation data will be available.

Since Accreditation Canada took the reins of the accreditation process in the rest of Canada in 2014, only British Columbia in 2016 and Alberta in 2019 regional trauma systems have undergone accreditation to date. It will be interesting to see if the apparent sustained effect of accreditation when centers go through their first accreditation cycle is verified in Alberta when more prospective data will be available.

Until recently, the accreditation process has focused on the structure and certain aspects of quality of care, and do not generally compare hospital-specific, risk-adjusted trauma outcomes(225). The large variation of risk-adjusted outcomes observed among accredited centers in this thesis has also been observed in the United States. This observation has prompted some researchers to state that the trauma center accreditation process may not ensure optimal outcomes across all accredited centers and that focus should be put on risk–adjusted benchmarking to measure performance and outcomes(74, 85, 226). The rationale is to help low-performing centers replicate structures and processes of high-performing trauma centers, through comparative analysis of outcomes across appropriately risk-adjusted populations. The

Trauma Quality Improvement Program (TQIP) offered by the American College of Surgeons, is an example of risk-adjusted benchmarking system of trauma centers whether accredited or not. For the actual ACS accreditation process in the United States, the presence of a risk-adjusted benchmarking system to measure performance and outcomes is assessed as a demonstration of commitment to improving performance(11). The new Quebec accreditation process also integrates risk-adjusted benchmarking as described in the first paragraph of this section.

Processes of care indicators such as timely trauma team activation, proportion of major joint dislocations reduced within 1h, airway secured in emergency department for patients with a Glasgow Coma Scale<9, thoracic or brain surgery<24hours were not evaluated in this thesis(123, 227). This is because necessary data to measure these indicators (specifically the numerator for each indicator) were not consistently collected for the entire study period. In addition, each indicator only concerns a small group of patients so sample sizes would have been prohibitively low.

Finally, it will be interesting to evaluate other outcomes such as staff recruitment or retention and patient-reported outcome measures (PROMs), which are used to assess a patient's health status at a particular point in time(228). PROMs are increasingly recognized as providing valuable and essential information on patients' perspective to more fully assess quality of care(229, 230). Unfortunately, such measures are not routinely collected.

7.4 Conclusion

Acknowledging the limitations of this thesis and considering the strategies used to mitigate them, this thesis provides a robust evaluation of the impact of trauma center accreditation on patient outcomes. Results suggest that accreditation may improve in-hospital mortality, complications and hospital length of stay in a mandatory context for centers with an increase in pre-accreditation trends, while in a voluntary context, indications of sustained improvements after the first accreditation cycle and temporary improvements for subsequent ones were observed.

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