Updating and External Validation of a Surgical Site Infection Risk-Index Tool

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1 Abstract

1.1 English Abstract

Introduction: Surgical site infections (SSIs) represent an important threat in surgical settings as they are associated with significant clinical and economic burden, on a patient and societal level. Due to the increasing emergence of resistant bacteria, focus must be shifted to SSI prevention as opposed to therapeutic intervention following SSI development. We therefore created the JSS-SSI Risk Scoring Tool, which identifies low-, moderate- and high-risk SSI patients. Following development of the risk tool, this study aimed to update and validate the model using an external population.

Methods: This retrospective study utilized surgical patient-level data from the National Surgical Quality Improvement Program between 2012 and 2014. Discrimination, calibration and overall fit of the original model were assessed with the aid of the Receiver Operating Characteristic (ROC) area under the curve (AUC), sensitivity, specificity, calibration plot, Hosmer-Lemeshow test and Brier score. Twelve updating methods were conducted. The final JSS-SSI Risk Scoring Tool was selected following the comparison of discrimination, calibration and overall fit of the updated tools. Variable score values were calculated for all included risk factors. Threshold values were established with ROC analysis. The discrimination, calibration and overall fit of the final JSS-SSI Risk Scoring Tool were evaluated. Multivariate logistic regression assessed the relative rate of observed SSIs in moderate and high-risk patients in comparison to the low-risk group.

Results: The external population included 1,459,481 patients of which 3.4% developed an SSI. The original risk tool yielded an AUC = 0.657, sensitivity = 79.6%, specificity = 58.3%, calibration slope = 0.37 and intercept = 0.02, a Hosmer-Lemeshow $p < 0.001$ and mean (SD) Brier score = 0.0331 (0.1606). Among the twelve updating methods assessed, the tool produced by Method 11, which solely included the risk factors with an odds ratio (OR) above 1.5 when associated with SSIs, had the highest predictive accuracy [mean (SD) Brier score = 0.0318 (0.1602)], and was thusly retained as the final JSS-SSI Risk Scoring

Tool. The SSI predictors included: discharge destination other than home (OR = 1.732; 16 points); surgery duration above 3 hours (OR = 2.139; 19 points); inpatient status (OR = 2.690; 24 points); general, gynecologic, otolaryngologic, thoracic or urologic surgery (OR = 2.525; 22 points); and Class III contaminated or Class IV dirty/ infected operative wound (OR = 2.169; 19 points). Following ROC analysis, threshold values of 42.997 and 58.468 were selected, therefore patients with scores of 0-42, 43-58 and 59-100 points had a low, moderate and high SSI risk, respectively. The final JSS-SSI Risk Scoring Tool demonstrated superior discrimination, calibration and overall fit than the original risk tool. As per the established threshold values, 60.7%, 21.6% and 17.8% of patients had a low, moderate and high SSI risk of which 1.4%, 3.7% and 9.9% of patients developed an SSI, respectively. Patients with a moderate and high risk were 2.776 and 7.919 times more likely to develop an SSI, respectively, when compared to low-risk patients (both $p < 0.001$).

Conclusion: This study updated and externally validated the JSS-SSI Risk Scoring Tool in a large external population. Applicability and implementation of this validated tool in surgical settings is henceforth advised to assist the decision-making of healthcare professionals during the identification of patients with an increased SSI risk.

1.2 French Abstract

Introduction: Les infections du site opératoire (ISOs) représentent une menace sérieuse dans les milieux chirurgicaux car elles sont associées à un fardeau clinique et économique important, au niveau du patient et de la société. En raison de l'émergence croissante de bactéries résistantes, l'accent doit être déplacé vers la prévention des ISOs par opposition à l'intervention thérapeutique suite à leur développement. Nous avons donc créé l'outil de risque 'JSS-SSI Risk Scoring Tool', qui identifie des patients avec un risque faible, modéré et haut d'atteindre un ISO. À la suite du développement de l'outil de risque, cette étude visait à mettre à jour et à valider le modèle avec une population externe.

Méthodes: Cette étude rétrospective a utilisé les données chirurgicales du Programme National d'Amélioration de la Qualité Chirurgicale de 2012 à 2014. La discrimination, l'étalonnage et l'ajustement global du modèle original ont été évalués à l'aide de la zone caractéristique de fonctionnement du récepteur (Receiver Operating Characteristic, ROC) sous la courbe (Area Under the Curve, AUC), de la sensibilité, de la spécificité, du graphique d'étalonnage, le test Hosmer-Lemeshow et le score Brier. Douze méthodes de mise à jour ont été menées. L'outil final JSS-SSI Risk Scoring Tool a été sélectionné suite à la comparaison de la discrimination, de l'étalonnage et de l'ajustement global des douze outils. Les valeurs de score variable ont été calculées pour chaque facteur de risque inclus. Les valeurs de seuil ont été établies avec l'analyse ROC. La discrimination, l'étalonnage et l'ajustement global de l'outil final ont été évalués. Une régression logistique multivariée a évalué le taux relatif d'ISOs observées chez les patients à risque modéré et élevé par rapport au groupe à faible risque.

Résultats: La population externe comprenait 1 459 481 patients dont 3,4% ont développé une ISO. L'outil de risque original a généré un AUC = 0,657, sensibilité = 79,6%, spécificité = 58,3%, pente d'étalonnage = 0,37 et interception = 0,02, Hosmer-Lemeshow $p < 0,001$ et moyenne (SD) score Brier = 0,0331 (0,1606). Parmi les douze méthodes de mise à jour, l'outil produit par la Méthode 11, qui comprenait uniquement les facteurs de risque avec un rapport de cotes (OR) supérieur à 1.5, avait la plus grande précision prédictive [score de Brier moyen (SD) = 0.0318 (0.1602)], et a donc été retenu comme outil de risque final. Les prédicteurs d'ISOs comprenaient: destination de sortie autre que la maison (OR = 1,732; 16 points); durée de la chirurgie supérieure à 3 heures (OR = 2,139; 19 points); statut d'hospitalisation (OR = 2,690; 24 points); chirurgie générale, gynécologique, otolaryngologique, thoracique ou urologique (OR = 2,525; 22 points); et blessure opératoire Classe III contaminée ou IV sale/ infectée (OR = 2,169; 19 points). À la suite de l'analyse ROC, des valeurs de seuil de 42,997 et 58,468 ont été sélectionnées, donc les patients avec des scores de 0-42, 43-58 et 59-100 points ont un risque d'ISO faible, modéré et élevé, respectivement. L'outil final de risque JSS-SSI a démontré une discrimination, étalonnage et l'ajustement global supérieurs que l'outil de risque d'origine.

Selon les valeurs de seuil établies, 60,7%, 21,6% et 17,8% des patients avaient un risque d'ISO faible, modéré et élevé dont 1,4%, 3,7% et 9,9% des patients ont développé une ISO, respectivement. Les patients présentant un risque modéré et élevé étaient de 2,776 et 7,919 fois plus susceptibles de développer une ISO, respectivement, par rapport aux patients à faible risque (tous deux $p < 0,001$).

Conclusion: Cette étude a mis à jour et validé de manière externe l'outil de risque 'JSS-SSI Risk Scoring Tool' dans une population externe. L'applicabilité et la mise en œuvre de cet outil validé en milieu chirurgical sont désormais conseillées d'aider à la prise de décision des professionnels de la santé lors de l'identification des patients présentant un risque accru d'ISO.

Acknowledgments

Let me preface this thesis with words of sincere gratitude. First and foremost, I wish to express extreme appreciation to my supervisor, Dr. John S. Sampalis, for the inspiration to pursue this doctoral degree, for introducing me to the world of clinical research and for the wonderful guidance over the years which has led me towards this professional path. Having a role model like you has motivated me to push boundaries (such as tackling statistical methods I never would have thought to perform) and to always strive for excellence, as you have done during your career. I cannot emphasize enough how grateful I am to have had you as my supervisor.

I further wish to thank all members of my Research Advisory Committee during my M.Sc. and Ph.D. degrees, Dr. Jacques Lapointe, Dr. Peter Metrakos and Dr. Moishe Liberman. Being surrounded by individuals like you who have achieved greatness constantly encouraged me to excel beyond all expectations.

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Preface and Contribution of Authors

I, Angeliki Karellis, am the sole author of this doctoral thesis. My supervisor, Dr. John S. Sampalis, reviewed the thesis prior to submission and approves the current content.

This thesis presents original work and aims to identify surgical patients who possess an increased risk of surgical site infection development.

The originality of the presented works lies in two main study characteristics which are described below.

Firstly, the sample size included approximately 1.46 million patients. The assessment of this large population allows to confirm the model's generalizability in numerous patient populations, which represents an essential component in external validation.

Moreover, if suboptimal predictive accuracy is observed in external validation studies, the most commonly observed method dismisses an originally developed tool and advocates the usage of an alternate tool created with the aid of the external population if the latter presents with superior external validity. However, this approach presents with an inherent limitation as the development population is disregarded. As an increased sample size is associated improved statistical power and tool generalizability, the method adopted in the present study, which created several updated tools, allowed to select a tool with higher predictive accuracy while accounting for both the development and validation populations.

2 Introduction

Surgical site infections (SSIs) represent the most frequent nosocomial infection following surgery (1-6) surpassing incidence rates of bloodstream infections and urinary tract infections (UTIs) (4), the latter previously identified as the most prevalent post-surgical infection (7-9). UTI prevalence rates declined from 36% in 2002 (7) to 12.9% in 2007 (10) in the United States. The increasing concern and awareness of UTIs over the last decades has led to the decrease of UTI rates over time. Conversely, the prevalence of SSIs increased from 14.8% in 1990-1992 as reported by the NNIS to 38% of all healthcare-associated infections (HAIs) in 2010-2012 in the United States. (8) SSIs represented the most prevalent HAI during the 30-month study led by Lewis et al. (0.82 infections per 100 surgeries). (11) Moreover, between 1986 and 1996, the NNIS reported that SSIs were the most frequent HAI among surgical patients, representing 38% of nosocomial infections (12) defined by the Center for Disease Control and Prevention (CDC) as 'systemic or localized conditions that result from the reaction by an infectious agent or toxin' (13, 14). In Canada, two million surgeries are performed annually resulting in 50,000 SSIs. (15) These rates may have been underestimated as approximately 50% of patients develop SSIs following hospital discharge. (16) Despite the high reported SSI incidence, 40-60% are considered preventable. (15)

SSIs lead to substantial clinical burden experienced by patients including an increased risk of morbidity and mortality. (17-21) Globally, an estimated 3% of SSI patients die (20) of which approximately 75% of SSI-related deaths are directly attributable to SSIs (18, 20). Compared to matched uninfected patients, SSI patients have a doubled mortality risk (RR = 2.2, 95% CI: 1.1, 4.5), are 60% more likely to require admission to the Intensive Care Unit (ICU) (RR = 1.6, 95% CI: 1.3, 2.0) and are over five times more likely to be readmitted to hospital following discharge (RR = 5.5, 95% CI: 4.0, 7.7). (22)

Moreover, SSIs incur substantial economic burden as increased hospital stay, diagnostic tests, costly medications, and in some cases readmission or reoperation, may be required. (23) Indeed, meta-analysis findings have shown that SSIs are significantly associated with

greater length of hospitalization, expenditures, risk of hospital readmission, reoperation and mortality. (24, 25) In 2009, SSIs were estimated to lengthen a patient's hospital stay by a mean 9.7 days and to increase the costs by $20,842 per admission. (26) Also, SSI patients incur approximately double the fees of patients who do not develop SSIs; a finding partly reflective of the length of hospitalization estimated to be double among SSI patients. (27)

On an individual level, patients' and caregivers' loss of earnings and out-of-pocket expenses during recovery combined with patients' possible pain, anxiety, depression and/or secondary complications lead to immense financial and emotional burden as well as reduced quality of life. (28-30)

The literature presents with variable results regarding SSI epidemiology and burden, though numerous authors concur that these infections incur a significant impact on a patient and societal level. (17-22, 24, 25, 27-30) Despite the release of SSI prophylactic guidelines (31, 32), incidence rates remain high. To reduce the substantial burden associated with SSIs, rigorous investigation is necessary to improve current SSI prophylaxis.

In a previous study (33), we developed the JSS-SSI Risk Scoring Tool, a user-friendly tool allowing the classification of surgical patients into low-, moderate- or high-risk SSI groups. The present study aims to improve and validate the JSS-SSI Risk Scoring Tool in a large external population to ensure generalizability of the tool across various surgical settings.

3 Review of the Literature

3.1 Surgical Site Infection Definition and Classification

As per the CDC, surgical site infections are defined as nosocomial infections of the surgical site occurring within 30 days of a surgical procedure or within one year following implant surgery. (1, 18, 34) SSIs can be classified into three categories according to the tissues and/or organs infected: superficial incisional SSI, deep incisional SSI and organ/space SSI. (17, 18, 21, 34-36) **Table 1** presents the diagnostic criteria for each type of SSI.

Table 1 Classification and Diagnostic Criteria of Surgical Site Infections (12, 17, 18)

Type of SSI	Characteristics
Superficial Incisional	Infection involves only the skin or subcutaneous tissue. Also presents with one or more of the following characteristics: - Purulent drainage from superficial incision (with or without laboratory confirmation); - Isolated organisms from a culture of fluid or tissue from the superficial incision obtained aseptically; - At least one of the symptoms of infection: pain or tenderness, localized swelling, redness, or heat *and* superficial incision has been opened by the surgeon intentionally; - The diagnosis of a superficial incisional SSI may be made by a surgeon or attending physician.
Deep Incisional	Infection involves deep soft tissues (such as the fascial and muscle layers) of the incision. Also presents with one or more of the following characteristics: - Purulent drainage from deep incision of the surgical site (not from the organ/space); - Deep incision spontaneously dehisces or is intentionally opened by the surgeon when the patient has at minimum one of the following signs or symptoms: fever (> 38^{o}C), localized pain, or tenderness; - The diagnosis of a deep incisional SSI may be made by a surgeon or attending physician.

Type of SSI	Characteristics
Organ/ Space	Involves any part of the anatomy (such as organs or spaces), other than the incision, which has been opened or manipulated during surgery. Must also present with at least one of the following criteria: - Purulent drainage from a drain placed through a stab wound into the organ/space; - Organisms have been isolated aseptically from a culture of fluid or tissue which is in the organ/space; - An abscess or other evidence of a present infection involving the organ/space of the surgical site is found on direct examination, during reoperation, or by histopathologic or radiologic examination; - The diagnosis of an organ/space SSI may be made by a surgeon or attending physician.

3.2 Causes

SSIs are caused by the entry and invasion of pathogenic micro-organisms in the surgical incision site at a level that is superior to the ability of the immune system to control. Typically, the causative bacteria originate from the patient's endogenous flora present on the skin, mucous membranes or hollow viscera. (37) The most frequent bacteria that infect the surgical site include *Staphylococcus aureus*, coagulase-negative *Staphylococci*, *Enterococci* spp. and *Escherichia coli*. However, these may vary based on the type of surgery as the bacterial flora differs throughout the organism. (38)

Several factors may influence the risk of SSI development, such as the patient's immune function and the pathogenic properties of the causative micro-organism. Firstly, surgery has been shown to compromise immunological activity (39, 40), therefore increasing the risk of any postoperative infection, including SSI (41). Secondly, SSI development is more likely to occur if the infection is caused by highly virulent bacteria. In addition to the weakened immunity experienced by surgical patients, toxin-producing bacteria further reduce the immune response. (42, 43) Thirdly, the level of bacterial inoculum that enters the surgical site impacts whether an infection will develop. Various studies that evaluated

laparoscopic surgery support this statement as decreased prevalence of port-site infections (PSIs) (defined as a type of SSI limited to laparoscopic surgery) was observed. For instance, PSIs have been reported to occur between 0.4% and 6.7% of patients who underwent laparoscopic cholecystectomy (44-55) whereas between 1.1% and 14.4% of patients acquired SSIs following open cholecystectomy (45, 49, 53, 56).

3.3 Treatment and Bacterial Resistance

Following SSI diagnosis, treatment typically consists of wound debridement and/or the administration of intravenous antibiotics. (32, 57-59) The selection of the appropriate antibiotic therapy varies according to the suspected causative organism. (60, 61)

Nonetheless, the misuse and overuse of antibiotic therapy in recent years has led to a considerable increase in drug resistance rendering many medications ineffective. (60, 61) Indeed, more than 70% of bacteria that cause healthcare-associated infections are resistant to at least one of the drugs generally used in their treatment hindering SSI management. (62) As resistant bacteria are generally comprised in the human flora in symbiosis with the organism, healthy individuals are typically unaffected by their presence; yet, opportunistic infections may occur in persons with a weakened immune system, such as surgical patients. (63)

Infections caused by drug-resistant bacteria are associated with high clinical and economic burden in hospital settings. For instance, recent meta-analysis findings indicate a doubled mortality rate among patients with carbapenem-resistant Enterobacteriaceae bacteremia when compared to patients infected with carbapenem-susceptible Enterobacteriaceae. (64) Drug-resistant infections have further been shown to increase morbidity and health care resource utilization such as the need for costly therapies and admission to or longer stay in the ICU. (65)

Since SSIs can ensue following any type of surgery and with the current challenge of treating infections caused by resistant bacteria, SSI prevention should constitute the key

focus of the surgical staff as opposed to treatment following the development of the infection. (17, 41)

3.4 Risk Factors

Numerous SSI predictors have been identified in the literature. Some risk factors are associated with the type of surgery and operative procedures performed by the surgical staff while others are associated with patient comorbidities and presurgical lifestyle. (12)

Specifically pertaining to the surgical procedure, the operative wound's contamination level represents one of the most significant SSI predictors. (36, 66-68) **Table 2** presents the classification of the operative wound as established by the CDC as well as the corresponding SSI incidence as reported in published literature. (36)

Table 2 Operative Wound Classification (17, 18)

Surgical Classification	Description	SSI Incidence
Class I Clean	Involves "uninfected operative wound in which the respiratory, gastrointestinal and genitourinary tracts were not entered; including incisional surgery due to blunt trauma". (17)	< 2%
Class II Clean-Contaminated	Enters the respiratory, gastrointestinal and/or urinary tracts however no unusual contamination has occurred.	5-15%
Class III Contaminated	Procedure on an open wound with major breaks in sterile technique.	15-30%
Class IV Dirty/ Infected	Surgery on an old wound with dead tissue or involved existing infection or perforated bowel. The SSI-causing pathogens were present at the site prior to surgery.	> 30%

Inherent to the ordinal scale of the operative wound classification, SSI risk is greatly increased when the procedure is classified as dirty/ infected as opposed to a clean surgery

as the latter is performed in uncolonized tissues. (17, 18) Indeed, Maksimovic et al. reported that contaminated or dirty/ infected surgeries are significantly associated with SSI outcome when compared to clean or clean/ contaminated surgeries (OR = 12.09; 95% CI, 5.56, 26.28). (68)

In addition, lengthy or emergent procedures, the use of nonabsorbable sutures, foreign bodies, abundant use of subcutaneous electrocautery, excessive blood loss and hypothermia have been shown to increase SSI risk. (69, 70)

However, the above-stated SSI predictors do not account for individual patient risk factors including comorbidities. (71) For instance, male sex (72-76), obesity (77-79), diabetes (80-84), preoperative hyperglycemia (85-89), inadequate nutrition (2, 90-93), tobacco use (94-96), alcohol abuse (97, 98), chronic obstructive pulmonary disease (COPD) (99), hypertension (100, 101), corticosteroid use (102), disseminated cancer (103) and the patient's ASA score (104) have been shown to be significantly associated with SSI development.

The caveat during preoperative SSI prophylaxis is that the majority of risk factors, such as surgical characteristics and patient comorbidities (for example autoimmune illness requiring corticosteroid use, inpatient status, caregiver dependence prior to surgery and the surgery's wound classification), cannot be modified (36, 66-68) therefore limiting the ability to maximize SSI prophylactic care. A potential method to circumvent this issue would be to identify patients with an increased SSI risk who would benefit from additional preoperative and/or intraoperative support. As such, the surgical staff must carefully review each patient's medical history and potentially determine certain procedural details prior to surgery in order to improve preoperative SSI risk assessment.

3.5 Surgical Site Infection Risk Classification

As patients present with varying medical histories and comorbidities, and therefore have diverse levels of SSI risk, individualized prophylactic measures should be taken to

minimize this likelihood. For instance, patients with high SSI risk may require additional prophylaxis whereas certain measures could be omitted in the preoperative care of low-risk SSI patients. The utilization of risk indexes is useful in this regard to classify surgical patients as per their SSI risk.

As of 1964, the surgery's operative wound classification was used as a proxy to predict SSI occurrence. (105-107) Reflective of the level of bacteria present at the surgical site, past guidelines (107) suggested that this method was sufficient in establishing SSI risk. However, over time, an inherent limitation was observed in the usage of this classification method. (108) Although high SSI rates were anticipated among contaminated and dirty/ infected wounds, high SSI incidence rates among patients with clean or clean-contaminated wounds were unexpected and prompted surgeons to identify potential areas requiring improvement with respect to their operating technique such as the surgeon's preoperative hand antisepsis, patient skin preparation, proper hair removal and surgical attire. (108, 109) Thus, SSI rates following clean surgeries declined as focus was generally applied to reduce SSIs. Despite the positive outcome among patients who underwent clean surgeries, the desired effect of diminishing SSI rates among all patient classifications was not achieved. (108)

As a result, additional risk indexes were developed to identify high-risk SSI patients thusly allowing the development of preoperative strategies to reduce morbidity and mortality rates associated with post-operative infections. (110)

The index created during the Study on the Efficacy of Nosocomial Infection Control (SENIC) (111) was the first SSI index developed to include intrinsic patient risk factors. The study analyzed a random sample of 58,498 patients who underwent at least one surgery and were admitted to hospital in 1970. Ten potential SSI predictors were evaluated. Four risk factors were significantly associated with SSI and were therefore included in the index: abdominal surgery (OR = 1.12, $p < 0.0001$), contaminated or dirty/ infected wound (OR = 1.04, $p < 0.0001$), more than two diagnoses at discharge (OR = 0.86, $p < 0.0001$), and surgery lasting more than two hours (OR = 1.04, $p < 0.0001$). (111)

The National Nosocomial Infection Surveillance (NNIS) system identified three risk factors as SSI predictors to be included in a predictive index: American Society of Anesthesiologists (ASA) preoperative assessment score greater than 2 (indicating a deteriorated physical condition), surgery classified as contaminated or dirty/ infected, and surgery duration longer than T (defined as the 75^{th} percentile of the average time for a surgical procedure). (71, 110)

4 Rationale

4.1 Limitations of Existing Surgical Site Infection Risk Models

Although several strategies have been proposed to identify patients with an increased risk of SSI, none have been shown to have superiority over others. (112) As such, there is a need for an alternate tool to be developed and validated with a large population to ensure generalizability across various surgical settings.

The existing SSI risk indexes, developed during the SENIC and by the NNIS, were established approximately 20 to 30 years ago, before the identification of several SSI predictors and the publication of validation and risk tool updating techniques. Indeed, the data utilized to create the above-mentioned risk tools assessed a maximum of 10 risk factors, though numerous additional SSI predictors have been identified in the literature since the development of these tools. Moreover, the developers of the NNIS risk tool included three risk factors presumed to best predict SSI outcome, though no statistical analyses were performed to identify significant SSI predictors. (113) Also, during the SENIC, an OR between 0 and 1 was observed in regard to the risk factor of "more than two diagnoses at discharge", therefore indicating a protective effect. As a result, these results should be interpreted with caution as certain confounding factors may have not been adjusted in the analysis. (111) For the above-stated reasons, an updated risk index tool is needed to classify surgical patients into SSI risk groups.

4.2 Development of the JSS-SSI Risk Scoring Tool

We therefore sought to create the JSS-SSI Risk Scoring Tool, a user-friendly tool which allows the quantification of surgical patients' risk of developing an SSI according to the presence of specific risk factors. The data utilized to construct the risk model were obtained from the National Surgical Quality Improvement Program (NSQIP) database at the Jewish General Hospital (JGH) in Montreal. This population will be referred to as the

'Development Population'. The sample included 2,907 patients who underwent surgery between November 2009 and December 2011.

Of the 37 evaluated risk factors included in the database (Appendix 1 – Section **11.1**), multivariate logistic regression was performed to identify SSI predictors due to the dichotomous nature of the outcome. This analysis identified five risk factors that had a significant ($p < 0.05$) and independent association with SSI development: male gender (OR = 1.854, $p = 0.005$), inpatient status (OR = 9.491, $p < 0.001$), hypertension (OR = 2.464, $p < 0.001$), corticosteroid use (OR = 2.485, $p = 0.042$) and dependence for everyday activities prior to surgery (OR = 2.577, $p = 0.047$).

Conversion of the odds ratios obtained via multivariate logistic regression to weighted relative scores allowed the creation of a user-friendly tool ranging between 0 and 100 points where male sex, inpatient status, hypertension, corticosteroid use and dependence for everyday activities would add 10, 50, 13, 13 and 14 points to a patient's SSI score, respectively.

In order to establish the cutoff values identifying low-, moderate- and high-risk patients, Receiver Operating Characteristic (ROC) curve analysis (74) was used. The optimal two cutoff points were selected by visual observation of the curve and assessment of sensitivity and specificity values associated with each potential threshold value. As such, threshold values of 43.17 and 63.40 were elected (**Figure 1**). Therefore, patients with scores below 43.17, between 43.17 and 63.40 and above 63.40 had a low, moderate and high risk for SSI development, respectively. Based on these JSS-SSI Risk Scoring Tool estimates, 31.8% (n = 925), 46.2% (n = 1342) and 22.0% (n = 640) of patients had a low, moderate and high risk of developing any type of SSI in the Development Population, respectively (**Figure 2**). Approximately 3% of low-risk, 10% of moderate-risk, 16% of high-risk and 9% of all patients developed any type of SSI postoperatively. These results internally validated the tool within the JGH.

Figure 1 Receiver Operating Curve Analysis for SSI Risk during the Development Phase

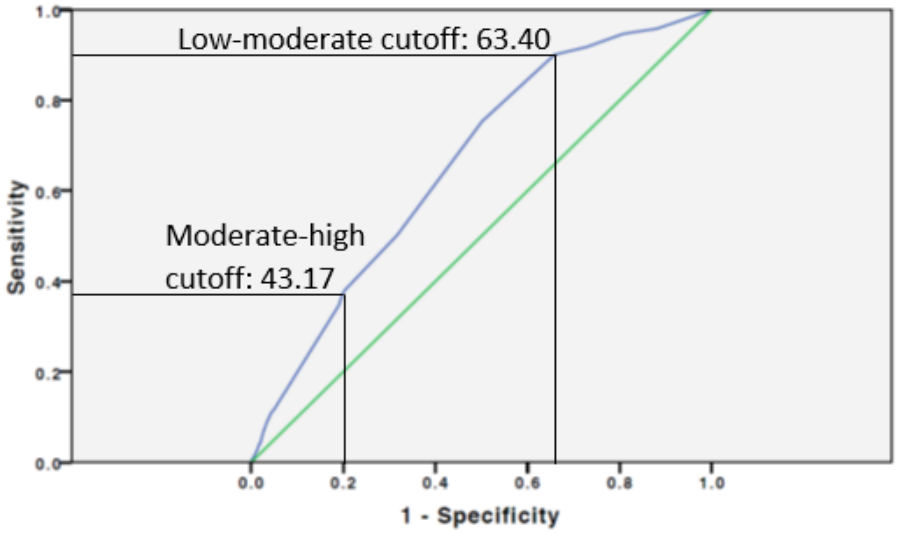
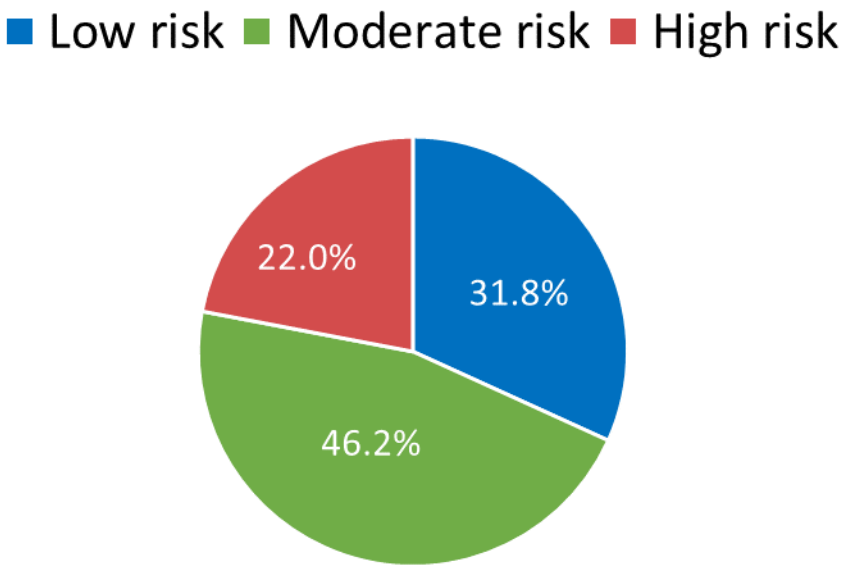


Figure 2 SSI Risk Distribution of the Original JSS-SSI Risk Scoring Tool in the Development Population



The thesis describing the development of the original JSS-SSI Risk Scoring Tool is presented in Appendix 2 (Section **11.2**).

4.3 Purpose of the Current Study

Following development on any risk model, validation in an external population other than the dataset utilized to create the tool is widely recommended to ensure generalizability in numerous populations. (114)

Although, in the event that a risk tool inadequately predicts the outcome, researchers are often inclined to disregard the initial model and develop a risk tool in a new patient population. (115) This approach however presents with certain limitations. Firstly, as improved results are generally obtained with an increased sample size, validation of a risk model while accounting for both the development and updating populations will increase the model's applicability in multiple settings. The creation of a new risk tool solely with the aid of an external population omits the development population. (115-118) Secondly, development of an alternate risk tool will increase the armamentarium of SSI predictive indexes, therefore obliging physicians to select the appropriate tool in their practice. (119) The utilization of an external patient population to update an existing risk model addresses the above-stated issues. Thus, the purpose of the current project is to improve and validate the predictive accuracy of the JSS-SSI-Risk Scoring tool in an external population.

5 Objectives

5.1 Primary Objectives

1. To assess the generalizability of the JSS-SSI Risk Scoring Tool in an external population.
2. To identify, assess and implement relevant modifications to the risk scoring tool that will maximize external validity.
3. To compare the discrimination, calibration and overall fit of the original and updated tools in order to select the final JSS-SSI Risk Scoring Tool with superior predictive accuracy.
4. To adjust the final JSS-SSI Risk Scoring Tool as per the results obtained in objective 2.
5. To assess the generalizability of the final JSS-SSI Risk Scoring Tool in an external population.

5.2 Exploratory Objectives

6. To determine the SSI prevalence rate among low-, moderate- and high-risk patients based on the final JSS-SSI Risk Scoring Tool.
7. To assess the relative rate of observed SSIs in moderate and high-risk patients in comparison to the low-risk group.

6 Methods

6.1 Definitions

1. Validity is the accuracy of measurement, in other words how accurately a model measures what it is meant to measure. High validity infers that the interpretation made on the assessment tool may be made with accuracy. (120)

2. External validation is the evaluation of a model's predictive accuracy in a population other than the population utilized for the development of the model. (121) The goal of external validation is to ensure generalizability or the applicability of the risk tool in various patient populations. (122)

3. Criterion-related validity, also referred to as "predictive validity", assesses the degree to which the risk tool adequately quantifies the risk of the outcome, in this case SSI development, which represents the "gold standard" in this analysis. (123, 124) In the scope of this Ph.D. project, criterion-related validity will measure whether the model can accurately identify patients who develop an SSI by assessing the model's discrimination (sensitivity and specificity).

4. Discrimination evaluates the risk tool's ability to accurately predict the outcome, in other words to distinguish cases from non-cases. Due to the binary nature of the outcome (SSI), discrimination was assessed with the Receiver Operating Characteristic (ROC) curve where the ordinate axis represents sensitivity and the abscissa axis represents 1 - specificity. The ROC curve depicts a plot of all sensitivity/ specificity combinations as a result of continuous variations of the decision cutoff over the full range of observed findings. (125)

    4.1 In this analysis, the area under the curve (AUC) represents the probability that a patient who developed an SSI has a higher risk score than a person who did not develop an SSI. (126) The AUC is used as an indicator of the test accuracy as it measures the ability of the model to correctly classify SSI cases from

non-SSI cases. The AUC may vary between 0.5 and 1 where the former represents no predictive accuracy and signifies that the model cannot accurately identify SSI patients, while the latter represents perfect predictive accuracy and signifies that the model can identify all SSI and non-SSI cases. (125, 127-130) To classify discriminative ability, the following AUC thresholds have been suggested in the literature: 0.9-1.0 = outstanding discrimination, 0.8-0.9 = excellent discrimination, 0.7-0.8 = acceptable discrimination, 0.5 = no discrimination. (131)

Table 3 Discrimination Estimates based on Scoring Risk and Outcome

		Outcome (SSI)		
		SSI	No SSI	
Scoring Risk (JSS-SSI Risk Scoring Tool)	High Risk	a	b	a + b
	Low or Moderate Risk	c	d	c + d
		a + c	b + d	Total

5. Sensitivity assesses the true positive rate, in other words the proportion of high-risk patients who develop an SSI relative to the total number of patients who develop an SSI. In **Table 3**, sensitivity is calculated as follows: a / (a + c) where a represents high-risk patients who developed an SSI and c represents low- or moderate-risk patients who develop an SSI. The sum (a + c) represents the total number of patients who developed an SSI, regardless of the tool's prediction. (132, 133)
6. Specificity assesses the true negative rate, in other words the proportion of low- or moderate-risk patients who do not develop an SSI relative to the total number of patients who do not develop an SSI. In **Table 3**, specificity is calculated as follows: d / (b + d) where d represents the low- or moderate-risk patients who do not develop an SSI and b represents the high-risk patients who do not develop an SSI. The sum (b

+ d) represents the total number of patients who did not develop an SSI, regardless of the tool's prediction. (132, 133)

7. Predicted SSI probability represents the individual risk of SSI development as calculated by: $p = (e^{\text{linear predictor}}) / (1 + e^{\text{linear predictor}})$ (118)
    7.1 Where the linear predictor is the following formula: [-5.975 + 0.617 x Male gender + 2.25 x Inpatient status + 0.902 x Hypertension + 0.910 x Steroid use + 0.947 x Dependent status], as obtained during the development of the JSS-SSI Risk Scoring Tool.
8. Calibration, or goodness-of-fit, is the level of agreement between predicted probabilities and observed outcome frequencies. (115) Calibration is commonly evaluated with the aid of calibration plots and the Hosmer-Lemeshow test.
    8.1 In the calibration plot, the ordinate axis represents observed proportions and the abscissa axis represents predicted probability. Perfect calibration of a risk tool is represented as a diagonal line illustrating that predicted probabilities coincide with the observed outcomes; where the intercept (denoted as $\alpha_{\text{calibration}}$) coincides with 0 on the ordinate and abscissa axes and the slope (denoted as $\beta_{\text{calibration}}$) is of 1. Conversely, a calibration curve to the left and right of the diagonal line implies that the model underestimates and overestimates the outcome, respectively. (134, 135)
    8.2 The Hosmer-Lemeshow test partitions the data into deciles (groups of 10) from low to high risk based on predicted probabilities, the first group representing the patients with the lowest risk and the last group representing patients with the highest risk. (128, 136) The calibration statistic, or goodness-of-fit statistic, is computed from the Chi-Square statistic by comparing the expected with the observed number of events. (128, 136) As the Hosmer-Lemeshow goodness of fit test approximately follows the Chi-Squared distribution, Chi-Square p-values > 0.05 indicate increased goodness-of-fit of the risk tool and statistical comparability between predicted probabilities and observed outcomes.

6.2 Methods Overview

The data utilized for this analysis, which comprised the 'Validation Population' included patients of all participating NSQIP hospitals who underwent surgery between 2012 and 2014 inclusively. The Validation Population was randomly split into four subpopulations in approximately a 1:1:1:1 ratio: the 'External Validation Population', the 'Updating Population', the 'Test Population' and the 'Comparison Population'. Firstly, the predictive accuracy of the original JSS-SSI Risk Scoring Tool created during the development phase was evaluated in the External Validation Population by assessing discrimination (with the aid of AUC, sensitivity and specificity), calibration (by producing a calibration plot and conducting the Hosmer-Lemeshow test) and overall fit of the model (by measuring Brier's score). If the risk tool did not exhibit optimal predictive accuracy in the External Validation Population, 12 methods utilizing the Updating Population aiming to improve the tool's predictive accuracy were performed by creating updated tools. The predictive accuracies of the original and updated tools were compared in the Test Population to select the final JSS-SSI Risk Scoring Tool. Simple algebraic functions were performed on the final risk tool for scores to range between 0 and 100 points. The final JSS-SSI Risk Scoring Tool was validated in the External Validation Population to ensure generalizability in a surgical patient population other than the one utilized for the tool's development. Relevant threshold cutoff values were identified by visual observation to classify surgical patients into low-, moderate- and high-risk SSI groups. Finally, the SSI prevalence rate in the Validation Population were assessed in all risk groups. The relative odds of SSI development were evaluated comparing the moderate- and high-risk classifications to the low-risk group.

6.3 Detailed Methodology

6.3.1 Study Design

This study was a retrospective chart review. The NSQIP database utilized in this analysis included patients who underwent surgery between January 1, 2012 and December 31, 2014. NSQIP is a surgical outcomes database of the American College of Surgeons. (34) The database originated in the mid-1980s as a result of an American governmental mandate (34) and now represents a prospective, comprehensive, validated, outcomes-based, risk-adjusted program that evaluates the quality of operative care. (137)

A single Surgical Clinical Reviewer (SCR) per hospital is designated to submit surgical data to NSQIP. In order to achieve high internal validity with respect to entered data, SCRs received initial and ongoing education, training and support by the American College of Surgeons. SCRs undergo annual certification exams to ensure understanding of NSQIP patient selection and variable definitions. (138)

Data from all participating NSQIP hospitals was acquired. Three-hundred seventy-four, 435 and 517 hospitals submitted data to NSQIP in 2012, 2013 and 2014, respectively. (139) The study follow-up duration was 30 days. As per the CDC, SSIs occur within 30 days following surgery, therefore this follow-up period was appropriate for the purposes of this study. (140)

NSQIP includes all major inpatient and outpatient surgical procedures as determined by the Current Procedural Terminology (CPT) code. Data is collected by medical chart review, and if necessary, communication to patients. (140)

Any of the following was regarded as a criterion for exclusion from the study: (140)

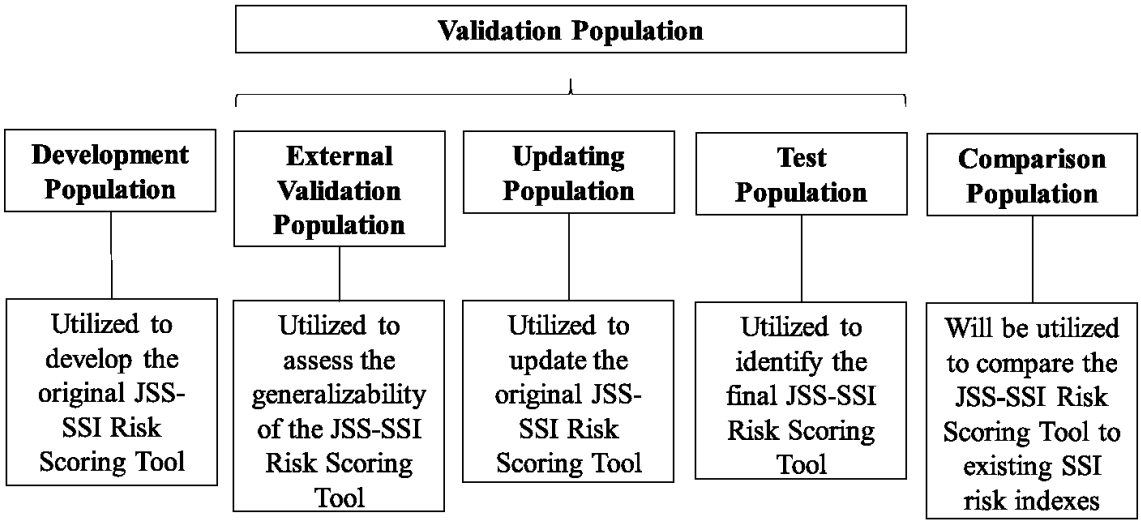
1. Patient under the age of 18 years.
2. More than 3 inguinal herniorrhaphies in an 8-day period.
3. More than 3 breast lympectomies in an 8-day period.
4. More than 3 laparoscopic cholecystectomies in an 8-day period.

5. If the site collects urology cases, more than 3 transurethral resections of the prostate or transurethral resections of bladder tumor in an 8-day period.

6.3.2 Analyzed Populations

During the validation phase, the utilization of an external population, named the 'Validation Population', different than the Development Population was necessary to establish the tool's predictive accuracy in a patient population other than the sample whose data it was derived. (116) The Validation Population comprises patients from the NSQIP database who underwent surgery and fulfilled the study inclusion criteria between January 2012 and December 2014. The Validation Population was randomly split in a 1:1:1:1 ratio, into an 'External Validation Population', 'Updating Population', 'Test Population' and 'Comparison Population'. As the names suggest, the External Validation Population was utilized to assess the generalizability of the JSS-SSI Risk Scoring Tool, the Updating Population was used to update and improve the tool's predictive accuracy, while the Test Population was utilized to compare the predictive accuracy of the original and updated risk models. The Comparison Population was not used in the current analysis; it will allow the future comparison of various SSI risk tools including the final JSS-SSI Risk Scoring Tool. An illustration of the analyzed populations is presented in **Figure 3**.

Figure 3 Analyzed Populations



6.3.3 Outcome Measures

6.3.3.1 Surgical Site Infection Assessment

The primary outcome measure of the analysis was an SSI infection defined as a nosocomial infection of the surgical site occurring within 30 days of a surgical procedure, as per the CDC. (1, 18, 34) SSIs can be classified into three categories according to the tissues and/or organs infected: superficial incisional SSI, deep incisional SSI and organ/space SSI. (17, 18, 21, 34-36) All three types of SSIs were included in the analysis. **Table 1** presents the diagnostic criteria for each type of SSI.

6.3.3.2 Surgical Site Infection Risk Factors

The following is a list of the 35 variables that were assessed as SSI predictors:

- **Patient Demographics:**
    - Age
    - Gender
    - BMI
    - Race

- Hispanic race

- **Surgical Profile:**
  - In/outpatient status
  - Transfer/ origin status
  - Principal anesthesia technique
  - Surgical specialty
- **Preoperative Risk Assessment:**
  - Diabetes mellitus (DM) with oral agents or insulin
  - Current smoker within one year (cigarette use only)
  - Dyspnea within the 30 days prior to surgery
  - Functional health status within the 30 days prior to surgery
  - Ventilator dependence at any time during the 48 hours preceding surgery
  - History of severe chronic obstructive pulmonary disease (COPD)
  - Ascites within 30 days prior to surgery
  - New diagnosis or new signs or symptoms of congestive heart failure within 30 days prior to surgery
  - Hypertension requiring medication within 30 days of surgery
  - Acute renal failure
  - Currently requiring or on dialysis
  - Disseminated cancer
  - Open wound (with or without infection)
  - Steroid use for a chronic condition in the 30 days prior to surgery
  - Decrease of more than 10% in body weight within 6 months of surgery
  - Bleeding disorder
  - Red blood cell preoperative transfusion
  - Sepsis within 48 hours prior to surgery
- Operative information:
  - Emergent case
  - Elective case

- Wound classification
- American Society of Anesthesiology (ASA) classification
- Operative times
- Other procedure
- Concurrent procedure

- **Postoperative Information:**
  - Discharge destination

A full description of the assessed risk factors is provided in Appendix 3 (Section **11.3**).

All potential SSI predictors in a continuous or categorical scale with more than two levels were adjusted to create meaningful dichotomous classifications as per **Table 4**.

Table 4 Criteria in Original and Dichotomized Classifications

Criteria	Original Classification	Dichotomized Classification
Race	1. American Indian or Alaska Native 2. Asian 3. Black or African American 4. Native Hawaiian or Pacific Islander 5. White	0. White 1. American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Pacific Islander
Age	In numerical values	0. Under 65 years of age 1. 65 years of age or older
Transfer Origin	1. Not transferred, admitted directly from home 2. Acute care hospital (inpatient) 3. Nursing home/ chronic care facility/ intermediate care unit 4. Transfer from other 5. Transfer from outside Emergency Department	0. Not transferred, admitted directly from home 1. Transfer from other or inpatient
Discharge Destination	1. Skilled care, not home 2. Unskilled facility, not home	0. Home 1. Facility, acute care or rehab

Criteria	Original Classification	Dichotomized Classification
	3. Facility which was home 4. Home 5. Separate acute care 6. Rehab	
Anesthesia Technique	1. General 2. Epidural 3. Spinal 4. Regional 5. Local 6. Monitored anesthesia care (MAC) 7. Other 8. None	0. Spinal, local, epidural, regional, MAC, other or none 1. General
Surgical Specialty	1. Cardiac surgery 2. General surgery 3. Gynecologic surgery 4. Neurosurgery 5. Orthopedic surgery 6. Otolaryngology (ENT) surgery 7. Plastic surgery 8. Thoracic surgery 9. Urologic surgery 10. Vascular surgery 11. Interventional radiology	0. Cardiac surgery, neurosurgery, orthopedic surgery, plastic surgery, vascular surgery, interventional radiology 1. General surgery, gynecologic surgery, ENT surgery, thoracic surgery, urologic surgery
BMI	In numerical values	0. Normal (BMI between 18.5 and 25) 1. Under/overweight (below 18.5 or above 25)
Diabetes	1. Non-diabetic 2. Diabetic requiring therapy with a non-insulin anti-diabetic agent 3. Diabetic requiring insulin therapy	0. Non-diabetic 1. Diabetic (type I or II)
Dyspnea	1. No dyspnea	0. No dyspnea

Criteria	Original Classification	Dichotomized Classification
	2. Dyspnea upon moderate exertion 3. Dyspnea at rest	1. Dyspnea (upon moderate exertion or at rest)
Functional Status prior to Surgery	1. Independent 2. Partially dependent 3. Totally dependent	0. Independent 1. Partially or totally dependent
Sepsis	1. No sepsis 2. SIRS 3. Sepsis 4. Septic shock	0. No sepsis 1. Sepsis (including SIRS and septic shock)
Wound Classification	1. Class I clean 2. Class II clean-contaminated 3. Class III contaminated 4. Class IV dirty/ infected	0. Class I or II (clean or clean-contaminated) 1. Class III or IV (contaminated or dirty/ infected)
ASA Class	1. ASA 1 (no disturb) 2. ASA 2 (mild disturb) 3. ASA 3 (severe disturb) 4. ASA 4 (life threat) 5. ASA 5 (moribund)	0. ASA 1 or 2 1. ASA 3, 4 or 5
Other Procedures	In numerical values	0. No other procedures 1. Yes, two or more procedures
Concurrent Procedures	In numerical values	0. No other procedures 1. Yes, two or more procedures
Procedure Duration	In numerical values	0. Duration shorter than 3 hours 1. Duration of 3 hours or longer

6.3.4 Statistical Methods

6.3.4.1 Descriptive Analyses

Descriptive analyses of the outcomes described in Sections **6.3.3.1** and **6.3.3.2** were conducted in the full Validation Population as well as in all subpopulations. The mean and standard deviation were assessed for continuous variables, and proportions were assessed for categorical variables.

Univariate Chi-Square analyses were performed in the Validation Population and all subpopulations where SSI constituted the dependent variable and the 35 NSQIP risk factors comprised the independent variables. Statistical significance was denoted by a p-value lower than 0.05.

6.3.4.2 Methods to Address Study Objectives

6.3.4.2.1 Objective 1

Given that the gold standard for predictive model is SSI outcome, the entire exercise of developing the scoring tool is an evaluation of criterion-related validity. The JSS-SSI Risk Scoring Tool's predictive validity was assessed in the External Validation Population by evaluating discrimination, calibration and overall fit of the model.

6.3.4.2.1.1 Discrimination

ROC analysis was performed to describe the accuracy of the predictive tool as a function of the true positive and true negative rates for each level of the tool. The tool's AUC, sensitivity and specificity as defined in Section **6.1** were assessed in the External Validation Population.

6.3.4.2.1.2 Calibration

The calibration of the JSS-SSI Risk Scoring Tool was evaluated in the External Validation Population by generating a calibration plot and with the aid of the Hosmer-Lemeshow test. As previously defined in Section **6.1**, the intercept α and slope β of the calibration plot were

evaluated. With respect to the Hosmer-Lemeshow test, which approximately follows the Chi-Squared distribution with degrees of freedom equivalent to the number of groups (128, 129, 136, 141, 142), a p-value above 0.05 indicates acceptable goodness-of-fit of the risk tool and statistical comparability between predicted probabilities as assessed by the JSS-SSI Risk Scoring Tool and observed outcomes. (142)

6.3.4.2.1.3 Overall Fit of Model

Brier's score is an evaluation of the overall accuracy of a model with a binary outcome which captures discrimination and calibration aspects. (128, 133, 143) This quadratic scoring rule (133) assessed the overall fit of each model by calculating the squared differences between SSI outcome (Y) and the predicted probability (p): $(Y - p)^2$. Brier's score varies between 0 and 1 where the former indicates perfect prediction and the latter indicates a noninformative model. (128, 133, 144)

6.3.4.2.2 Objective 2

Based on discrimination and calibration aspects previously described, various updating methods may be employed to improve a risk tool's predictive accuracy. Re-calibration entails an update of the risk tool's intercept α and regression coefficients based on multiplication of the original coefficients with the calibration slope β. A simpler updating method may solely require modification of the calibration intercept α. More extensive updating methods, such as 'model revision' and 'model extension', re-estimate some or all of the regression variable coefficients and consider additional variables for inclusion in the risk tool, respectively. (145)

Therefore, the original JSS-SSI Risk Scoring Tool created utilizing the Development Population was modified. The effect of twelve updating methods on the risk tool's discrimination, calibration and overall fit of the model were tested using the Updating Population.

6.3.4.2.2.1 Method 1

Method 1 entails no updating of the risk tool. All variables previously comprised in the tool were included. Also, the variable coefficients and intercept α were maintained at their original values. This method provides a reference upon which improvement of the risk tool is expected with the remaining updating methods.

6.3.4.2.2.2 Method 2

Method 2 updated the value of the calibration intercept α in order to render the average predicted probability (represented as the abscissa axis on the calibration plot) equal to the observed overall SSI rate (represented as the ordinate axis on the calibration plot). (134, 145) The adjustment was performed by fitting a logistic regression model in the Updating Population with the linear predictor as an offset variable. (134, 145) This adjustment is expected to account for the potential differences in regard to the SSI incidence between the Development and Updating Populations; in particular, this change may have been warranted due to the possible change in surgical or SSI care protocol over time. (146)

6.3.4.2.2.3 Method 3

Method 3 allowed the modification of the original JSS-SSI Risk Scoring Tool's intercept and predictors' regression coefficients (relative weights representing the predictive strength of each SSI risk factor). (115)

The calibration slope β was used to recalibrate the logistic regression coefficients, in other words the original coefficients of the JSS-SSI Risk Scoring Tool were multiplied by the calibration slope β to produce updated variable coefficients. A calibration slope β equal to 1 would signify that the original logistic regression coefficients do not require adjustment. The intercept of the original JSS-SSI Risk Scoring Tool was adjusted by adding the value of the calibration intercept α to this estimate. (115, 134, 145)

6.3.4.2.2.4 Method 4

As first step of Method 4, all previously described methods in section **6.3.4.2.2.3** (Method 3) were conducted followed by testing of the effect of the individual SSI predictors to evaluate if differences were observed between the Development Population and the Updating Population with respect to the variable coefficients. Likelihood ratio tests in a forward stepwise manner were performed in the Updating Population to compare the goodness-of-fit of the original and updated risk tools. A stopping threshold of $p = 0.05$ was utilized. For each risk factor, if significant differences were observed between both risk tools' coefficients ($p < 0.05$), the regression coefficient obtained from the Updating Population were included in the updated JSS-SSI Risk Scoring Tool. (115, 134, 145)

6.3.4.2.2.5 Method 5

For Method 5, all original SSI predictors identified during the development of the JSS-SSI Risk Scoring Tool were maintained. The updated risk tool included re-estimated intercept α and variable coefficients as obtained during logistic regression analysis utilizing the Updating Population. (115, 134, 145)

6.3.4.2.2.6 Method 6

The steps described in section **6.3.4.2.2.5** (Method 5) were performed. In addition, the analyses leading to the development of the risk tool were repeated in the Updating Population. Multivariate logistic regression analysis was used to identify the variables that were significantly associated with SSI outcome. The classification cutoff in the present logistic regression represented the prevalence rate of SSIs in the Updating Population. All SSI significant predictors ($p < 0.05$) identified were included in the updated risk tool with their corresponding variable coefficients. (115, 145)

6.3.4.2.2.7 Method 7

The methods described in section **6.3.4.2.2.5** (Method 5) were repeated. Bivariate Chi-Square analysis was used to identify variables that were associated with SSI development.

Those variables with an association that had a significance level less than 15% ($p < 0.15$) were considered as potential predictors and were entered into a logistic regression model to identify significant SSI predictors. The classification cutoff in the present logistic regression represented the prevalence rate of SSIs in the Updating Population. All SSI significant predictors ($p < 0.05$) identified were included in the updated risk tool with their corresponding variable coefficients. (115, 145)

6.3.4.2.2.8 Method 8

The steps detailed in section **6.3.4.2.2.3** (Method 3) were re-executed. Moreover, the analyses leading to the development of the risk tool were repeated in the Updating Population. Logistic regression analysis was used to identify the variables that were associated with SSI outcome. The classification cutoff in the present logistic regression represented the prevalence rate of SSIs in the Updating Population. Risk factors with a p-value lower than 0.05 were considered as SSI predictors in the Updating Population. (115)

6.3.4.2.2.9 Method 9

The methods detailed in section **6.3.4.2.2.3** (Method 3) were performed. Moreover, bivariate chi-square analysis was used to identify the variables that were associated with SSI outcome. Those variables with an association that had a significance level less than 15% ($p < 0.15$) were considered as potential predictors and were entered into a logistic regression model to identify significant SSI predictors. The classification cutoff in the present logistic regression represented the prevalence rate of SSIs in the Updating Population. Risk factors with a p-value lower than 0.05 were considered as SSI predictors in the Updating Population. (115)

6.3.4.2.2.10 Method 10

The methods described in section **6.3.4.2.2.5** (Method 5) were performed utilizing the combined data of the Development and Updating Population. (134)

6.3.4.2.2.11 Method 11

Method 11 entailed the inclusion of all assessed risk factors with an increased association with SSI (OR > 1.5), as assessed with logistic regression, regardless of the significance level (p-value) with the outcome. The variable coefficients and intercept α value were obtained during logistic regression analysis in the Updating Population. The classification cutoff in the present logistic regression represented the prevalence rate of SSIs in the Updating Population.

6.3.4.2.2.12Method 12

Method 12 repeated the analyses of section **6.3.4.2.2.11** (Method 11) though solely included risk factors with OR > 2 in the risk tool as per the previously performed logistic regression.

6.3.4.2.3 Objective 3

The discrimination, calibration and overall fit of the model of the original and updated tools were evaluated in the Test Population to identify the tool with improved predictive accuracy in an external population than that which was utilized during the tools' development.

6.3.4.2.3.1 Discrimination

The discrimination of the original and updated risk tools was assessed by constructing ROC curves in the Test Population. The risk tool with the highest area under the ROC curve was considered as the tool with superior discriminative ability in the identification of SSI cases.

6.3.4.2.3.2 Calibration

Calibration of the original and updated tools were compared in the Test Population. Similarly to the steps performed in Section **6.3.4.2.1.2**, (128, 129, 136, 141, 142) the calibration of the JSS-SSI Risk Scoring Tool was evaluated with the aid of the generation of calibration plots and the Hosmer-Lemeshow test. As previously defined in Section **6.1**, the intercept α and calibration slope β were evaluated. With respect to the Hosmer-

Lemeshow test, which approximately follows the Chi-Squared distribution with degrees of freedom equivalent to the number of groups (128, 129, 136, 141, 142), a p-value above 0.05 indicates acceptable goodness-of-fit of the risk tool and statistical comparability between predicted probabilities as assessed by the JSS-SSI Risk Scoring Tool and observed outcomes in the Updating Population. (142) The model with the Hosmer-Lemeshow p-value closest to 1, indicating minimal difference between the observed and expected outcomes, as well as a slope β and intercept α closest to 1 and 0, respectively, observed in calibration plots constituted the model with the highest calibration.

6.3.4.2.3.3 Overall Fit of Model

Overall fit of the original and updated tools was measured with the aid of Brier's score as was performed in Section **6.3.4.2.1.3**. (128, 133, 143) The model with the lowest Brier's score constituted the best overall predictor of SSI outcome.

6.3.4.2.3.4 Selection of the Final JSS-SSI Risk Scoring Tool

Based on the results obtained in Sections **6.3.4.2.3.1**, **6.3.4.2.3.2** and **6.3.4.2.3.3**, the final JSS-SSI Risk Scoring Tool was selected. The tool with the superior discrimination, calibration and overall model fit in the Test Population was considered as the final tool to be utilized in the remainder of the analysis. In the case of inconsistent outcomes of these parameters, the tool with superior results in two out of three tests was considered the final tool to be utilized in the remainder of the analysis. In case of discordant findings between all assessments, the model with the lowest Brier score was retained as the final JSS-SSI Risk Scoring Tool.

6.3.4.2.4 Objective 4

A scoring scale was developed based on the updated tool's included risk factors and variable coefficients. This was accomplished by converting the risk assessment scoring scale to a simple mathematical calculation that is limited to the addition of integers. While the risk scoring scale may involve complex mathematical operations including several multiplications and divisions by integer and non-integer values, the user-friendliness of the

tool is ensured as only additions of simple integers, based on the presence or absence of each risk factor, is necessary to calculate the patient's SSI score. Moreover, the tool ranges between 0 and 100 points further facilitating interpretability of patient scores.

The conversions were based on algebraic functions (multiplications and divisions) of the weights, as estimated from the risk factors' coefficient variables obtained during logistic regression analysis, for each question and potential answers on the scale.

The final logistic regression model was assessed with the aid of ROC curve analysis in the Validation Population combining the External Validation, Updating and Test Populations. As was performed during the development of the original JSS-SSI Risk Scoring Tool, two cutoff values corresponding to the highest ordinate (vertical axis of 'Sensitivity') and the lowest abscissa (horizontal axis of '1 – Specificity') were identified by visual observation of the curve. These two cutoff values classified patients according to their SSI risk (low, moderate and high risk). If no clear threshold values could be visually identified, cutoffs were to be established at the sensitivity and specificity values separating the ROC curve into three equal parts.

6.3.4.2.5 Objective 5

The discrimination, calibration and overall fit of the final JSS-SSI Risk Scoring tool were assessed in the External Validation Population. The steps performed in Section **6.3.4.2.1** (Objective 1) were repeated to ensure the tool's applicability in a population other than the one utilized to develop the tool. High generalizability was indicated by a high AUC (close to 1); high sensitivity and specificity (close to 100%); intercept α and slope β of the calibration plot close to 0 and 1, respectively; high Hosmer-Lemeshow p-value (close to 1); and low Brier score (close to 0).

6.3.4.2.6 Objective 6

Patients of the Validation Population, including the External Validation, Updating and Test Populations, were classified into low-, moderate- and high-risk SSI groups as per the

established cutoffs identified in Section **6.3.4.2.4**. Descriptive statistics were performed to assess SSI prevalence in each risk group.

6.3.4.2.7 Objective 7

The SSI score classification was validated in the Validation Population using multivariate logistic regression analysis to assess the relative rate of SSI development among the moderate- and high-risk SSI groups in comparison to low-risk SSI patients.

6.3.5 Ethical Considerations

The principles of the Declaration of Helsinki (2013) have been addressed. As this constitutes a non-interventional study utilizing electronic patient records, no harm was inflicted on the patient. It is therefore considered that the benefits of this study far outweigh the risks.

7 Results

7.1 Patient Characteristics

The Validation Population comprised 1,459,481 patients. This population was divided into three subpopulations: the External Validation Population included 486,104 patients while the Updating Population and the Test Population included 487,236 and 486,141 patients, respectively.

The mean (SD) age of the population was 56.4 (16.56) years. In total, 49,474 patients (3.4%) developed an SSI of which 24,878 (1.7%), 9,106 (0.6%) and 16,938 (1.2%) developed a superficial incisional, deep incisional and organ/ space SSI, respectively. Certain patients were diagnosed with more than one type of SSI. The mean (SD) time to SSI diagnosis was 13.7 (7.29), 14.4 (7.52) and 12.4 (7.09) days for superficial incisional, deep incisional and organ/ space SSI patients, respectively. (**Table 5**)

Table 5 Surgical Site Infection Characteristics

Parameter	**Validation Population (N = 1,459,481)**
Any SSI, n (%)	49,474 (3.4%)[1]
Superficial Incisional SSI, n (%)	24,878 (1.7%)
Deep Incisional SSI, n (%)	9,106 (0.6%)
Organ/ Space SSI, n (%)	16,938 (1.2%)
Days following Operation until SSI Diagnosis, mean (SD)	
Superficial Incisional SSI	13.7 (7.29)
Deep Incisional SSI	14.4 (7.52)
Organ/ Space SSI	12.4 (7.09)

[1]A patient may have developed more than one type of SSI.

7.2 Risk Factor Assessment

Table 6 presents the prevalence of each risk factor by subpopulation. Of the 35 risk factors assessed, the most frequent (> 30%) in the Validation Population were general anesthesia (90.1%); underweight/ overweight (75.1%); a procedure of general, gynecologic, ENT, thoracic or urologic surgical specialty (65.7%); inpatient status (61.3%); hypertension requiring medication (45.5%); ASA class III, IV or V (45.3%); male sex (42.8%); and age ≥ 65 years (34.7%). In addition, 28.3% of patients received at least one other procedure, 20.0% underwent non-elective surgery, 18.2% were current smokers, 16.2% required a procedure over 3 hours, 15.6% were of non-Caucasian race (American Indian, Alaska native, Asian, Black, African American, native Hawaiian, Pacific Islander), 15.3% were diabetic, 11.2% had a Class III (contaminated) or IV (dirty/ infected) operative wound, 10.5% were to temporarily or permanently reside in a facility, acute care center, rehabilitation center or other residence following hospital discharge, 9.7% underwent an emergent procedure, 8.3% were of Hispanic race, 6.1% had dyspnea (at rest or upon moderate exertion), 5.3% had preoperative sepsis, 4.6% had a history of severe COPD, 4.5% had a preoperative bleeding disorder, 4.2% were transferred from a location other than home, 3.7% received steroids, 3.1% required at least one concurrent procedure, 3.1% had an open wound, 2.8% were partially or totally dependent for everyday activities prior to surgery, 2.2% had disseminated cancer, 1.4% were receiving dialysis, 1.3% had lost more than 10% of their body weight in the 6 months preceding surgery, 1.1% required a preoperative transfusion (within 72 hours of surgery), 0.8% had congestive heart failure, 0.4% had ascites, 0.4% had preoperative renal failure and 0.4% required preoperative ventilator use. Similar proportions were observed between all subpopulations.

Table 6 Risk Factor Assessment by Population

Risk Factor, %		External Validation Population (n = 486,104)	Updating Population (n = 487,236)	Test Population (n = 486,141)	Validation Population (N = 1,459,481)
Age[1]	< 65 years	65.3	65.4	65.3	65.3
	≥ 65 years	34.7	34.6	34.7	34.7
Anesthesia Technique	Spinal, local, epidural, regional, MAC or none	10.0	9.9	9.8	9.9
	General	90.0	90.1	90.2	90.1
ASA Class	I or II	54.7	54.7	54.7	54.7
	III, IV or V	45.3	45.3	45.3	45.3
Ascites	No	99.6	99.6	99.6	99.6
	Yes	0.4	0.4	0.4	0.4
Preoperative Bleeding Disorder	No	95.6	95.5	95.5	95.5
	Yes	4.4	4.5	4.5	4.5
BMI[2]	Normal (18.5-25)	24.8	25.0	24.9	24.9
	Underweight (< 18.5) or overweight (> 25)	75.2	75.0	75.1	75.1
Concurrent Procedures	No	96.8	96.9	96.8	96.9
	Yes	3.2	3.1	3.2	3.1
	No	99.2	99.2	99.2	99.2

Risk Factor, %		External Validation Population (n = 486,104)	Updating Population (n = 487,236)	Test Population (n = 486,141)	Validation Population (N = 1,459,481)
Congestive Heart Failure	Yes	0.8	0.8	0.8	0.8
History of Severe COPD	No	95.4	95.4	95.4	95.4
	Yes	4.6	4.6	4.6	4.6
Diabetes	Non-diabetic	84.7	84.7	84.7	84.7
	Diabetic (type I or type II)	15.3	15.3	15.3	15.3
Dialysis	No	98.6	98.6	98.6	98.6
	Yes	1.4	1.4	1.4	1.4
Disseminated Cancer	No	97.7	97.8	97.8	97.8
	Yes	2.3	2.2	2.2	2.2
Discharge Destination	Home	89.6	89.5	89.5	89.5
	Facility, acute care, rehab or other	10.4	10.5	10.5	10.5
Duration of Surgery[3]	0-3 hours	83.8	83.7	83.7	83.8
	> 3 hours	16.2	16.3	16.3	16.2
Dyspnea	No	93.8	93.9	93.9	93.9
	Yes (at rest or upon moderate exertion)	6.2	6.1	6.1	6.1
	No	20.1	20.0	20.0	20.0

Risk Factor, %		External Validation Population (n = 486,104)	Updating Population (n = 487,236)	Test Population (n = 486,141)	Validation Population (N = 1,459,481)
Elective Surgery	Yes	79.9	80.0	80.0	80.0
Emergency	No	90.3	90.3	90.3	90.3
	Yes	9.7	9.7	9.7	9.7
Functional Status prior to Surgery	Independent	97.2	97.2	97.2	97.2
	Partially or totally dependent	2.8	2.8	2.8	2.8
Hispanic Race	No	91.7	91.7	91.8	91.7
	Yes	8.3	8.3	8.2	8.3
Hypertension Requiring Medication	No	54.5	54.5	54.5	54.5
	Yes	45.5	45.5	45.5	45.5
Inpatient Status	No (outpatient)	38.8	38.7	38.8	38.7
	Yes (inpatient)	61.2	61.3	61.2	61.3
Open Wound	No	96.9	96.9	96.9	96.9
	Yes	3.1	3.1	3.1	3.1
Other Procedures	No	71.8	71.5	71.7	71.7
	Yes	28.2	28.5	28.3	28.3
Race	Caucasian	84.3	84.4	84.4	84.4
	American Indian, Alaska native, Asian, Black,	15.7	15.6	15.6	15.6

Risk Factor, %		External Validation Population (n = 486,104)	Updating Population (n = 487,236)	Test Population (n = 486,141)	Validation Population (N = 1,459,481)
	African American, native Hawaiian, Pacific Islander				
Preoperative Renal Failure	No	99.7	99.6	99.6	99.6
	Yes	0.3	0.4	0.4	0.4
Preoperative Sepsis	No	94.7	94.8	94.7	94.7
	Yes	5.3	5.2	5.3	5.3
Sex	Female	57.1	57.2	57.2	57.2
	Male	42.9	42.8	42.8	42.8
Current Smoker	No	81.8	81.8	81.8	81.8
	Yes	18.2	18.2	18.2	18.2
Steroid Use	No	96.3	96.3	96.3	96.3
	Yes	3.7	3.7	3.7	3.7
Surgical Specialty	Cardiac, neurosurgery, orthopedics, plastics, vascular, interventional radiology	34.3	34.3	34.3	34.3
	General, gynecology, ENT, thoracic, urology	65.7	65.7	65.7	65.7
Transfer Status	Not transferred, admitted directly from home	95.8	95.8	95.8	95.8

Risk Factor, %		External Validation Population (n = 486,104)	Updating Population (n = 487,236)	Test Population (n = 486,141)	Validation Population (N = 1,459,481)
	Transfer from other or inpatient	4.2	4.2	4.2	4.2
Preoperative Transfusion (within 72 Hours)	No	98.9	98.9	99.0	98.9
	Yes	1.1	1.1	1.0	1.1
Preoperative Ventilator Use	No	99.6	99.6	99.6	99.6
	Yes	0.4	0.4	0.4	0.4
> 10% Weight Loss in 6 Months prior to Surgery	No	98.7	98.7	98.7	98.7
	Yes	1.3	1.3	1.3	1.3
Wound Class	Class I (clean) or II (clean-contaminated)	88.8	88.8	88.9	88.8
	Class III (contaminated) or IV (dirty/ infected)	11.2	11.2	11.1	11.2

[1]Mean (SD) age = 56.4 (16.56) years.

[2]Mean (SD) BMI = 30.1 (7.81).

[3]Mean (SD) duration of surgery = 112.1 (94.83) minutes.

As obtained in univariate Chi-Square analysis, significant ($p < 0.05$) associations with SSI outcome were observed for the following risk factors: age, anesthesia technique, ASA class, ascites, preoperative bleeding disorder, BMI, concurrent procedures, congestive heart failure, history of severe COPD, diabetes, dialysis, disseminated cancer, discharge destination, duration of surgery, dyspnea, elective surgery, emergency, functional status prior to surgery, Hispanic race, hypertension requiring medication, inpatient status, open wound, other procedures, preoperative renal failure, preoperative sepsis, sex, current smoker, steroid use, surgical specialty, transfer status, preoperative transfusion (within 72 hours), preoperative ventilator use, > 10% weight loss in 6 months prior to surgery and wound class. Race was not significantly associated with SSI development ($p > 0.05$). (**Table 7**)

Table 7 Chi-Square Risk Factor Assessment by SSI Outcome

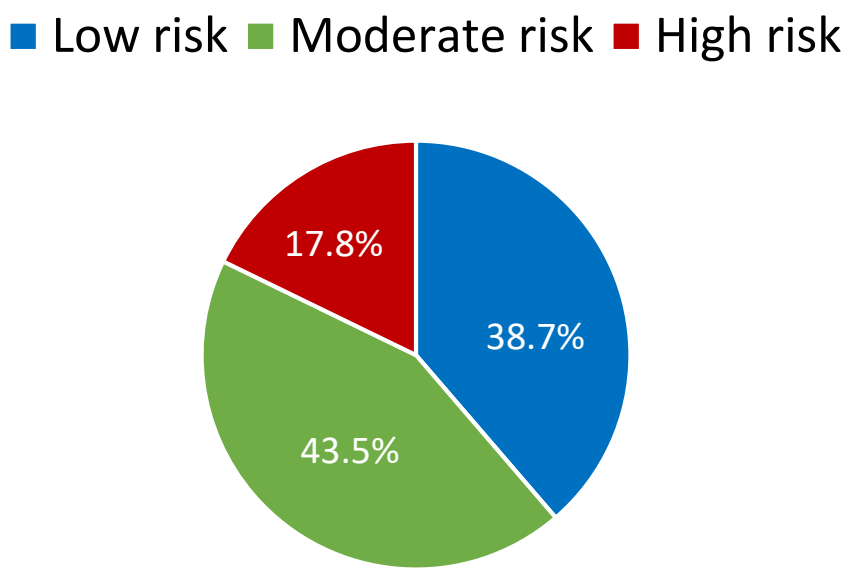
Risk Factor, %	**No SSI (n = 1,410,007)**	**SSI (n = 49,474)**	**p-value**
Age ≥ 65 Years	34.6	36.1	< 0.001
General Anesthesia	89.9	96.2	< 0.001
ASA Class III, IV Or V	44.6	63.7	< 0.001
Ascites	0.4	1.2	< 0.001
Preoperative Bleeding Disorder	4.4	7.1	< 0.001
Over/ Underweight	75.0	77.0	< 0.001
Concurrent Procedures	3.0	7.3	< 0.001
Congestive Heart Failure	0.8	1.4	< 0.001
History of Severe COPD	4.5	7.2	< 0.001
Diabetes	15.1	20.8	< 0.001
Dialysis	1.3	2.2	< 0.001
Disseminated Cancer	2.1	5.8	< 0.001
Discharge Destination (Facility, Acute Care, Rehab or Other)	10.2	20.0	< 0.001
Duration of Surgery > 3 Hours	15.5	38.5	< 0.001
Dyspnea	6.1	8.5	< 0.001

Risk Factor, %	No SSI (n = 1,410,007)	SSI (n = 49,474)	p-value
Elective Surgery	80.5	66.0	< 0.001
Emergency	9.4	17.3	< 0.001
Dependent Functional Status prior to Surgery	2.7	4.8	< 0.001
Hispanic Race	8.3	7.3	< 0.001
Hypertension Requiring Medication	45.3	51.1	< 0.001
Inpatient Status	60.4	87.7	< 0.001
Open Wound	2.9	8.0	< 0.001
Other Procedures	28.5	25.0	< 0.001
American Indian, Alaska Native, Asian, Black, African American, Native Hawaiian, Pacific Islander Race	15.6	15.9	0.058
Preoperative Renal Failure	0.3	0.8	< 0.001
Preoperative Sepsis	4.9	14.2	< 0.001
Male Sex	42.7	46.5	< 0.001
Current Smoker	18.0	24.1	< 0.001
Steroid Use	3.6	6.9	< 0.001
Surgical Specialty (General, Gynecology, ENT, Thoracic, Urology)	65.2	79.9	< 0.001
Transfer Status (Transfer from Other or Inpatient)	4.0	8.4	< 0.001
Preoperative Transfusion (within 72 Hours)	1.0	2.6	< 0.001
Preoperative Ventilator Use	0.3	0.9	< 0.001
> 10% Weight Loss in 6 Months prior to Surgery	1.2	4.1	< 0.001
Wound Class III Or IV	10.5	28.8	< 0.001

7.3 External Validation of the Original JSS-SSI Risk Scoring Tool (Objective 1)

In the External Validation Population (n = 486,104), 16,377 (3.4%) patients developed an SSI. Moreover, 2.8% were partially or totally dependent prior to surgery, 45.5% had hypertension, 61.2% were inpatients, 42.9% were male and 3.7% were steroid users. (**Table 6**) The mean (SD) SSI score utilizing the original JSS-SSI Risk Scoring Tool was 41.7 (27.39) points. As illustrated in **Figure 4**, 186,828 (38.7%), 209,981 (43.5%) and 86,020 (17.8%) had scores between 0-43, 44-63 and 64-100 points and therefore had a low, moderate and high risk of SSI development, respectively.

Figure 4 SSI Risk Distribution of the Original JSS-SSI Risk Scoring Tool in the External Validation Population



As presented in **Table 8** and **Figure 5,** the ROC analysis shows that the predictive ability of the original JSS-SSI Risk Scoring Tool was significantly higher than that expected by

chance alone (95% CI: 0.653, 0.661; $p < 0.001$). The area under the ROC curve was 0.657. The sensitivity and specificy were 87.9% and 39.7%, respectively.

The original tool was not well calibrated in the External Validation Population; the calibration slope β of 0.37 indicated that the model overestimated the outcome. The intercept α of the calibration slope β was 0.02; this value close to 0 suggests that patients with a null predicted probability generally do not develop the outcome. (**Table 8** and **Figure 6**) Moreover, the significant p-value ($p < 0.001$) of the Hosmer-Lemeshow test is suggestive of statistical difference between predicted probability and observed outcome.

Regarding overall fit of the model, the mean (SD) Brier score was 0.0331 (0.1606).

Table 8 External Validation Findings of the Original JSS-SSI Risk Scoring Tool

	External Validation Population (n = 486,104)
Area under the ROC Curve, 95% CI	0.657 (0.653, 0.661)
Sensitivity, %	87.9
Specificity, %	39.7
Calibration Plot Slope β	0.37
Calibration Plot Intercept α	0.02
Hosmer-Lemeshow P-value	< 0.001
Brier Score, mean (SD)	0.0331 (0.1606)

Figure 5 ROC Analysis of the Original JSS-SSI Risk Scoring Tool in the External Validation Population

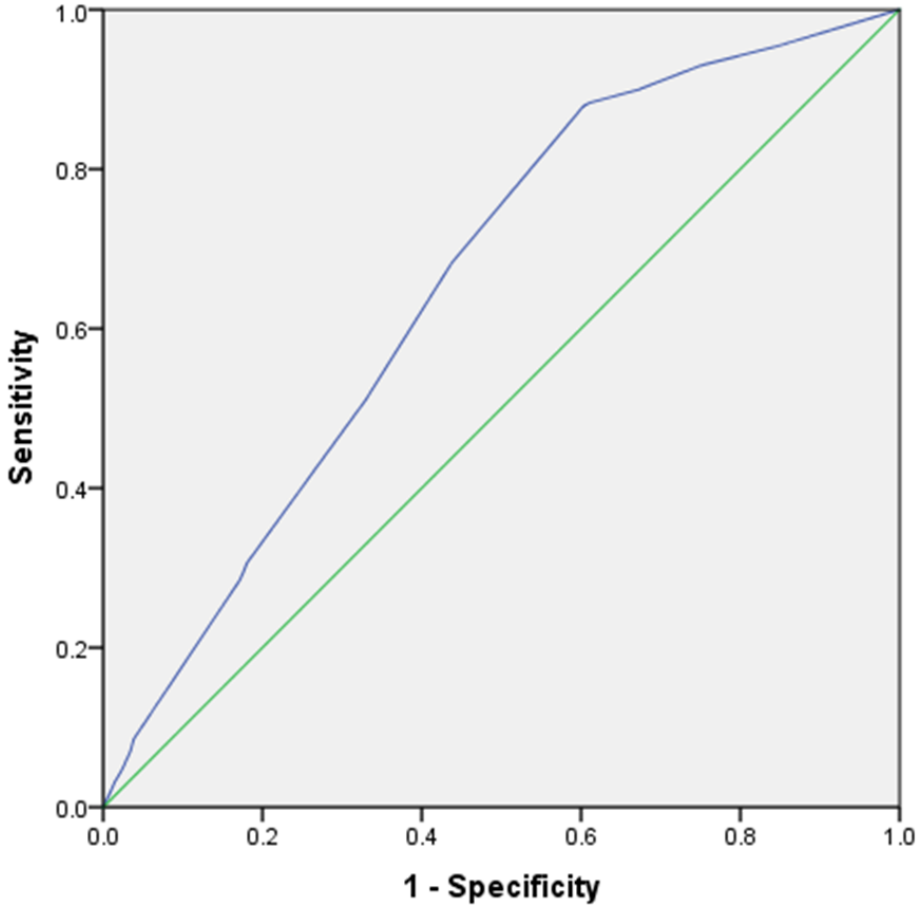
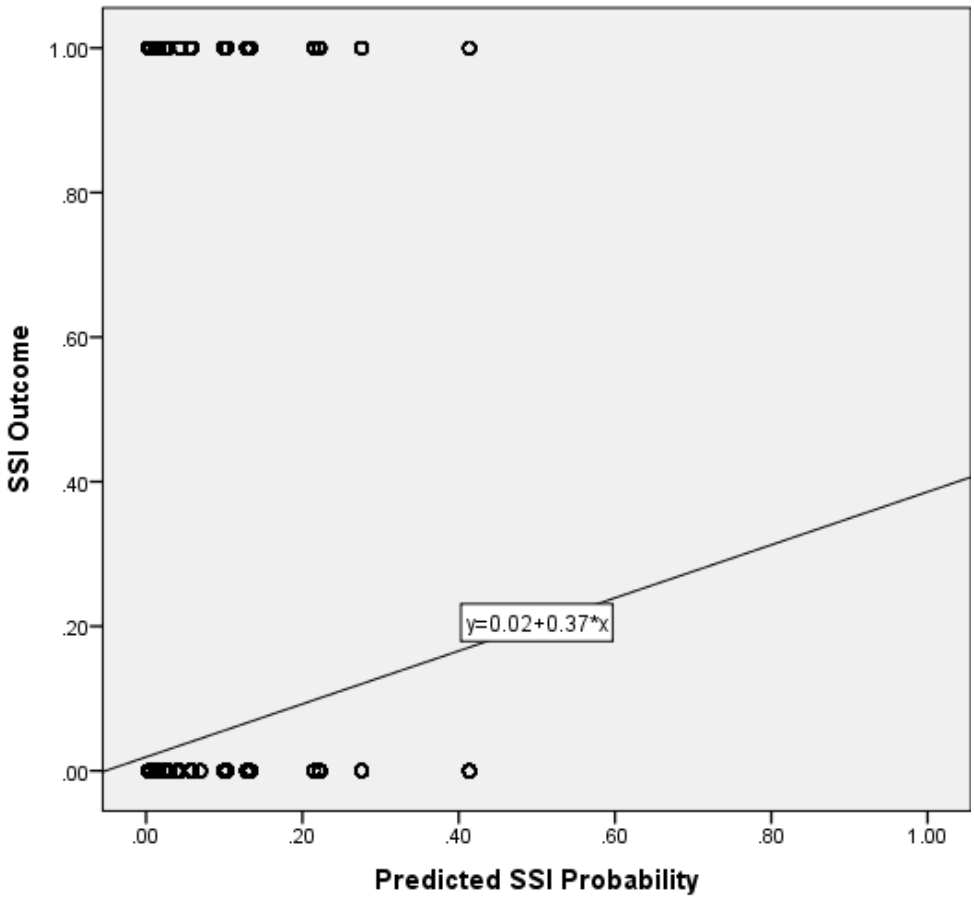


Figure 6 Calibration Plot of the Original JSS-SSI Risk Scoring Tool in the External Validation Population



7.4 Updating of the JSS-SSI Risk Scoring Tool (Objective 2)

7.4.1 Method 1

As previously described in Section **6.3.4.2.2.1**, Method 1 entailed no updating to the original JSS-SSI Risk Scoring Tool and therefore serves as reference for the remaining updating methods.

The five risk factors identified as significant ($p < 0.05$) SSI predictors during the development of the model were included in the tool of Method 1: male sex, inpatient status,

hypertension, steroid use, and dependent functional status. The logistic regression formula where the dependent variable was SSI development and the independent variables were the included risk factors was as follows: logit (SSI) = -5.975 + 0.617 * Sex + 2.25 * Inpatient + 0.902 * Hypertension + 0.910 * Steroid + 0.947 * Dependent Status

The OR of each risk factor is shown in **Table 9**. Inpatient status was the most influential risk factor with an OR of 9.488, followed by dependent functional status (OR = 2.578), steroid use (OR = 2.484), hypertension (OR = 2.465) and male sex (OR = 1.853).

Table 9 Method 1 SSI Predictors and Odds Ratios

Risk Factor	Odds Ratio
Male Sex	1.853
Inpatient Status	9.488
Hypertension	2.465
Steroid Use	2.484
Dependent Functional Status	2.578

7.4.2 Method 2

The tool of Method 2 included the same risk factors as Method 1 and preserved the ORs previously identified (as shown in **Table 9**). Solely the model's intercept α was modified. As such, the formula of Method 2 is: logit (SSI) = -8.208 + 0.617 * Sex + 2.25 * Inpatient + 0.902 * Hypertension + 0.910 * Steroid + 0.947 * Dependent Status

7.4.3 Method 3

The tool of Method 3 comprised equivalent risk factors as Method 1 and presented with a logistic regression formula as follows: logit (SSI) = -4.391 + 0.257 * Sex + 0.938 * Inpatient + 0.376 * Hypertension + 0.379 * Steroid + 0.395 * Dependent Status

The risk factors' ORs are presented in **Table 10**.

Table 10 Method 3 SSI Predictors and Odds Ratios

Risk Factor	Odds Ratio
Male Sex	1.293
Inpatient Status	2.556
Hypertension	1.457
Steroid Use	1.462
Dependent Functional Status	1.484

7.4.4 Method 4/5

The likelihood ratio tests performed in Method 4 demonstrated superiority of all risk factor coefficients utilizing the Updating Population. As such, the formula and ORs for Methods 4 and 5 are identical. The formula is: logit (SSI) = -4.585 + 0.151 * Sex + 1.474 * Inpatient + 0.028 * Hypertension + 0.500 * Steroid + 0.262 * Dependent Status

The risk factors' ORs are shown in **Table 11**.

Table 11 Method 4/5 SSI Predictors and Odds Ratios

Risk Factor	Odds Ratio
Male Sex	1.163
Inpatient Status	4.367
Hypertension	1.028
Steroid Use	1.649
Dependent Functional Status	1.300

7.4.5 Method 6

Method 6 introduced new variables into the model by including all risk factors shown to be significantly associated with SSI outcome obtained via multivariate logistic regression utilizing the Updating Population: age ≥ 65, general anesthesia, ASA class III/ IV, bleeding disorder, under/ overweight, concurrent procedures, diabetes, discharge destination other than home, disseminated cancer, surgery duration > 3 hours, elective surgery, emergency,

dependent functional status, inpatient status, open wound, other procedures, race other than Caucasian, sepsis, male sex, smoker, steroid use, surgical specialty (general, gynecology, ENT, thoracic, urology), ventilator use, weight loss > 10%, wound class III/ IV, and hypertension.

The formula of Method 6's tool is shown below:

Logit (SSI) = -5.654 + -0.114 * Age + 0.400 * Anesthesia + 0.285 * ASA Class + 0.117 * Bleeding Disorder + 0.191 * Under/ Overweight + 0.141 * Concurrent Procedures + 0.116 * Diabetes + 0.556 * Discharge Destination + 0.294 * Disseminated Cancer + 0.760 * Surgery Duration + -0.170 * Elective Surgery + 0.094 * Emergency + 0.262 * Dependent Status + 1.474 * Inpatient Status + 0.368 * Open Wound + -0.066 * Other Procedures + -0.094 * Race + 0.145 * Sepsis + 0.151 * Male Sex + 0.255 * Smoker + 0.500 * Steroid Use + 0.926 * Surgical Specialty + -0.496 * Ventilator Use + 0.206 * Weight Loss + 0.774 * Wound Class + 0.028 * Hypertension

All included risk factors in the tool of Method 6 as well as their ORs are presented in **Table 12**.

Table 12 Method 6 SSI Predictors and Odds Ratios

Risk Factor	Odds Ratio
Age ≥ 65 Years	0.892
General Anesthesia	1.492
ASA Class III/ IV	1.330
Bleeding Disorder	1.124
Under/ Overweight	1.211
Concurrent Procedures	1.151
Diabetes	1.123
Discharge Destination other than Home	1.743
Disseminated Cancer	1.342
Surgery Duration > 3 Hours	2.139
Elective Surgery	0.843

Risk Factor	Odds Ratio
Emergency	1.098
Dependent Functional Status	0.808
Inpatient Status	2.690
Open Wound	1.445
Other Procedures	0.936
Race other than Caucasian	0.910
Sepsis	1.156
Male Sex	1.056
Smoker	1.290
Steroid Use	1.190
Surgical Specialty (General, Gynecology, ENT, Thoracic, Urology)	2.525
Ventilator Use	0.609
Weight Loss > 10%	1.229
Wound Class III/ IV	2.169
Hypertension	0.988

7.4.6 Method 7

All risk factors included in the tool of Method 6 are included in the tool of Method 7 apart from race. Method 7's formula is:

Logit (SSI) = -5.681 + -0.110 * Age + 0.387 * Anesthesia + 0.281 * ASA Class + 0.135 * Bleeding Disorder + 0.183 * Under/ Overweight + 0.138 * Concurrent Procedures + 0.108 * Diabetes + 0.566 * Discharge Destination + 0.307 * Disseminated Cancer + 0.756 * Surgery Duration + -0.158 * Elective Surgery + 0.095 * Emergency + 0.262 * Dependent Status + 1.474 * Inpatient Status + 0.354 * Open Wound + -0.069 * Other Procedures + 0.142 * Sepsis + 0.151 * Male Sex + 0.250 * Smoker + 0.500 * Steroid Use + 0.929 * Surgical Specialty + -0.511 * Ventilator Use + 0.230 * Weight Loss + 0.769 * Wound Class + 0.028 * Hypertension

The predictors and ORs of the tool of Method 7 are shown in **Table 13**.

Table 13 Method 7 SSI Predictors and Odds Ratios

Risk Factor	Odds Ratio
Age ≥ 65 Years	0.896
General Anesthesia	1.472
ASA Class III/ IV	1.325
Bleeding Disorder	1.114
Under/ Overweight	1.200
Concurrent Procedures	1.148
Diabetes	1.114
Discharge Destination other than Home	1.762
Disseminated Cancer	1.359
Surgery Duration > 3 Hours	2.130
Elective Surgery	0.854
Emergency	1.099
Dependent Functional Status	1.300
Inpatient Status	4.367
Open Wound	1.425
Other Procedures	0.934
Sepsis	1.152
Male Sex	1.163
Smoker	1.284
Steroid Use	1.649
Surgical Specialty (General, Gynecology, ENT, Thoracic, Urology)	2.531
Ventilator Use	0.600
Weight Loss > 10%	1.258
Wound Class III/ IV	2.157
Hypertension	1.028

7.4.7 Method 8

The risk factors included in the tool of Method 8 were the same as those in Method 6. The model's formula is presented below:

Logit (SSI) = -4.391 + -0.114 * Age + 0.400 * Anesthesia + 0.285 * ASA Class + 0.117 * Bleeding Disorder + 0.191 * Under/ Overweight + 0.141 * Concurrent Procedures + 0.116 * Diabetes + 0.556 * Discharge Destination + 0.294 * Disseminated Cancer + 0.760 * Surgery Duration + -0.170 * Elective Surgery + 0.094 * Emergency + 0.395 * Dependent Status 0.938 * Inpatient Status + 0.368 * Open Wound + -0.066 * Other Procedures + -0.094 * Race + 0.145 * Sepsis + 0.257 * Male Sex + 0.255 * Smoker + 0.380 * Steroid Use + 0.926 * Surgical Specialty + -0.496 * Ventilator Use + 0.206 * Weight Loss + 0.774 * Wound Class + 0.376 * Hypertension

The SSI predictors of Method 8's tool and their corresponding ORs are shown in **Table 14**.

Table 14 Method 8 SSI Predictors and Odds Ratios

Risk Factor	Odds Ratio
Age ≥ 65 Years	0.892
General Anesthesia	1.492
ASA Class III/ IV	1.330
Bleeding Disorder	1.124
Under/ Overweight	1.211
Concurrent Procedures	1.151
Diabetes	1.123
Discharge Destination other than Home	1.743
Disseminated Cancer	1.342
Surgery Duration > 3 Hours	2.139
Elective Surgery	0.843
Emergency	1.098
Dependent Functional Status	1.484
Inpatient Status	2.556
Open Wound	1.445
Other Procedures	0.936
Race other than Caucasian	0.910
Sepsis	1.156

Risk Factor	Odds Ratio
Male Sex	1.293
Smoker	1.290
Steroid Use	1.462
Surgical Specialty (General, Gynecology, ENT, Thoracic, Urology)	2.525
Ventilator Use	0.609
Weight Loss > 10%	1.229
Wound Class III/ IV	2.169
Hypertension	1.457

7.4.8 Method 9

The risk factors included in the tool of Method 9 were the same as those retained in the tool of Method 7. The formula of Method 9's tool is below:

Logit (SSI) = -4.391 + -0.110 * Age + 0.387 * Anesthesia + 0.281 * ASA Class + 0.135 * Bleeding Disorder + 0.183 * Under/ Overweight + 0.138 * Concurrent Procedures + 0.108 * Diabetes + 0.566 * Discharge Destination + 0.307 * Disseminated Cancer + 0.756 * Surgery Duration + -0.158 * Elective Surgery + 0.095 * Emergency + 0.395 * Dependent Status + 0.938* Inpatient Status + 0.354 * Open Wound + -0.069 * Other Procedures + 0.142 * Sepsis + 0.257 * Male Sex + 0.250 * Smoker + 0.380 * Steroid Use + 0.929 * Surgical Specialty + -0.511 * Ventilator Use + 0.230 * Weight Loss + 0.769 * Wound Class + 0.376 * Hypertension

The risk factors as well as their ORs of the tool of Method 9 are presented in **Table 15**.

Table 15 Method 9 SSI Predictors and Odds Ratios

Risk Factor	Odds Ratio
Age ≥ 65 Years	0.896
General Anesthesia	1.472
ASA Class III/ IV	1.325
Bleeding Disorder	1.114

Risk Factor	Odds Ratio
Under/ Overweight	1.200
Concurrent Procedures	1.148
Diabetes	1.114
Discharge Destination other than Home	1.762
Disseminated Cancer	1.359
Surgery Duration > 3 Hours	2.130
Elective Surgery	0.854
Emergency	1.099
Dependent Functional Status	1.484
Inpatient Status	2.556
Open Wound	1.425
Other Procedures	0.934
Sepsis	1.152
Male Sex	1.293
Smoker	1.284
Steroid Use	1.462
Surgical Specialty (General, Gynecology, ENT, Thoracic, Urology)	2.531
Ventilator Use	0.600
Weight Loss > 10%	1.258
Wound Class III/ IV	2.157
Hypertension	1.457

7.4.9 Method 10

The tool of Method 10 comprises the same SSI predictors as those in Methods 1 to 5. The formula of the tool is: logit (SSI) = -4.585 + 0.151 * Sex + 1.474 * Inpatient + 0.028 * Hypertension + 0.500 * Steroid + 0.262 * Dependent Status

The risk factors' ORs are shown below in **Table 16**.

Table 16 Method 10 SSI Predictors and Odds Ratios

Risk Factor	Odds Ratio
Male Sex	1.163
Inpatient Status	4.368
Hypertension	1.028
Steroid Use	1.648
Dependent Functional Status	1.300

7.4.10 Method 11

Discharge destination other than home, surgery duration > 3 hours, inpatient status, surgical specialty (general, gynecology, ENT, thoracic, urology), and wound class III/ IV are the risk factors included in the tool of Method 11. The corresponding formula is: logit (SSI) = -5.654 + 0.556 * Discharge destination + 0.760 * Surgery duration + 1.474 * Inpatient status, 0.926 * Surgical specialty + 0.774 * Wound class

The predictors' ORs are displayed below in **Table 17**.

Table 17 Method 11 SSI Predictors and Odds Ratios

Risk Factor	Odds Ratio
Discharge Destination other than Home	1.743
Surgery Duration > 3 Hours	2.139
Inpatient Status	2.690
Surgical Specialty (General, Gynecology, ENT, Thoracic, Urology)	2.525
Wound Class III/ IV	2.169

7.4.11 Method 12

The same SSI predictors included in the tool of Method 11, with the exception of discharge destination, were comprised in the tool of Method 12. The tool's formula is: logit (SSI) =

-5.654 + 0.760 * Surgery duration + 1.474 * Inpatient status, 0.926 * Surgical specialty + 0.774 * Wound class

The risk factors and the corresponding ORs are shown in **Table 18**.

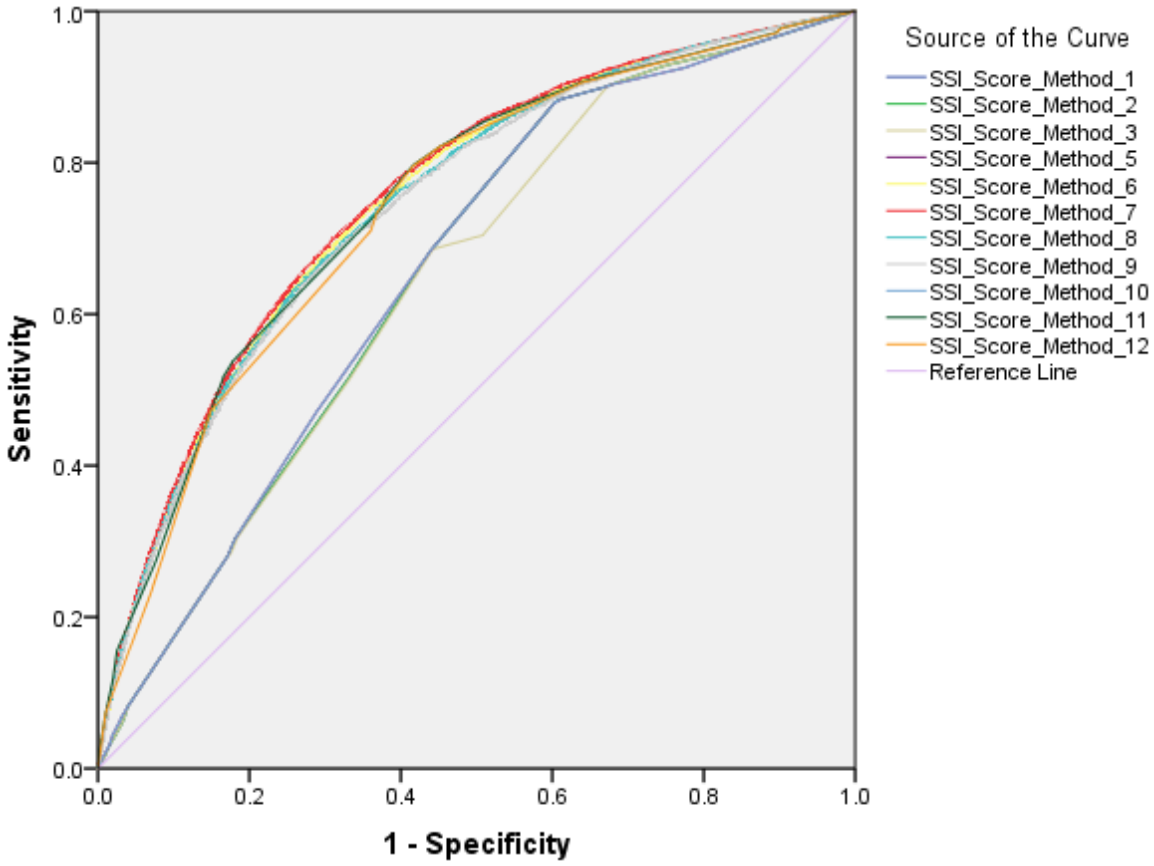
Table 18 Method 12 SSI Predictors and Odds Ratios

Risk Factor	Odds Ratio
Surgery Duration > 3 Hours	2.139
Inpatient Status	2.690
Surgical Specialty (General, Gynecology, ENT, Thoracic, Urology)	2.525
Wound Class III/ IV	2.169

7.5 Comparison of the Original and Updated JSS-SSI Risk Scoring Tools (Objective 3)

The area under the ROC curves of the tools produced by Methods 1 to 12 varied between 0.645 and 0.756. As shown in **Figure 7** and **Table 19**, the tool with the highest AUC was obtained from Method 7 (AUC = 0.756), though the tools produced by Method 6 (AUC = 0.751), Method 11 (AUC = 0.748), Method 8 (AUC = 0.747) and Method 9 (AUC = 0.743) were similar.

Figure 7 ROC Analysis of all Tools in the Test Population



Calibration considerably varied between models. Slopes of the calibration plot ranged between 0.28 and 1.23 while the intercept α ranged between -0.007 and 0.030. The models with the highest calibration were produced by Method 4/5 and 10 as these three tools had a slope β of 1.03 and an intercept α of -0.001. The tools obtained following Method 3 (slope β = 1.07; intercept α = -0.001), Method 2 (slope β = 0.92; intercept α = 0.030), Method 11 (slope β = 1.16; intercept α = -0.002), and Method 12 (slope β = 1.23; intercept α = -0.001) were also well calibrated.

The mean (SD) Brier scores varied between 0.0318 (0.1602) and 0.0531 (0.1207). The tool with the lowest mean (SD) Brier score, therefore indicating superior fit of the model, was obtained from Method 11 [mean (SD) = 0.0318 (0.1602)], though the tools produced by

Method 12 [mean (SD) = 0.0319 (0.1625)], Method 3 [mean (SD) = 0.0327 (0.1667)], and Method 4/5 [mean (SD) = 0.0338 (0.1790)] were low as well.

Table 19 presents the discrimination, calibration and overall fit assessments of all risk tools when applied to the Test Population.

Due to discordant findings between discrimination and calibration assessments, the model with the lowest Brier score was selected as the final tool. As such, the tool produced with Method 11 which yielded an AUC of 0.748, calibration slope β of 1.16, calibration intercept α of -0.002, Hosmer-Lemeshow p-value of < 0.001 and mean (SD) Brier score of 0.0318 (0.1602) was maintained as the final JSS-SSI Risk Scoring Tool utilized for the remainder of the analyses.

Table 19 Discrimination, Calibration and Overall Fit of the Updated Risk Tools in the Test Population

	Discrimination	Calibration			Overall Fit
	Area under the ROC Curve	**Calibration Slope β**	**Calibration Intercept α**	**Hosmer-Lemeshow p-value**	**Mean (SD) Brier Score**
Method 1	0.656	0.36	0.020	< 0.001	0.0335 (0.1618)
Method 2	0.656	0.92	0.030	< 0.001	0.0338 (0.1790)
Method 3	0.645	1.07	-0.001	< 0.001	0.0327 (0.1667)
Method 4/5	0.657	1.03	-0.001	< 0.001	0.0326 (0.1657)
Method 6	0.751	0.51	0.001	< 0.001	0.0338 (0.1399)
Method 7	0.756	0.52	0.001	< 0.001	0.0336 (0.1405)
Method 8	0.747	0.28	-0.007	< 0.001	0.0531 (0.1207)
Method 9	0.743	0.28	-0.007	< 0.001	0.0531 (0.1206)
Method 10	0.657	1.03	-0.001	< 0.001	0.0326 (0.1657)
Method 11	0.748	1.16	-0.002	< 0.001	0.0318 (0.1602)
Method 12	0.739	1.23	-0.001	< 0.001	0.0319 (0.1625)

7.6 Adjustment of the Final JSS-SSI Risk Scoring Tool (Objective 4)

According to the risk factors' respective ORs previously presented in Section **7.4.10**, a specific weight was calculated and assigned to each significant variable. These, as well as the relative scores, are summarized in **Table 20**. The score values summed to 100 points where a discharge destination other than home; surgery duration > 3 hours; inpatient status; surgery of the following specialties: general, gynecology, ENT, thoracic, urology; and wound class III or IV would add 16, 19, 24, 22 and 19 points, respectively. As such, patients who possess all 5 risk factors would obtain a score of 100 points while patients who possess no risk factors would obtain a null score. The individualized patient assessment is illustrated in Appendix 4 (Section **11.4**).

Table 20 Odds Ratios and Score Weights of the Final JSS-SSI Risk Scoring Tool Variables

Risk Factor	Negative (0)	Positive (1)	Odds Ratio	Relative SSI Weight	Variable Score Value
Discharge Destination	Home	Facility, acute care center, rehab center or other	1.743	0.155	16
Surgery Duration	0-3 hours	> 3 hours	2.139	0.190	19
Inpatient Status	No (outpatient)	Yes (inpatient)	2.690	0.239	24
Surgical Specialty	Cardiac, neurosurgery, orthopedics, plastics, vascular, interventional radiology	General, gynecology, ENT, thoracic, urology	2.525	0.224	22
Wound Class	Class I or II	Class III or IV	2.169	0.193	19
Total			11.266	1	100

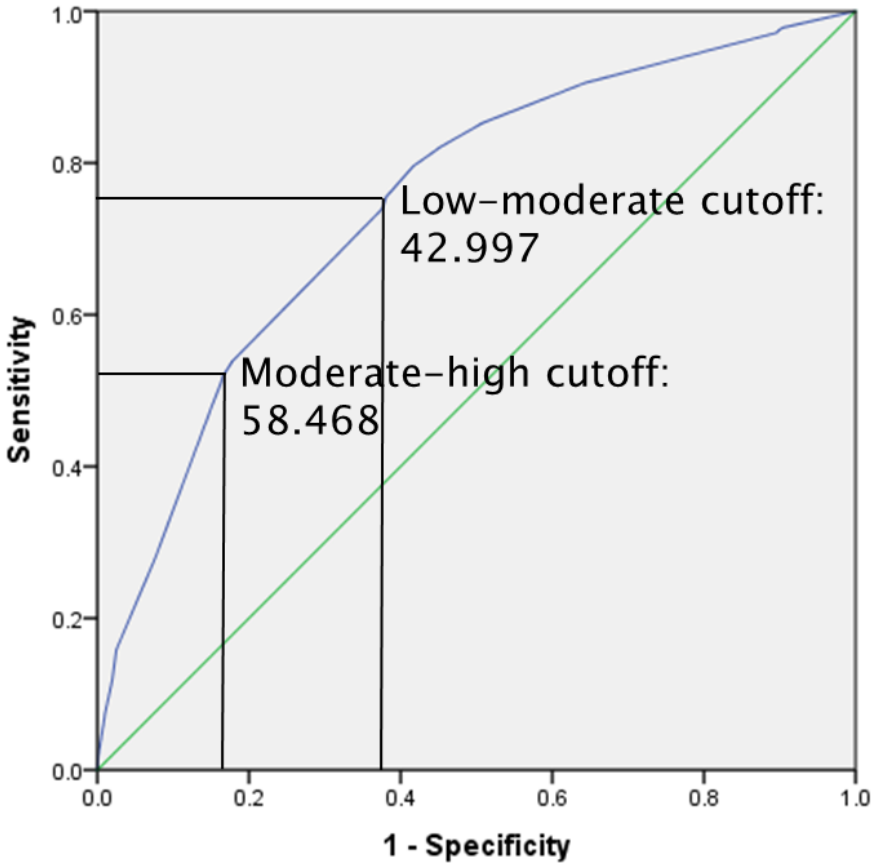
The mean (SD) SSI score of the Validation Population was 36.2 (20.25) points. Scores were generally similar between subpopulations, as shown in **Table 21**. Patients in the Development Population had a marginally higher SSI risk as illustrated by a mean (SD) score of 38.1 (17.95).

Table 21 Mean SSI Scores of the Final JSS-SSI Risk Scoring Tool by Population

Population	Mean (SD) SSI Score of the Final JSS-SSI Risk Scoring Tool
Development Population (n = 2,907)	38.1 (17.95)
Validation Population (N = 1,459,481)	36.2 (20.25)
External Validation Population (n = 486,104)	36.2 (20.24)
Updating Population (n = 487,236)	36.2 (20.23)
Test Population (n = 486,141)	36.2 (20.24)

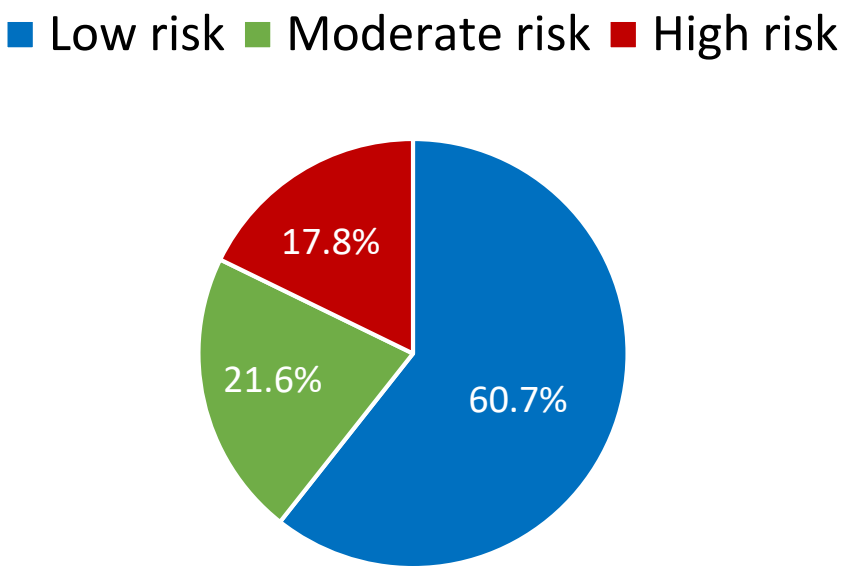
ROC analysis utilizing the Validation Population yielded the curve displayed in **Figure 8**. The two threshold values selected to classify patients into low-, moderate- and high-risk SSI groups were 42.997 and 58.468. Thus, patients with a score between 0 and 42 points, between 43 and 58 points, and between 59 and 100 points would be classified in the low-, moderate- and high-risk categories, respectively.

Figure 8 ROC Analysis in the Validation Population including the Selected Threshold Values



As per these threshold values, the majority of patients (n = 885,485; 60.7%) had a low risk of SSI development while 21.6% (n = 314,893) and 17.8% (n = 259,103) of patients had a moderate and high SSI risk, respectively. (**Figure 9**)

Figure 9 SSI Risk Distribution of the Final JSS-SSI Risk Scoring Tool in the Validation Population



7.7 External Validation of the Final JSS-SSI Risk Scoring Tool (Objective 5)

The final JSS-SSI Risk Scoring Tool was applied to the External Validation Population, which yielded an AUC of 0.748. (**Table 22** and **Figure 10**) The model had a sensitivity of 79.6% and specificity of 58.3%. The tool was fairly well calibrated: the slope β and intercept α of the calibration plot were 1.16 and -0.003, respectively. (**Table 22** and **Figure 11**) However, the Hosmer-Lemeshow test revealed a statistically significant difference between probabilities predicted by the risk tool and observed outcomes ($p < 0.001$). The mean (SD) Brier score was 0.0313 (0.1590) indicating good fit of the model. (**Table 22**)

Overall, when applied to the same External Validation Population, the final JSS-SSI Risk yielded superior predictive ability than the original JSS-SSI Risk Scoring Tool.

Table 22 External Validation Assessments of the Final JSS-SSI Risk Scoring Tool

	External Validation Population (n = 486,104)
Area under the ROC Curve, 95% CI	0.748 (0.746, 0.750)
Sensitivity, %	79.6
Specificity, %	58.3
Calibration Plot Slope β	1.16
Calibration Plot Intercept α	-0.003
Hosmer-Lemeshow P-Value	< 0.001
Brier Score, mean (SD)	0.0313 (0.1590)

Figure 10 ROC Analysis of the Final JSS-SSI Risk Scoring Tool in the External Validation Population

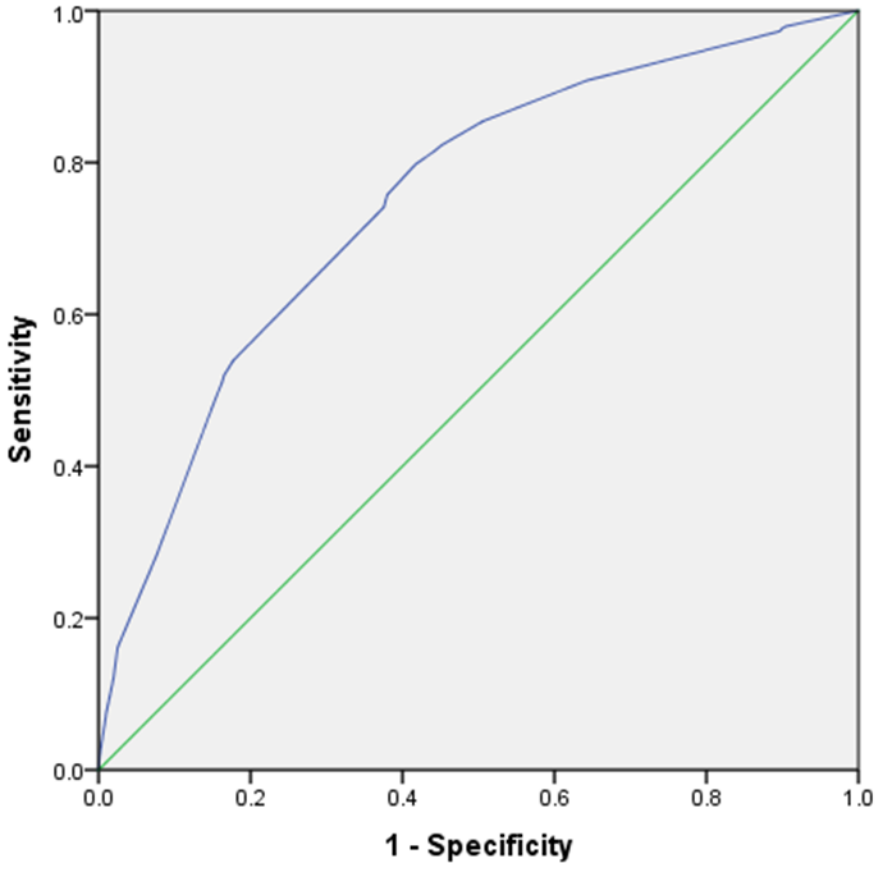
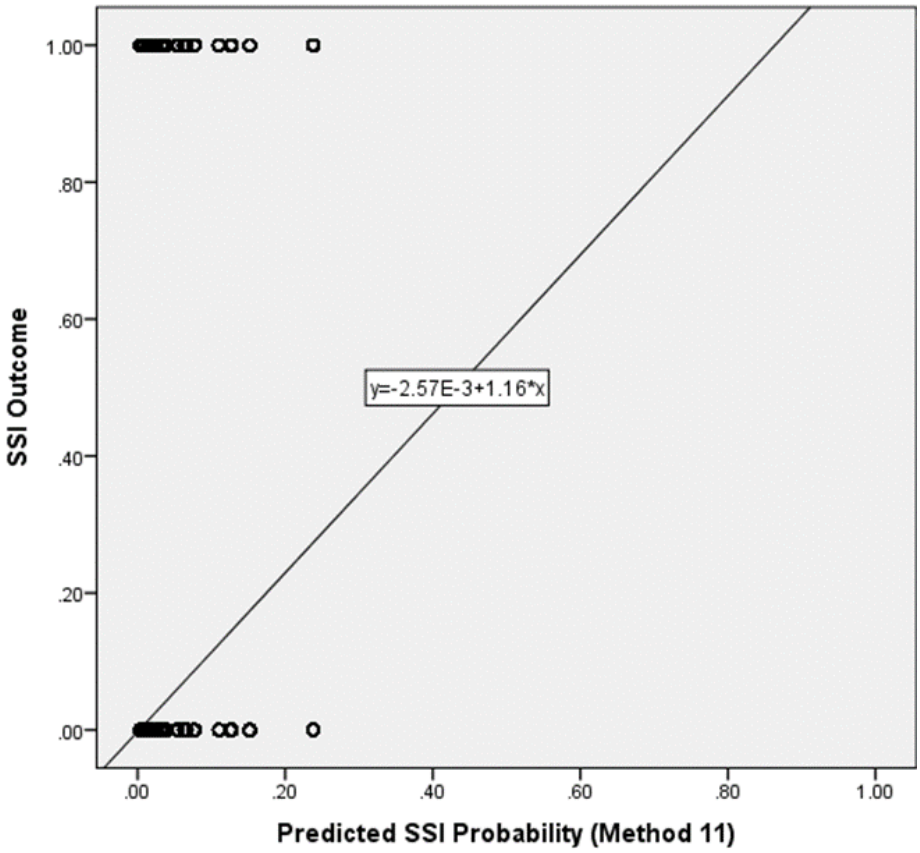


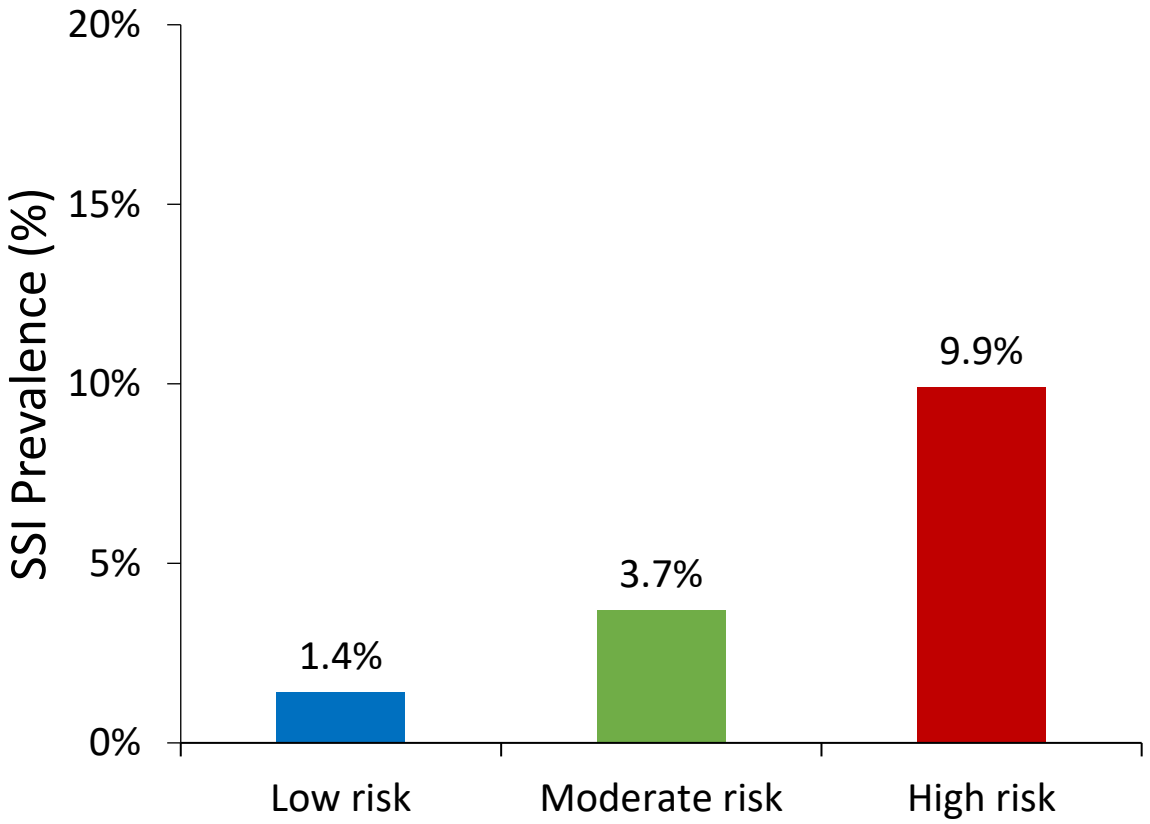
Figure 11 Calibration Plot of the Final JSS-SSI Risk Scoring Tool in the External Validation Population



7.8 SSI Prevalence (Objective 6)

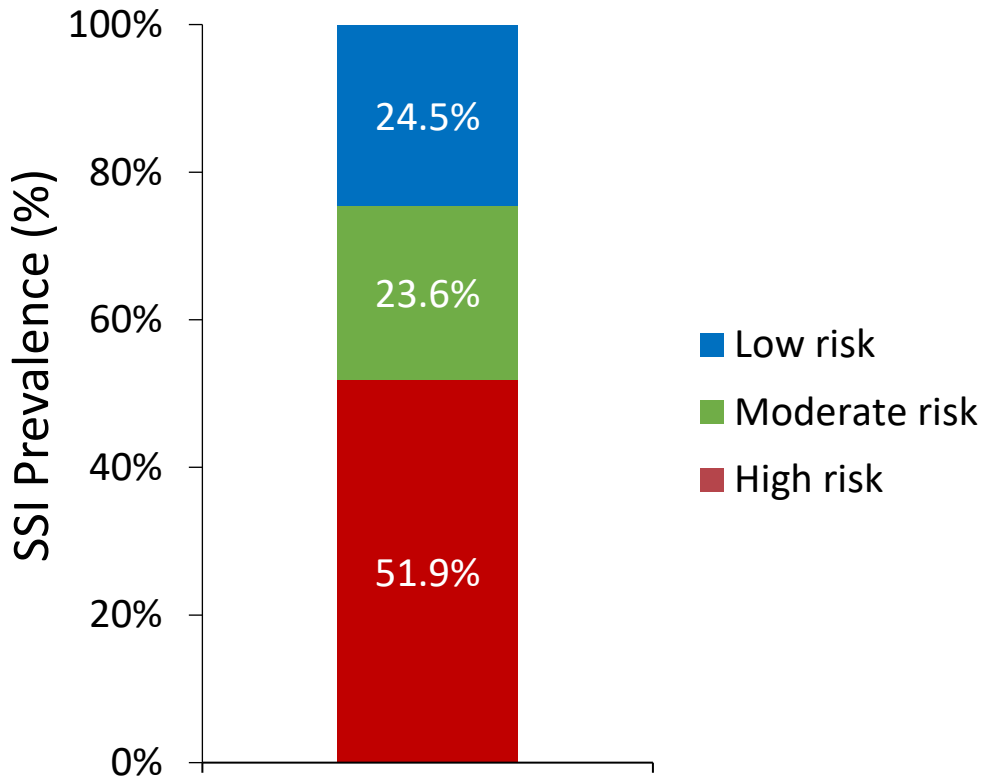
Among the 885,485; 314,893 and 259,103 patients with a low, moderate or high risk of SSI development in the Validation Population (**Figure 9**), 1.4%, 3.7% and 9.9% of patients in these groups developed any type of SSI postoperatively, respectively. (**Figure 12**)

Figure 12 SSI Prevalence of the Final JSS-SSI Risk Scoring Tool by Risk Classification in the Validation Population



Although the high-risk SSI group comprised a minority (17.8%) of the total population, the largest proportion of SSIs (51.9%) were observed among these patients. Conversely, although the low- and moderate-risk groups included 82.2% of the population, 48.1% of all SSIs were developed by patients in these classifications. (**Figure 13**)

Figure 13 Risk Classification among SSI Patients in the Validation Population



7.9 Relative Surgical Site Infection Risk among Moderate- and High-Risk Groups (Objective 7)

When compared to the low-risk SSI group, patients with a moderate risk had a nearly three-fold increased risk of SSI development [OR (95% CI): OR = 2.776 (2.706, 2.849), $p < 0.001$], while patients in the high-risk were nearly 8 times more likely to develop an SSI [OR = 7.919 (7.746, 8.095), $p < 0.001$]. (**Table 23**)

Table 23 SSI Risk among Moderate- and High-Risk Patients when Compared to the Low-Risk SSI Group in the Validation Population

	Odds Ratio	95% CI	p-value
Moderate Risk	2.776	2.706, 2.849	< 0.001
High Risk	7.919	7.746, 8.095	< 0.001

8 Discussion

8.1 Study Aim

SSIs represent an important burden during postsurgical care on a patient and societal level, especially in light of current challenges associated with bacterial resistance leading to arduous infection treatment. The substantial impact of SSIs on surgical patients' risk for mortality, morbidity, increased hospital stay and costs make it necessary to implement effective prophylactic measures to reduce their incidence. (17, 41) In order to focus on SSI prevention, the JSS-SSI Risk Scoring Tool was developed in 2012 which allowed to preoperatively classify surgical patients in low-, moderate- and high-risk categories. (33) In the present study, the previously created risk tool was updated and validated in a large external population other than the one utilized during the model's development to ensure the tool's generalizability in various surgical settings in Canada and worldwide. The SSI prevalence rate in the study sample and the increased SSI risk among patients in the moderate or high risk classifications were further examined.

8.2 Result Interpretation

Due to the low predictive accuracy of the original JSS-SSI Risk Scoring Tool in the External Validation Population (**Table 8**), updating of the risk tool was warranted. Various updating techniques were conducted to improve the tool's generalizability, namely the model's discrimination, calibration and overall fit. The intercepts α of all updated risk tools were close to 0 suggesting the models' ability to predict the absence of SSI development among patients with a null predicted probability. Moreover, all tools showed significant variability between predicted probabilities and observed outcomes as indicated by a strong p-value ($p < 0.001$) of the Hosmer-Lemeshow test. As intercepts α of the calibration plot and Hosmer-Lemeshow p-values between risk models were similar (**Table 19**), selection of the final JSS-SSI Risk Scoring Tool relied on the comparison of AUCs, calibration slopes β and Brier scores.

AUCs and calibration slopes β remarkably varied between updated risk tools. For instance, Methods 1 and 2, which entailed minimal updating, exhibited low discrimination (both AUC = 0.656) and calibration (slopes β of 0.36 and 0.92, respectively). The low AUCs revealed negligible

ability to distinguish SSI and non-SSI cases while the low calibration slopes β indicated an overestimation of SSI development. Methods 3 and 4/5 had fair AUCs (0.645 and 0.657) and near-perfect calibration slopes β (1.03 and 1.07); these models poorly discriminated SSI cases from non-SSI cases though fairly well predicted SSI outcome as per patients' probability of SSI. Conversely, Methods 6, 7, 8 and 9 yielded acceptable AUCs (between 0.743 and 0.756) and low calibration slopes β (between 0.28 and 0.52) suggesting that the models had increased accuracy in regard to SSI vs. non-SSI identification though they overestimated the outcome.

Due to these differing results, the model with the lowest Brier score was designated as the optimal tool as this assessment encompasses discrimination and calibration components. The tool produced by Method 11, which solely included the most influential risk factors in regard to SSI development (OR > 1.5), was selected as the final JSS-SSI Risk Scoring Tool as this model demonstrated the highest overall fit within the external patient sample. The final tool's mean (SD) Brier score was 0.0318 (0.1602) indicating overall good fit of the model while the remaining tools resulted in mean (SD) Brier scores between 0.0319 (0.1625) and 0.0531 (0.1207). (**Table 19**)

The final JSS-SSI Risk Scoring Tool comprises five SSI predictors: discharge destination, surgery duration, inpatient status, surgical specialty and wound class. More specifically, patients who were to be discharged in a facility, acute care center, rehabilitation center or location other than home; whose surgery lasted over 3 hours; who were inpatients; who underwent general, gynecologic, ENT, thoracic or urologic surgery; or who had a Class III contaminated or Class IV dirty/ infected operative wound were at least 50% more likely to develop an SSI. Among these risk factors, inpatient status was the most clinically relevant SSI predictor with an OR of 2.690, followed by surgical specialty (OR = 2.525), wound class (OR = 2.169), surgery duration (OR = 2.139) and discharge destination (OR = 1.743). (**Table 17**)

The AUC of the final JSS-SSI Risk Scoring Tool was 0.748, indicating acceptable discrimination as per the thresholds proposed by Hosmer and Lemeshow. (131) According to the sensitivity and specificity estimates obtained, the model accurately identifies 79.6% of true positive SSI cases and 58.3% of true negative non-SSI cases. With respect to calibration, the values of the slope β (1.16) and intercept α (-0.002) of the calibration plot were close to 1 and 0, respectively, suggesting good calibration. However, the Hosmer-Lemeshow result showed a significant difference between observed outcomes and predicted probabilities for all updated models ($p < 0.001$). As the Hosmer-

Lemeshow test approximately follows the Chi-Square distribution, the large sample size and low SSI prevalence may explain the strong statistical significance obtained. The numerous significant differences between SSI and non-SSI patients obtained in univariate Chi-square analysis (**Table 7**) further support this premise. Although widely used to assess calibration for binary outcomes, the Hosmer-Lemeshow test has been criticized in published literature as goodness-of-fit is commonly rejected among large samples and due to the test's dependence on arbitrary patient groupings. (129, 147, 148) Calibration plot findings are generally preferred over Hosmer-Lemeshow results and therefore were favored in this analysis. (147)

The similarity of the discrimination, calibration and overall fit of the final JSS-SSI Risk Scoring Tool findings between the Test Population (**Table 19**) and the External Validation Population (**Table 22**) confirms the generalizability of the risk model in various populations therefore fulfilling the primary study objective. The superiority of the final tool's predictive accuracy (**Table 22**) when compared to the original JSS-SSI Risk Scoring Tool (**Table 8**) can further be observed, particularly as the same External Validation Population was utilized to assess external validity.

Following selection of the final JSS-SSI Risk Scoring Tool, adjustments were performed to increase the user-friendliness of the tool while maintaining the factors included in the risk model and their individual impact on SSI outcome. Variable score values proportional to each factor's OR were calculated; as inpatient status was shown to be the most influential SSI predictor, this risk factor was assigned the highest point value (24 points) while wound class had the lowest variable score, representative of this variable's lower OR (19 points). (**Table 20**). The conversion of ORs to variable scores allowed for clearer understanding of patients' SSI risk than raw OR interpretation, as the values of the risk model ranged between 0 and 100 points, while maintaining each risk factor's individual effect on SSI development.

With the aid of a subsequent ROC analysis, threshold values of 42.997 and 58.468 points were identified. As a result, patients with scores of 0-42, 43-58 and 59-100 had a low, moderate or high SSI risk, respectively. (**Figure 8**)

Multivariate analysis of the final JSS-SSI Risk Scoring Tool in the Validation Population showed that patients with a moderate and high risk had a 278% and 792% increased risk of SSI development when compared to low-risk patients, both results of which were found to be statistically significant ($p < 0.001$). (**Table 23**) Although 17.8% of the population had a high SSI

risk as per the established threshold values, more than 50% of SSIs were observed in this classification, further confirming the validity of the risk tool. (**Figure 13**)

Unexpectedly, several risk factors significantly associated with SSI outcome were shown to have a protective effect. These included age of at least 65 years (OR = 0.892), dependent functional status (OR = 0.808), the need for other procedures (OR = 0.936), preoperative ventilator use (OR = 0.609) and hypertension requiring medication (OR = 0.988). (**Table 12**) Although these results were obtained during multivariate analysis, certain effects may not have been captured. For instance, the significant association between ventilator use, the most protective factor, and SSI development may have been biased due to a survivor effect, as elective surgery would generally not be performed among patients who required extended ventilator use, considering that they were more likely in a worsened health state. Moreover, patients who were elderly, required assistance for daily activities or received other surgical procedures may have received additional care by the surgical staff which may have slightly protected these patients against postoperative complications. Although hypertension was only mildly protective, no theory to my knowledge can explain this positive association with SSI development. Further study is required to confirm these findings.

8.3 Comparison with Published Findings

The positive associations observed in this analysis concur with published literature. For instance, among the assessed 1,459,481 surgical patients in the Validation Population, 3.4% of patients developed any type of SSI. Although prevalence rates in the literature vary considerably between studies, which may be due to differing prophylactic procedures over time and between countries, the rate observed falls within the reported rates (1% - 18%). (3, 26, 149, 150)

Moreover, due to the increased bacterial colonization in the operative wound (17, 18), patients who undergo a lengthy surgery (69, 70, 151, 152), with a Class III or IV operative wound (68, 149) or who receive general or thoracic surgery (3, 150, 153, 154) have been shown to possess an increased SSI risk. Although inpatient status was the strongest SSI predictor, this has not been previously examined in previous studies to my knowledge. Nonetheless, Hennessey et al. showed a significant negative association between duration of inpatient stay and preoperative albumin

levels, the latter of which has been identified as an independent SSI risk factor. (155) A prolonged hospital stay prior to surgery may further cause patients to be exposed to microorganisms not generally included in their bacterial flora. This reasoning combined with the fact that inpatients may have an underlying morbidity can explain the increased risk of infection, as was speculated by Jeon et al. who observed higher rates of healthcare-associated bloodstream infections among inpatients with a lengthier hospital stay. (156) In addition, the findings of statistical significance and high clinical relevance in the present analysis with respect to inpatient status support the results obtained during the development of the original JSS-SSI Risk Scoring Tool as this risk factor was the most influential significant SSI predictor (OR = 9.491) in the initial analysis. (33) Finally, discharge destination has not been previously evaluated in SSI-related studies to my knowledge. The significant association between discharge destination other than home with SSI outcome is a new finding of this analysis and could be indicative of a worsened patient health state as increased health care and regular assistance in everyday activities may be required among these patients.

8.4 Limitations and Strengths

These findings should be interpreted in consideration of the study limitations. For example, the use of data extracted from medical charts increases the possibility of information bias including missing, inconsistent or incorrect information, as well as the likelihood of human error during transcription. Although clear definitions regarding the outcome and exposures are provided to an SCR each year, the validity of the data entry could not be confirmed in this study. As such, the ability to perform data cleaning was limited.

Furthermore, although NSQIP data was utilized during the development of the original JSS-SSI Risk Scoring Tool and in the present analysis, the database has evolved over time leading to the omission and addition of certain variables. This may have caused certain significant SSI predictors not to be identified in this study, and also not adjusted for in multivariate analysis. More specifically, although 28 variables were common between the populations assessed during the development and validation of the risk tool, alcohol abuse, preoperative pneumonia, myocardial infarction within 6 months of surgery, history of angina within 30 days of surgery, peripheral vein disease, gangrene, chemotherapy or radiotherapy within 90 days of surgery, level of supervision

(attending vs. attending/ resident vs. resident alone in operating room) and resident level (number of years of residency) were removed from the database since 2012 and were thusly not included in the current study. Conversely, age, discharge destination, duration of surgery, elective surgery, Hispanic race and preoperative renal failure were solely included during the validation phase. Of note, the five risk factors identified as significant SSI predictors during the development of the risk tool (male sex, inpatient status, hypertension, corticosteroid use and dependent functional status) were included in both samples though solely inpatient status was retained in the final JSS-SSI Risk Scoring Tool. As inpatient status had the highest OR during the development of the tool, one can assume that the risk factors excluded from the present analysis, which were not significantly associated with SSI outcome in the development of the tool, would not have been included in the final risk model due to lower presumed association with SSI development. However, this fact could not be verified due to the above-stated limitation.

Furthermore, as NSQIP has limited exclusion criteria (145) and due to the prospective, non-biased and comprehensive nature of the database, selection bias is minimized.

The large sample utilized for the analysis simultaneously represents a study strength and limitation. Multiple benefits resulted from utilization of the NSQIP database between 2012 and 2014 including over a million surgical patients. Firstly, the numerous significant associations observed were likely due to the large patient population. Secondly, the analysis required subdivision of the full population into subpopulations to ensure that the same cases were not used to update or externally validate the tool as well as test the updated tools. A fourth subpopulation was excluded from the present study to allow for future comparison of the JSS-SSI Risk Scoring Tool with existing SSI risk models. The immensity of the Validation Population ensured that the statistical analyses in the subpopulations were sufficiently powered. Finally, the inclusion of all NSQIP-participating hospitals increased the generalizability of the results and the applicability of the JSS-SSI Risk Scoring Tool in various surgical settings worldwide. However, certain limitations can be noted due to the size of the population assessed. The large sample and low outcome prevalence likely drove statistical significance for multiple examined risk factors during univariate Chi-Square analysis and the strong p-value observed during the Hosmer-Lemeshow test, as the latter approximately follows a Chi-Squared distribution. Although difficult to confirm whether these significant findings were amplified as a result of the sample size, this possibility should be noted.

Nonetheless, the results of the adjusted multivariate analysis were used for model development and validation while unadjusted univariate results were solely used for descriptive purposes.

Finally, the requirement of a single person per hospital to collect the patient information for NSQIP data entry also simultaneously represents a strength and limitation as within-hospital variability is minimized, though consistency between hospitals cannot be guaranteed. However, the detailed definitions in the NSQIP user guide likely led to decreased misclassification of outcome and exposure.

8.5 Implications

The implementation of the JSS-SSI Risk Scoring Tool will have important implications in surgical departments. As shown in **Table 12**, the majority (26 out of 35) of assessed risk factors were significantly associated with SSI development in multivariate analysis. Although several of these factors are unfeasible to modify prior to surgery (e.g. sex, race, comorbidities), these findings highlight that various factors could be monitored preoperatively to assist in establishing patients' individual SSI risk. However, the tool obtained from Method 11 solely included the variables with an increased OR (> 1.5), thusly eliminating all predictors with a weaker association with the outcome. As the five risk factors included in the final JSS-SSI Risk Scoring Tool were significantly associated with SSI development ($p < 0.05$), this method allowed to select the statistically significant and clinically relevant SSI predictors which should be carefully assessed by the surgical staff preoperatively. The high predictive accuracy demonstrated by this tool highlights the importance of clinical relevance in risk tool development.

Patients identified to have a high SSI risk with the aid of the risk model are advised to receive additional preoperative care to reduce their SSI risk. As a minority of surgical patients possess a high SSI risk, the administration of supplemental support in this subgroup of patients can be assumed to be cost-effective though further study is required to confirm this hypothesis. The decision to implement further preoperative measures among moderate-risk patients may be reached by the surgical staff though this would have substantial economic and resource utilization implications as more than 20% of patients are included in this risk classification.

Although certain preoperative and intraoperative actions are warranted for all procedures, such as the appropriate surgical site preparation, the surgical team's proper hand washing, normothermia and maintenance of glycemic control, the individualization of preoperative care may be merited to reflect each patient's SSI risk. (157) Several prophylactic guidelines have been published (31, 32) recommending various methods to prevent SSIs that may be performed among patients who may require supplementary care. For instance, the *Safer Healthcare Now!* and CDC guidelines advocate preoperative showering with soap or an antiseptic agent the night prior to surgery and intraoperative skin preparation with an alcohol-based antiseptic agent. (157, 158) Several studies, which have illustrated that preoperative antiseptic showers can significantly reduce bacterial colony counts, support this recommendation. (159, 160) Hair removal immediately prior to surgery is further recommended, though shaving the surgical site is discouraged as the microscopic skin cuts due to shaving have been associated with increased SSI risk. Hair clipping or the use of depilatory agents is advocated as these are associated with a lower risk of SSI. (32, 161-166) *Safer Healthcare Now!* guidelines further suggest nasal bacterial decolonization with the aid of mupirocin nasal ointment, photodynamic therapy and the use of antiseptic coated sutures for SSI prevention. (158) The administration of prophylactic antibiotics also represents an important aspect of SSI prevention. Although preoperative antibiotic administration has been shown to decrease SSI rates and the emergence of bacterial resistance, drug selection, dosage, timing and duration are to be tailored to the specific surgery in order to target the pathogens likely present at the surgical site. (5, 43, 158, 167-177) However, the administration of prophylactic antibiotics may not be required among low-risk SSI patients receiving clean surgeries. (178) All in all, the selection of which procedures to perform remains in the surgical staff's discretion.

8.6 Future Research

Future planned research includes comparison of the predictive accuracy of the JSS-SSI Risk Scoring Tool, the NNIS index and risk model developed during the SENIC utilizing the Comparison Population previously described in Section **6.3.2**. Additional external validation will be conducted by surgical subspecialty to examine the applicability of the JSS-SSI Risk Scoring Tool in various medical fields. Finally, for exploratory purposes, due to the constantly evolving nature of medicine and the increasing awareness of the importance of preventive medicine over

time, the temporal variation of SSI prevalence will be ascertained as well as differences with respect to the surgical patient profile utilizing NSQIP data from 2005 to 2014. The final JSS-SSI Risk Scoring Tool will further be made available for use as a mobile phone application to assist HCPs' usage of the risk model.

9 Final Conclusion and Summary

Surgical site infections represent an important complication in surgical settings. Due to the increasing emergence of bacterial resistance in recent years, SSI prevention is of paramount importance.

The present study aimed to increase the predictive accuracy of the JSS-SSI Risk Scoring Tool utilizing a large surgical population. Several updating techniques were assessed. The final risk model included the most influential significant SSI predictors: discharge destination, surgery duration, inpatient status, surgical specialty and wound class. As per the strong statistical significance and clinical relevance obtained in multivariate analysis, these risk factors are advised to be carefully evaluated preoperatively in order to establish surgical patients' individual SSI risk.

The objective of external validation set forth in this study was achieved as the final risk tool yielded improved discrimination, calibration and overall fit when compared to the initial model. Due to the risk tool's high external validity, the implementation of the JSS-SSI Risk Scoring Tool in surgical settings is recommended and will likely be associated with improved HCP decision-making with respect to SSI prophylaxis as well as multiple clinical and economic benefits. Following identification of high-risk SSI patients, the administration of supplemental preoperative and intraoperative care in this subpopulation, who comprise a minority of surgical patients yet experience more than 50% of all SSIs, may lead to decreased SSI prevalence. Overall, use of the JSS-SSI Risk Scoring Tool may reduce SSI-related mortality, morbidity and patient distress, as well as decreased length of stay following surgery, the need for costly and arduous therapies and the potential need for repeat hospitalization or surgery.

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11 Appendices

11.1 Appendix 1: Criteria and Variables Included in the NSQIP Database during the Development of the JSS-SSI Risk Scoring Tool

Criteria	Variables
Gender	Male; Female
Patient status	Inpatient; Outpatient
Emergent surgery status	Elective; Emergent
Transfer origin	Not transferred, admitted directly from home; Transfer from other or inpatient
Anesthesia technique	General; Spinal, local, epidural, regional or MAC
Surgical subspecialty	Vascular; General
BMI	Normal (BMI 18.5 to 25); Under/overweight (below 18.5 or above 25)
Diabetes	Non-diabetic; Diabetic (type I or II)
Smoker	No; Yes
Alcohol abuse	No; Yes
Dyspnea	No; Yes (upon moderate exertion or at rest)
Functional status prior to surgery	Independent; Partially or totally dependent
Ventilator usage	No; Yes
COPD	No; Yes
Pneumonia[1]	No; Yes
Congestive heart failure[2]	No; Yes
Myocardial infarction[3]	No; Yes
History of angina[2]	No; Yes
Hypertension[4]	No; Yes
PVD[5]	No; Yes
Gangrene[6]	No; Yes
Renal failure[7]	No; Yes
Dialysis[8]	No; Yes
Disseminated cancer	No; Yes

Criteria	Variables
Open wound[9]	No; Yes
Steroid use[10]	No; Yes
Weight loss >10%[11]	No; Yes
Bleeding disorders	No; Yes
Preoperative transfusion[12]	No; Yes
Chemotherapy[13]	No; Yes
Radiotherapy[13]	No; Yes
Sepsis[14]	No; Yes (SIRS, sepsis or septic shock)
Highest level of resident	5 to 8 years of residency; 0 to 4 years of residency
Wound classification	Class I or II (clean or clean/ contaminated); Class III or IV (contaminated or dirty/ infected)
ASA class	ASA 1 or 2 (no disturb or mild disturb); ASA 3 or 4 (severe disturb or life threat)
Other procedures[15]	No; Yes
Concurrent procedures[16]	No; Yes

[1] Patient must be on current antibiotic treatment at the time he/she is brought to the OR; must meet specific radiologic and symptomatic criteria.

[2] Within 30 days prior to surgery.

[3] Within 6 months prior to surgery.

[4] Patient has persistent elevation of systolic blood pressure >140 mmHg **or** a diastolic pressure >90mmHg **or** requires an antihypertensive treatment at the time the patient is being considered as a candidate for surgery.

[5] A history of any type of angioplasty or revascularization procedure for atherosclerotic PVD or a patient who has had any type of amputation procedure for PVD.

[6] Rest pain or gangrene. Includes patients with ischemic ulceration and/or tissue loss related to peripheral vascular disease. Does not include Fournier's gangrene.

[7] Elevated levels of BUN and creatinine (the latter above 3 mg/dl).

[8] Currently requiring or on dialysis.

[9] With or without infection. The wound must communicate to the air by direct exposure.

[10] Patient has required the regular administration of oral or parenteral corticosteroid medications in the 30 days prior to surgery for a chronic medical condition.

[11] Within 6 months prior to surgery. Patients who have intentionally lost weight are excluded.

[12] Preoperative blood loss necessitating any transfusion (minimum of 1 unit) of whole blood/packed red cells transfused during the 72 hours prior to surgery.

[13] Within 90 days prior to surgery.

[14] Within 48 hours prior to surgery. Includes any case of SIRS, sepsis or septic shock.

[15] An additional operative procedure performed by the same surgical team under the same anesthetic which has a CPT code different from that of the Principal Operative Procedure.

[16] An additional operative procedure performed by a different surgical team under the same anesthetic which has a CPT code different from that of the Principal Operative Procedure.

11.2 Appendix 2: M.Sc. Thesis

Development of Risk-Index Tool to Predict Surgical Site Infections

M.Sc. Thesis written by Angeliki Karellis

Supervisor: Dr. John S. Sampalis.

Experimental Surgery, McGill University, Montreal.

Submitted March 2013.

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of M.Sc. Experimental Surgery.

Table of Contents

English Abstract

Surgical site infections (SSI) are one of the most common complications following surgery. SSIs can incur many consequences for the patient including extended hospital stay, increased hospital costs, increased risk of entering the ICU as well as increased risk of morbidity and mortality. There are three types of SSIs: superficial incisional SSIs, the most common yet the least severe, deep incisional SSIs and organ/space SSIs, the most life-threatening. Due to the high emergence of resistant bacteria, treatment with common antibiotics is ineffective in the majority of patients with an SSI. Therefore, more attention must be paid preoperatively and intraoperatively to prevent SSIs rather than to treat these infections. The data of the literature have identified risk factors that predispose surgical patients to SSIs, however validated risk-index tools have not been developed to quantify the risk of SSI. The data for this study was obtained from the NSQIP (National Surgical Quality Improvement Program) database established at the JGH and included patients undergoing surgery at this institution between November 2009 and December 2011. The database was selected because it is prospective, non-biased and comprehensive. Bivariate analyses and stepwise multivariate logistic regression were used to identify the following five risk factors that were independently and significantly associated with the risk of an SSI: male gender, inpatient status, hypertension, corticosteroid use and partial or total dependence for

everyday activities prior to surgery. Logistic regression models with an ROC curve analysis were used to develop a risk scoring tool for SSI and limits for incremental risk categories. Patients with a score below 43.17 were at low-risk, those with a score between 43.17 and 63.40 were at moderate-risk and those with a score above 63.40 were at high-risk for SSI development. Compared to low-risk patients, moderate-risk patients had a relative risk of 3.963 ($p<0.001$, 95% CI=2.58-6.08) of developing an SSI and high-risk patients had a relative risk of 6.48 ($p<0.001$, 95% CI=4.16-10.10) of acquiring an SSI. Overall, approximately 3% of low-risk patients, 10% of moderate-risk patients and 16% of high-risk patients of the NSQIP database developed any type of SSI. In this study, a simple risk tool for quantifying SSI risk created at the JGH was developed. The tool has external validity for the JGH population. Validation in other populations will be required in future studies.

French Abstract

Les infections du site opératoire (ISO) constituent une des plus fréquentes complications à la suite d'une chirurgie. Les ISOs ont plusieurs conséquences chez le patient incluant un séjour prolongé à l'hôpital, des coûts d'hôpitaux plus élevés, un risque plus accru de requérir des soins intensifs ainsi qu'un risque de morbidité et de mortalité plus élevé. Il existe trois types d'ISOs : ISO incisionelle superficielle, le plus commun néanmoins le moins sérieux, ISO incisionelle profonde et ISO d'organe et/ou d'espace, le plus dangereux des trois. À cause de l'émergence accrue des bactéries résistantes aux antibiotiques, les traitements de certaines ISOs sont inefficaces chez la majorité des patients avec une ISO. En conséquence, plus d'attention doit être fournie avant et pendant la chirurgie afin de prévenir à tout prix les ISOs au lieu de se concentrer sur les traitements de cettes infections. Les données pris de la littérature scientifique ont identifié des facteurs de risque qui prédisposent les patients chirurgicaux pour le développement des ISOs. Cependant, aucun modèle de risque valide n'a été produit afin de quantifier le risque de développer un ISO. Les données pour cette étude ont été obtenues grâce à la base de données NSQIP (National Surgical Quality Improvement Program) établie à l'Hôpital Général Juif et incluent les patients qui ont subi une chirurgie à cet hôpital entre novembre 2009 et décembre 2011. Nous avons choisi d'utiliser la base de données NSQIP puisqu'elle est prospective, impartiale et compréhensive. Des analyses bivariées et des régressions logistiques multivariées ont été employées

afin d'identifier les cinq facteurs de risque suivants qui sont indépendamment et significativement associés avec le risque d'un ISO : le sexe male, l'hospitalisation du patient, l'hypertension, l'usage de corticostéroïdes et la dépendance (partielle ou totale) pour des activités quotidiennes avant la chirurgie. Des modèles de régression logistique avec une analyse de courbe ROC ont été utilisés pour développer un outil de pointage de risque pour ISO et délimite les catégories en incréments de risque. Les patients avec un score inférieur de 43.17 sont considérés des patients à risque minime de développer un ISO, ceux avec un score entre 43.17 et 63.40 ont un risque modéré d'acquérir un ISO et ceux avec un score de 63.40 ou plus haut ont un risque élevé pour le développement d'un ISO. Comparé à des patients qui ont un risque minime, les patients avec risque modéré ont un risque relatif de 3.96 fois ($p<0.001$, 95% CI=2.58-6.08) de développer un ISO et les patients à risqué élevé ont un risque relatif de 6.48 ($p<0.001$, 95% CI=4.16-10.10) d'acquérir un ISO. Dans cette étude, un outil de risque simple afin de quantifier le risque d'ISO à l'hôpital Général Juif a été développé. L'outil possède la validité externe pour la population de cet hôpital. La validation pour les autres populations sera requise dans des études futures.

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Dr. John S Sampalis: Has provided continued support in every stage of the risk-index tool development. Dr. Sampalis has provided guidance in the creation of the idea of this M.Sc. project and direction for the execution of statistical analyses and in the composition of the thesis.

Rashi Khare: Provided access to the NSQIP database and guidance in the evaluation of the data.

I. Introduction

Surgical site infections (SSI) are one of the most common complications following surgery. The CDC (Center for Disease Control and Prevention) estimates that 25% of the annual 1.8 million health-care associated infections are SSIs. (Mangram, Horan, Pearson, Silver, & Jarvis, 1999) This high incidence of SSIs is due to the increasing number of surgeries. (Setiawan, 2011) The NNIS states that 38% of nosocomial infections among surgical patients are SSIs and, among all hospitalized patients, SSIs occupy between 4% and 16% of all nosocomial infections. (Spear, 2008) In Canada, two million surgeries are performed per year and 50,000 SSIs occur, accounting for approximately 14 to 16% of all hospital-acquired infections. However, 40 to 60% of all SSIs are considered preventable. (McElroy) Therefore, there is a need to implement effective prevention interventions. Reported rates of SSI are most likely underestimates since a majority of the SSIs occur after discharge and, as a result, are never included in federal and provincial records. In 2009, the study conducted by McIntyre et al. showed that 50% of all SSIs were diagnosed after discharge. (McIntyre, Warner, Nester, & Nathens, 2009)

SSIs have long-term effects for the patient and for society. These surgical complications increase hospital costs, the length of the hospital stay and morbidity, disability and mortality rates. (Setiawan, 2011) (Mangram, Horan, Pearson, Silver,

& Jarvis, 1999) Globally, 77% of all surgical patient deaths are related to infections (Mangram, Horan, Pearson, Silver, & Jarvis, 1999) and, compared to non-infected patients, SSI patients are twice as likely to die, are 60% more likely to stay in the Intensive Care Unit (ICU) and are five times more likely to be readmitted to hospital after discharge.

If a patient develops an SSI, he/she will also require additional treatment and therefore this complication will extend the hospital stay by an average of 16.8 days. The patient's hospital costs will also rise. These expenses can reach over $35,000 if the causing bacteria are MRSA (methicillin-resistant *Staphylococcus aureus*) which do not respond to antibiotics. (Kirkland, Briggs, Trivette, Wilkinson, & Sexton, 1999) Any surgical complication, including SSIs, will cause an added burden on the patient that may affect his/her overall health post-surgically. (Barie, Nichols, & Wilson, 2006)

All surgical patients are at risk of developing an SSI since natural flora bacteria such as *Staphylococcus aureus* can cause opportunistic infections particularly if they are immunocompromised. (Tietjen, Bossemeyer, & McIntosh, 2003) Furthermore, SSIs can occur following any type of surgery. Also, due to the increase of resistant bacteria in the community which incurs added difficulty of treating infections, more effort must be devoted to prevent SSIs as opposed to discovering new treatments. (Setiawan, 2011) (Tietjen, Bossemeyer, & McIntosh, 2003)

There are known risk factors that can predispose a patient to develop an SSI. Some of these elements are dependent on the surgical staff and the hospital while others are patient-dependent related to his/her lifestyle presurgically. (Spear, 2008)

Objectives: Identification of patients at increased risk for an SSI can lead to focused interventions for these populations. This more devoted and focused approach to prevention should be easier to implement compared to general policies. The aim of the current study will be to develop a user-friendly quantitative tool for identifying patients at high risk for an SSI.

Rationale: To date there is no quantitative tool for measuring the risk of an SSI. Identifying patients at high risk for an SSI can increase the effectiveness of preventive intervention with controlling costs.

II. Review of the Literature

Definition and characteristics of SSIs. According to the Centers for Disease Control and Prevention (CDC), a surgical site infection is defined as a nosocomial infection occurring on the surgical site within 30 days of an operation and up to one year following an implant surgery. (Mangram, Horan, Pearson, Silver, & Jarvis, 1999) SSIs can be classified into three categories: superficial incisional SSI, deep incisional SSI and organ/space SSI. Information characterizing these infections is shown in Table I.

Causes of SSIs. The cause of an SSI is the entry of a pathogenic microorganism in the body in the area of the surgical incision. Most often, the causing bacteria originate from the patient's endogenous flora present on the skin, mucous membranes or hollow viscera. Many factors determine whether an infection will occur or not, such as the bacterial inoculum, its virulence and the effect of the microenvironment. A larger incision will permit a high amount of potentially pathogenic bacteria to enter the organism and cause an opportunistic infection.

Table I: Classification and criteria of diagnosis of surgical site infections
(Mangram, Horan, Pearson, Silver, & Jarvis, 1999)(Setiawan, 2011)(Horan, Gaynes, Martone, Jarvis, & Emori, 1992)

Type of SSI	Characteristics of the infection
Superficial incisional	Infection involves only the skin or subcutaneous tissue. Also presents with one or more of the following characteristics:
	- Purulent drainage from superficial incision (with or without laboratory confirmation).
	- Isolated organisms from a culture of fluid or tissue from the superficial incision obtained aseptically.
	- At least one of the symptoms of infection: pain or tenderness, localized swelling, redness, or heat *and* superficial incision has been opened by the surgeon intentionally.
	- The diagnosis of a superficial incisional SSI may be made by a surgeon or attending physician.
Deep incisional	Infection involves deep soft tissues (such as the fascial and muscle layers) of the incision. Also presents with one or more of the following characteristics:
	- Purulent drainage from deep incision of the surgical site (not from the organ/space).
	- Deep incision spontaneously dehisces or is intentionally opened by the surgeon when the patient has at minimum one of the following signs or symptoms: fever (>38^{o}C), localized pain, or tenderness.
	- The diagnosis of a deep incisional SSI may be made by a surgeon or attending physician.
Organ/space	Involves any part of the anatomy (such as organs or spaces), other than the incision, which has been opened or manipulated during surgery. Must also present with at least one of the following criteria:
	- Purulent drainage from a drain placed through a stab wound into the organ/space.
	- Organisms have been isolated aseptically from a culture of fluid or tissue which is in the organ/space.
	- An abscess or other evidence of a present infection involving the organ/space of the surgical site is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
	- The diagnosis of an organ/space SSI may be made by a surgeon or attending physician.

This is why laparoscopic surgeries are associated with a decreased amount of SSIs. For instance, Boni et al. observed that 1.1% and 4% of patients undergoing cholecystectomies laparoscopically and with open surgery, respectively, had a surgical site infection. Moreover, bacteria virulence also affects the development of the infection. Highly virulent bacteria can produce toxins or other factors that increase their chance of invading a tissue and causing infection. (Boni, et al., 2006) Finally, the resistance of the patient is correlated with the risk of infection. An immunocompromised patient is more likely to develop an SSI than an immunocompetent patient. (Spear, 2008) (Boni, et al., 2006) One can calculate the overall risk of acquiring an SSI using the effect of the three factors mentioned above using the following formula: Risk of SSI = (Dose of bacterial contamination) X (virulence) / (Resistance of patient) (Boni, et al., 2006)

The pathogens that cause post-surgical wound infections are most often Gram-positive cocci (notably *Staphylococci*) but this varies according to the type of bacteria present near the area. Groin/perineal infections are typically caused by Gram-negative bacteria. Moreover, SSIs following gastrointestinal surgery are most likely caused by one of the bacteria in the intrinsic bowel flora, for example Gram-negative bacilli (such as *Escherichia coli*) and other Gram-positive microbes. Overall, the most common microorganism that causes SSIs is *Staphylococcus aureus*. These cause approximately 20% of all SSIs, followed by coagulase-negative *Staphylococci* (14%) and *Enterococci* (12%). (Mangram, Horan, Pearson, Silver, & Jarvis, 1999)

Risk factors of SSIs. The risk of acquiring an SSI is strongly correlated with the type of surgery. The classification of surgeries can be found on Table II.

Table II: Classification of surgeries according to operative wound (Setiawan, 2011) (Mangram, Horan, Pearson, Silver, & Jarvis, 1999)

Type of operation	Characteristics	Incidence of SSIs
Class I Clean	Involves "uninfected operative wound in which the respiratory, gastrointestinal and genitourinary tracts were not entered; including incisional surgery due to blunt trauma". (Setiawan, 2011)	<2%
Class II Clean-Contaminated	Enters the respiratory, gastrointestinal and/or urinary tracts however no unusual contamination has occurred.	5-15%
Class III Contaminated	Procedure on an open wound with major breaks in sterile technique.	15-30%
Class IV Dirty/ infected	Surgery on an old wound with dead tissue or involved existing infection or perforated bowel. The pathogens that cause SSI were present at the site before the operation.	>30%

Clearly, the level of contamination influences the risk of acquiring an SSI. A patient undergoing a dirty surgery is much more likely to develop an SSI than a patient undergoing a clean surgery not only because of the type and quantity of bacteria present, but also because of the length of the surgery and the surgeon's technique. (Setiawan, 2011) (Mangram, Horan, Pearson, Silver, & Jarvis, 1999)

It is however important to consider other factors in the risk of developing an SSI.

Research on risk factors for SSIs typically focuses on individual variables. Studies done by Miki et al., Korinek et al., Jeong et al., Tang et al. and Askarian et al. show that male sex is an independent risk factor for SSI. (Miki, Inoue, Mohri, Kobayashi, & Kusunoki, 2006) (Korinek, et al., 2005) (Jeong, et al., 2012) (Tang, et al., 2001) (Askarian, Yadollahi, & Assadian, 2012)

Obesity could increase a patient's risk of surgical site infection. (Harrop, Styliaras, Cher Ooi, Radcliff, Vaccaro, & Wu, 2012) (Lynch, Ranney, Shijie, Lee, Samala, & Englesbe, 2009) Since the patient has a larger skin surface, and therefore more bacteria on the skin, the risk of bacteria entering the organism during surgery is larger. Also, the surgeon must make a larger and deeper incision in order to reach the organ of interest. This increases the number of pathogenic microorganisms entering the body and hence the risk of SSI rises. In fact, the risk of superficial incisional SSI is increased "because of the amount of dead space created during surgical wound closure and associated local fat necrosis". (Harrop, Styliaras, Cher Ooi, Radcliff, Vaccaro, & Wu, 2012) A study conducted by Giles

et al. including patients who underwent lower extremity bypass demonstrated that obesity independently predicts postoperative SSI. (Giles, Hamdan, Pomposelli, Wyers, Siracuse, & Schermerhorn, 2010)

Another important risk factor for the development of SSI is diabetes. More than 9 million Canadians have been diagnosed with diabetes or prediabetes. (Canadian-

Diabetes-Association, 2012) Diabetes is a risk factor for many other illnesses and complications, such as heart failure, kidney disease, bone and joint disorders, ocular complications and nerve disease. (MedlinePlus, 2012) (Morricone, et al., 1999) (McCormack & Leith, 1998) The glucose level in the blood also diminishes immune function and thus increases the risk of developing an SSI. The study conducted by Ferrazzi et al. showed that, of the patients who underwent CABG surgery (coronary artery bypass graft), 35% to 50% of patients with complications (including SSI) had diabetes. (Ferrazzi, Allen, Crupi, Reyes, Parenzan, & Maisonnet, 1986) It is important that surgical patients have their glucose levels monitored prior to surgery by testing for fasting serum glucose (FSG) and Hemoglobin A1c (HbA1c), which will evaluate the presence or absence of diabetes. If the tests are positive and the surgery is elective, the procedure should be postponed while the patient's diet is altered to follow a predetermined regimen that has been shown to control serum glucose levels. (Dronge, Perkal, Kancir, Concato, Aslan, & Rosenthal, 2006) (Hoogwerf, 2006) In fact, the majority of surgical patients experience perioperative hyperglycemia, even if they are not insulin resistant or diabetic. Some believe that this predisposes the patient to an SSI even if not diabetic; however this is not a consensus among scientists. (Helblad, Nilsson, Engstrom, Berglund, & Janzon, 2002) (Parsons, et al., 2002)

Some have shown that preoperative hyperglycemia is a risk factor for postoperative mortality and morbidity, including SSI. Capes et al. conducted a meta-analysis which showed that non-diabetic patients with glucose ranging from 6.1 to 9.0 mmol/L had an increased risk (RR = 3.9) of morbidity or mortality. They also stated

that non-diabetic patients with higher levels of glucose (above 8.0 mmol/L) had an increased risk of cardiovascular complications such as congestive heart failure or cardiogenic shock. (Capes, Hunt, Malmberg, & Gerstein, 2000)

Proper nutrition can prevent any sort of surgical complications, including nosocomial infections. (Ulicny & Hiratzka, 1991) (Sungurtekin, Sungurtekin, Balci, Zencir, & Erdem, 2004) (Nozoe, Kimura, Ishida, Saeki, Korenaga, & Sugimachi, 2002) Conversely, malnutrition can predispose a patient to develop an SSI postsurgically. For instance, a prospective, randomized, double-blind trial by Snyderman et al. that studied oncologic surgical patients determined that perioperative adequate nutrition diminished the patient's risk of postoperative infection considerably compared to patients not provided with the nutritional supplemented formula. In fact, 25% of the Impact groups (who received supplemental nutrition) developed a postoperative infection compared to 41% of the "Standard" groups who acquired a nosocomial infection. Of these hospital-acquired infections, 18% were SSIs, 44% involved the lungs, 15% involved the gastrointestinal tract, 8% involved the genitourinary tract and 15% occurred in other sites. (Snyderman, et al., 1999)

Malnutrition can also be linked to a high weight loss (more than 10% of the patient's body mass) six months or less before surgery. Malone et al. found a significant association between the amount of weight loss and SSI risk. In their study, 12.3% of patients who lost more than 10% of their body weight had an SSI as opposed to 7.1% of patients who maintained their body weight. (Malone, Genuit, Tracy, Gannon, & Napolitano, 2002)

There has been much evidence that tobacco use has many negative health effects. One of these is that smoking can predispose a surgical patient to a postoperative infection. In the study by Jacob et al., mice exposed to a water-soluble condensate of tobacco smoke (WSC) were incapable of responding to an antigen due to the immunosuppression of T lymphocytes in their spleens. The T cells were also unable to interact with B cells and macrophages to appropriately destroy the antigen. This effect was not observed in the mice not exposed to WSC; therefore one can conclude that smoking is a risk factor for any type of infection, including SSI. (Jacob, Stelzer, & Wallace, 1980) Tobacco has many components that decrease many immune cells' function. (Sopori, 2002) (Stämpfli & Anderson, 2009) For instance, nicotine skews the effector macrophage function towards the T_H-2 type immune response, hydrocarbons affect gene regulation mediated by loop-helix-loop proteins and adaptively upregulates metabolic and bio-transforming enzymes, not to mention the multiple effects of the oxidants and reactive nitrogen moieties in the tobacco. (Stämpfli & Anderson, 2009) As a result, it is not surprising that, in a study by Delgado-Rodriguez et al., past smokers had an increased risk of SSI (adjusted OR = 1.46, CI 95% = 1.02-2.09). This however was not observed with current smokers. Furthermore, a long history of smoking (≥51 pack-years) increases the patient's risk of staying in the intensive care unit (adjusted OR = 2.86, CI 95% = 1.21-6.77) and of dying in the hospital (adjusted OR = 2.56, CI 95% = 1.10-5.97). (Delgado-Rodriguez, et al., 2003) Smoking has other consequences that affect SSI development and healing. For example, one of the effects of smoking is

decreased circulation of oxygen in the bloodstream. This has many consequences during and following surgery. Oxygen stimulates the immune system to kill antigens and promotes wound healing. Consequently, the wound of a patient who smokes will heal slower than a non-smoking patient. (Haridas & Malangoni, 2008)

Alcohol abuse has been identified as an independent risk factor for SSIs. Tonnesen et al. found elevated rates of morbidity following colorectal surgeries in patients who consumed 60 gm or more of alcohol daily. Thirty percent of the complications consisted of SSIs. (Tonnesen, et al., 1992) (Rantala, Lehtonen, & Njinikoski, 1997) However, the exact mechanism of the interaction between alcohol and the immune system is currently unknown. (Rantala, Lehtonen, & Njinikoski, 1997) (Tonnesen, et al., 1992) It is however known that alcohol affects many physiological systems such as the hemostatic, cardiovascular, central nervous system and the immune systems. (Tonnesen, et al., 1992)

Functional status prior to surgery is an important risk factor for postoperative surgical site infection caused by Methicillin-Resistant *Staphylococcus aureus* (MRSA). As will be discussed later, it is difficult to treat an infection caused by resistant bacteria, such as MRSA, with common antibiotics. Anderson et al. compared patients infected by MRSA to two groups: to patients infected with MSSA (Methicillin-Sensitive *Staphylococcus aureus*) and to uninfected patients. The need for assistance with 3 or more daily activities increases the patient's risk of developing an SSI. In fact, the OR for SSI of the dependent patients compared

with uninfected patients was 3.97. The OR for SSI of the dependent patients compared to patients infected with MSSA was 3.88. We can therefore state that functional status can increase the risk of mortality and of hospital stay since infections caused by resistant bacteria are more difficult to treat. Anderson et al. further state that poor functional status is an important risk factor for SSI regardless of the patient's age. (Anderson, et al., 2008) It has yet to be shown if functional status preoperatively is an independent risk factor for SSI caused by bacteria other than MRSA. Further studies are required to make this type of association.

Patients with chronic obstructive pulmonary disease (COPD) also have an increased risk of SSI due to the lower amount of oxygen circulating in the patient's body. Oxygen stimulates the immune system to kill pathogenic microorganisms. Furthermore, tissue oxygenation accelerates wound healing. One could therefore assume that a patient with COPD has an increased risk of postoperative SSI and, also, the wound of this type of patient will heal at a slower pace than patients with a healthy respiratory system. (Haridas & Malangoni, 2008)

Hypertension is another risk factor for SSIs. Many researchers have found that patients with elevated blood pressure have an increased risk of developing an SSI. Cardoso Del Monte et al. demonstrated that female hypertensive patients who underwent a cesarean section had an RR of 2.47 (95% CI, 1.21-5.04) of developing an SSI compared to patients with healthy blood pressure who underwent the same procedure. (Cardoso Del Monte & Pinto Neto, 2010) Also, the meta-analysis by

Xue et al. shows that hypertensive patients undergoing breast surgery have an increased risk of 1.69 (RR) of acquiring an SSI as opposed to non-hypertensive patients. (Xue, Qian, Yang, & Wang, 2012)

A patient with a pre-exisiting auto-immune illness who has been prescribed corticosteroids will have a weakened immune system since these drugs target immune cells to diminish auto-immune symptoms such as inflammation. Therefore, a patient who undergoes surgery who presents with a weakened immune system has an increased risk of developing any sort of postoperative infection, including SSI. Lee et al. confirm the fact that steroid use is one of the risk factors predisposing surgical patients undergoing midline laparotomies to SSIs. (Lee, et al., 2011)

Disseminated cancer is also a risk factor in the development of an SSI postsurgically since it affects the regulation of at least two organs and therefore modifies the body's homeostasis. This could affect the patient's ability to combat infection. In fact, SSI consists of the most frequent comorbidity following colorectal oncologic surgeries. (Biondo, Kresisler, Fraccalvieri, Basany, Codina-Cazador, & Ortiz, 2012)

Chemotherapy and radiotherapy are two processes that can affect many cells of the organism, including white blood cells, and therefore the ability to kill pathogens. However, the processes in which the two procedures affect the immune system

differ. In the case of chemotherapy, for the treatment to be effective, the drugs must interact with the immune system. Therefore, a patient undergoing chemotherapy will have an increased risk of infection since the immune system is already attempting to destroy the cancerous cells. (McDonnell, Nowak, & Lake, 2011) Radiotherapy, on the other hand, damages cancerous cells as well as human cells. The latter cells can repair themselves as opposed to neoplastic cells which do not possess the ability to do so. Nonetheless, many cells of the immune system are vastly affected by radiotherapy and these effects could persist for a long period of time. Following external beam radiotherapy (RT), Standish et al. observed that women with stage I-III breast cancer presented with lymphopenia, low functional activity of natural killer (NK) lymphocytes, decreased monocyte phagocytosis and decreased production of the anti-inflammatory cytokine TNF-alpha. Lymphocyte count did not increase in the duration of the six-week follow-up period. However, the patients did not experience neutropenia, anemia or interferon-gamma production. These results demonstrate the large effect of radiotherapy on the immune system and on the diminishment of its ability to combat infection (Standish, et al., 2008)

Finally, many researchers use the ASA score to predict SSI risk since it categorizes patients according to their general health. An ASA of 1 indicates that a patient is healthy as opposed to an ASA of 5 which states that the patient is moribund and is not expected to survive regardless if he/she has a surgery. However, Peersman et al. concluded that this “is not a good predictor of infection” unless it is cross-

checked with present co-morbidities, for example current infections. (Peersman, Laskin, Davis, Peterseon, & Richart, 2008)

Most of these risk factors are in the patient's control and can be modified. For instance, obesity, diabetes, nutrition, tobacco use, functional status, COPD, cardiac failure and hypertension are elements that can be regulated by the patient. On the other hand, some risk factors, such as admission status of the patient (inpatient/outpatient), the anesthesia technique and the level of the resident are controlled by the surgical staff. Some factors cannot be controlled by the patient or by the surgical staff, such as gender, auto-immune illness, state of the case (emergent/elective), sepsis, the patient's transfer origin, the wound classification, surgical subspecialty of the operation and the ASA class. It is however important for the surgical staff to closely monitor all co-morbidities and every aspect of the case to adequately prepare for surgery and for possible postsurgical complications such as SSI.

If a risk factor is modifiable by the patient or by the surgical staff, every precaution should be taken to prevent surgical complications. For instance, the patient should consume a healthy diet regularly in his/her daily life prior to surgery to prevent obesity, type 2 diabetes mellitus, malnutrition, cardiac failure and hypertension. Regular exercise will also maintain the patient's health and will keep him/her physically functional prior to surgery. The individual should also avoid tobacco and not abuse alcohol. Moreover, the surgical staff should monitor the patient's nutrition before surgery. Finally, if the patient has cancer and must undergo

chemotherapy or radiotherapy, it is preferable for these to occur after the surgery to maximize the immune system's ability to fight infection. If the risk factors are not monitored by the patient and by the surgical staff, the patient has an increased risk of postsurgical consequences, such as surgical site infection. This complication could contribute to the many added costs, length of stay in the hospital, possibility of entering the ICU and risk of mortality. (Setiawan, 2011) (Mangram, Horan, Pearson, Silver, & Jarvis, 1999)

Bacterial resistance and treatments of SSIs. Treatments for SSIs differ depending on the specific case. Most cases are treated by debridement of the wound and/or by administering intravenous antibiotics, depending on the severity of the case. (Pull ter Gunne, Mohamed, Skolasky, van Laarhoven, & Cohen, 2010) (Mulholland & Doherty, 2011)

Nonetheless, treatment is difficult if the infection is caused by resistant bacteria such as MRSA or VRE (vancomycin-resistant *Enterococci*). Many beta-lactam-based antibiotics, such as cephalosporins and penicillins, have proven to be ineffective to treat infections caused by resistant strains of bacteria, the most common and known in the scientific community being MRSA, a *Staphylococcus aureus*. Many bacteria have acquired resistance in nature by genetically exchanging genes located on plasmids known as cassettes, such as *mec* for *S. aureus* strains. (Barie, Nichols, & Wilson, 2006) (van Duijn, Dautzenberg, & Oostdijk, 2011) Many healthy individuals possess these strains without even having knowledge of it, since these bacteria are generally on the flora of human beings yet do not cause

infection. However, in the case of individuals with an altered immune system, such as surgical patients, if these bacteria move to another part of the organism than where they usually reside in, for example during surgery, they can cause opportunistic infections.

The problem with resistant bacteria escalated in the mid-1980s when antibiotics were initially overused. This caused the gradual emergence of resistant strains of bacteria. For instance, in 1987, close to 20% of the *S. aureus* strains were MRSA and this rate climbed to 59% in 2004. (Barie, Nichols, & Wilson, 2006) (Lowy, 1998) (NNIS, 2004) This rise of bacterial resistance is not showing any signs of stabilizing or declining. (Barie, Nichols, & Wilson, 2006) (Rao, 1998) Moreover, treatment of an infection caused by resistant bacteria is very difficult since the microorganisms have developed mechanisms to prevent the antibiotics' activity or to not be perceived by the drug by modifying bacterial properties. Also, an infection caused by resistant bacteria will extend the patient's hospital stay and increase his/her hospital costs, not to mention the patient's added emotional and physical burden. These reasons are why the surgical staff must always focus on prevention of SSI rather than treating an infection after it arises.

*Current SSI prophylactic guidelines at the Jewish General Hospital. A*t the JGH in Montreal, guidelines have been created in order to prevent SSIs. The surgical department implemented an SSI prevention program in 2008, which includes six main guidelines: proper administration of prophylactic antibiotics, timing and location of hair removal prior to surgery, preoperative warming of the patient,

adequate skin preparation, maintenance of perioperative glucose and adequate nutritional support. Firstly, prophylactic antibiotics must be administered within one hour of surgery and the infusion must be completed before the initial incision is made. It is also important to properly choose the antibiotic according the most probable bacteria entering the body during surgery. In order to accomplish this task, a guide is present in every Operating Room (OR) in the JGH to choose the appropriate drug for each surgical procedure. It is also essential to keep in mind to administer additional doses every four hours in the cases of long operations. Secondly, appropriate hair removal is important to prevent SSIs. If possible, no hair removal is the best option in this regard, however in many cases it is required to clear the skin (where the incision will be made) of any hair. If necessary, clipping the hair is the recommended guideline and should be done as close to the beginning of surgery as possible. Thirdly, hypothermia of the patient must be avoided at all costs due to the many effects of temperature on the immune system, as mentioned earlier. The patient should be warmed with forced-air as well as with a blanket intraoperatively. The ambient temperature in the OR should also be monitored. Other precautions to be taken are that the patient should wear hats and booties perioperatively and receive warm liquid lavages. In the case of abdominal surgeries, the patient should receive warmed IV fluids. Furthermore, an adequate antiseptic skin preparation of chlorexhidine should be administered twice before surgery (one preoperative shower the night preceding surgery and one the morning of the surgery). Moreover, the patient's glucose levels must be maintained perioperatively and be tested the day prior to surgery and the day of the operation. All these

precautions as well as adequate nutritional support are current guidelines at the JGH in the surgical department and they will decrease all patients' risk of developing a surgical site infection. (Morin et al., April 2012) However, the same prophylactic measures are provided for every surgical patient even though many high-risk patients may require additional care or other low-risk patients do not necessitate certain measures such as prophylactic antibiotic administration. The risk-index tool created in this M.Sc. project will provide the knowledge to determine which patients are considered low-risk, moderate-risk and high-risk which will subsequently allow appropriate prophylactic SSI management.

SSI facts of common surgeries in accordance with NICE guidelines. The National Institute of Clinical Excellence (NICE) has drafted a document which includes all studies concerning SSIs and the adequate precautions for many types of surgeries. (Collier, et al., 2008) This document includes guidelines for the most common cardiac surgery, the coronary artery bypass graft (CABG) (Benetis, 2005) (Crestanello, et al., 2012) (Hekmat, et al.,2005), as well as the most common general surgery, the hernia repair (hernioplasty) (Rutkow & Robbins, 1993) (Bringman, et al., 2003). The most common orthopedic and spinal surgeries are knee arthroscopy and lumbar discectomy, respectively. (Lubowitz & Appleby, 2011) (Rose, 2008) (Babcock, Matava, & Fraser, 2002) (Parker, et al., 2010) (Nandoe Tewarie, Bartels, & Peul, 2007) (DeBerard, LaCaille, Spielmans, Colledge, & Parlin, 2009) Unfortunately, no information entailing SSI prevention is provided concerning these two types of surgeries.

The NICE guidelines have detailed several methods to diminish SSIs following CABG surgery. For instance, one study proved that antibiotic prophylaxis was effective in reducing SSI rates. In fact, patients who were administered prophylactic antibiotic had an OR of 0.08 compared to patients who received a placebo preoperatively (95% CI 0.03-0.27). However, a variety of other studies examining the effectiveness of disposable or reusable gowns, antiseptic skin preparation and closing of the skin (staples or sutures) showed no statistical difference between the tested methods. (Collier, et al., 2008)

Additional information was provided concerning SSI prevention for hernia repairs (hernioplasties). For example, antibiotic prophylaxis was also shown to be effective in preventing surgical site infections compared to administration of a placebo preoperatively (OR 0.48, 95% CI 0.27-0.85). Moreover, there was no statistical difference while studying the effectiveness of disposable or reusable drapes and gowns in the prevention of SSIs for elective surgeries (of which the majority of surgeries were hernia repairs and uncomplicated cholecystectomies). (Collier, et al., 2008)

As a result of these conclusions, NICE has composed a set of guidelines concerning SSI prevention separated into preoperative, intraoperative and postoperative phases. In the preoperative phase, it is advised that patients bathe the night before or the morning of the surgery. Furthermore, if necessary to remove the hair of the surgical site, NICE suggests utilizing electric clippers with a single-use disposable head on the day of the surgery. Antibiotic prophylaxis is recommended prior to

clean-contaminated and contaminated surgery. If the clean surgery involves the placement of a prosthesis or an implant, it is also recommended to give prophylactic antibiotics and, in the case of dirty or infected surgeries, it is advised to administer additional antibiotic treatment. The staff should also be dressed appropriately in specific non-sterile theatre wear. (Collier, et al., 2008)

Intraoperatively, NICE recommends the operating team to wear sterile gowns and wash their nails and hands using an antiseptic surgical solution (as well as prior to any subsequent operations). The patient's skin should be prepared with an antiseptic preparation, such as povidone-iodine or chlorhexidine, immediately before the first incision. In addition, patient homeostasis should be closely monitored throughout the procedure. For instance, patient temperature should be maintained and should not become hypothermic. Optimal oxygenation during and following surgery (haemoglobin saturation above 95%) and adequate perfusion are essential.

Following surgery, the main guideline is the adequate dressing and cleansing of the wound. An aseptic non-touch technique is appropriate for changing or removing dressings and sterile saline is utilized to cleanse the wound for up to 48 hours following surgery (after use regular tap water if the wound has been opened). If an SSI is suspected, antibiotic treatment should be given. Once again, it is important to choose the proper antibiotic which targets the most likely pathogen. It is important to recall resistance patterns during the selection of the drug.

III. Methods

Data Acquisition. Data was obtained from electronic medical records from the NSQIP (National Surgical Quality Improvement Program) database in the Jewish General Hospital. This information concerning SSI risk factors was acquired in May 2012.

The NSQIP database was created in 2009 and includes all patients who underwent surgery at the Jewish General Hospital. The database constitutes a valid, prospective, non-biased and comprehensive source of records. By utilizing this database, selection bias is eliminated. However, one inconvenient of NSQIP is the generalization of patients.

Thirty-seven potential risk factors were evaluated to assess their association with an SSI. All risk factors included in the database were included in the project in order to make as many conclusions as possible concerning which risk factors could predispose a patient to an SSI. Table III describes the classification of the risk factors. The outcomes evaluated were as follows: any type of SSI, postoperative superficial incisional SSI, postoperative deep incisional SSI, postoperative organ/space SSI.

Patient Population. Inclusion criteria consisted of all surgical cases in the NSQIP database from November 2009 to December 2011. In total, data concerning 2907

patients was acquired. Surgical cases were categorized according to the type of procedure performed. The patients who underwent operations with no incision and those whose hospital stay did not exceed 24 hours were excluded from the study population.

Table III: Criteria and their variables included in statistical analyses

Criteria	Variables
Gender	Male; Female
Patient status	Inpatient; Outpatient
Emergent surgery status	Elective; Emergent
Transfer origin	Not transferred, admitted directly from home; Transfer from other or inpatient
Anesthesia technique	General; Spinal, local, epidural, regional or MAC
Surgical subspecialty	Vascular; General
BMI	Normal (BMI 18.5 to 25); Under/overweight (below 18.5 or above 25)
Diabetes	Non-diabetic; Diabetic (type I or II)
Smoker	No; Yes
Alcohol abuse	No; Yes
Dyspnea	No; Yes (upon moderate exertion or at rest)
Functional status prior to surgery	Independent; Partially or totally dependent
Ventilator usage	No; Yes
COPD	No; Yes
Pneumonia[1]	No; Yes
Congestive heart failure[2]	No; Yes
Myocardial infarction[3]	No; Yes
History of angina[2]	No; Yes
Hypertension[4]	No; Yes
PVD[5]	No; Yes

Gangrene[6]	No; Yes
Renal failure[7]	No; Yes
Dialysis[8]	No; Yes
Disseminated cancer	No; Yes
Open wound[9]	No; Yes
Steroid use[10]	No; Yes
Weight loss >10%[11]	No; Yes
Bleeding disorders	No; Yes
Preoperative transfusion[12]	No; Yes
Chemotherapy[13]	No; Yes
Radiotherapy[13]	No; Yes
Sepsis[14]	No; Yes (SIRS, sepsis or septic shock)
Highest level of resident	5 to 8 years of residency; 0 to 4 years of residency
Wound classification	Class I or II (clean or clean-contaminated); Class III or IV (contaminated or dirty/ infected)
ASA class	ASA 1 or 2 (no disturb or mild disturb); ASA 3 or 4 (severe disturb or life threat)
Other procedures[15]	No; Yes
Concurrent procedures[16]	No; Yes

1 Patient must be on current antibiotic treatment at the time he/she is brought to the OR; must meet specific radiologic and symptomatic criteria. 2 Within 30 days prior to surgery.
3 Within 6 months prior to surgery.
4 Patient has persistent elevation of systolic blood pressure >140 mmHg **or** a diastolic pressure >90mmHg **or** requires an antihypertensive treatment at the time the patient is being considered as a candidate for surgery.
5 A history of any type of angioplasty or revascularization procedure for atherosclerotic PVD or a patient who has had any type of amputation procedure for PVD.
6 Rest pain or gangrene. Includes patients with ischemic ulceration and/or tissue loss related to peripheral vascular disease. Does not include Fournier's gangrene.
7 Elevated levels of BUN and creatinine (the latter above 3 mg/dl).
8 Currently requiring or on dialysis.
9 With or without infection. The wound must communicate to the air by direct exposure.
10 Patient has required the regular administration of oral or parenteral corticosteroid medications in the 30 days prior to surgery for a chronic medical condition.
11 Within 6 months prior to surgery. Patients who have intentionally lost weight are excluded.
12 Preoperative blood loss necessitating any transfusion (minimum of 1 unit) of whole blood/packed red cells transfused during the 72 hours prior to surgery. 13 Within 90 days prior to surgery.
14 Within 48 hours prior to surgery. Includes any case of SIRS, sepsis or septic shock.
15 An additional operative procedure performed by the same surgical team under the same anesthetic which has a CPT code different from that of the Principal Operative Procedure.

16 An additional operative procedure performed by a different surgical team under the same anesthetic which has a CPT code different from that of the Principal Operative Procedure.

Data adjustments. All data adjustments are shown in Table IV. It is important to mention that all criteria were transformed into numerical value where 1 was the risk factor and 0 was not in order to follow with statistical analyses.

Table IV: Criteria in original classifications and following adjustments

Criteria	Original classification	Altered classification
Transfer origin	1. Not transferred, admitted directly from home 2. Acute care hospital (inpatient) 3. Nursing home/ chronic care facility/ intermediate care unit 4. Transfer from other 5. Transfer from outside Emergency Department	0. Not transferred, admitted directly from home 1. Transfer from other or inpatient
Anesthesia technique	1. General 2. Epidural 3. Spinal 4. Regional 5. Local 6. Monitored anesthesia care (MAC) 7. Other 8. None	0. Spinal, local, epidural, regional or MAC 1. General
BMI	In numerical values	0. Normal (BMI between 18.5 and 25) 1. Under/overweight (below 18.5 or above 25)
Diabetes	1. Non-diabetic 2. Diabetic requiring therapy with a non-insulin anti-diabetic agent	0. Non-diabetic 1. Diabetic (type I or II)

	3. Diabetic requiring insulin therapy	
Dyspnea	1. No dyspnea 2. Dyspnea upon moderate exertion 3. Dyspnea at rest	0. No dyspnea 1. Dyspnea (upon moderate exertion or at rest)
Functional status prior to surgery	1. Independent 2. Partially dependent 3. Totally dependent	0. Independent 1. Partially or totally dependent
Sepsis	1. No sepsis 2. SIRS 3. Sepsis 4. Septic shock	0. No sepsis 1. Sepsis (including SIRS and septic shock)
Highest level of resident	In numerical values (each year is equivalent to 1)	0. 5 to 8 years of residency 1. 0 to 4 years of residency
Wound classification	1. Class I clean 2. Class II clean-contaminated 3. Class III contaminated 4. Class IV dirty/ infected	0. Class I or II (clean or clean-contaminated) 1. Class III or IV (contaminated or dirty/ infected)
ASA class	1. ASA 1 (no disturb) 2. ASA 2 (mild disturb) 3. ASA 3 (severe disturb) 4. ASA 4 (life threat) Note: No patients had an ASA of 5.	0. ASA 1 or 2 1. ASA 3 or 4
Other procedures	In numerical values (for example, if two procedures were performed: the value of 2 was noted)	0. No other procedures 1. Yes, two or more procedures

Statistical Analyses. All statistical analyses were performed using the Statistical Packages for Social Sciences v16.0 (SPSS). In order to determine all potential significant risk factors that predispose a patient for developing an SSI (in general), a superficial incisional SSI, a deep incisional SSI and an organ/space SSI, bivariate binary logistic regression analyses and Chi Square tests were performed. All results with p-values under 0.05 were considered significant. Those factors with a significant association for SSI risk with bivariate analysis were entered in a multivariate logistic regression model.

The variables that remained significantly associated with the risk of an SSI in the multivariate logistic regression analysis were used to develop the SSI risk score. The weight of each variable was a function of the logistic regression parameter estimate. More specifically the weight was the proportion of the variable parameter estimate to the score of the parameter estimates over all variables. Therefore the total score will have a range between 0 and 100.

Each patient was assigned an SSI score based on the presence or absence of each risk factor. To establish the cutoff values defining low, moderate and high-risk patients, ROC curve analyses were used.

The SSI score classification was validated using logistic regression models to assess the relative rate of observed SSIs in moderate and high-risk patients in comparison to the low-risk group.

IV. Results

Patient Characteristics. Two thousand nine-hundred and seven patients were included in the analyses. Fifty and a half percent (1468) of the patients were male and the majority were inpatients (68.2%; 1982 patients). The mean patient age was 61 years old though the age range varied from 18 to 95 years old. In total, 260 different types of surgeries were performed. The most common surgeries were as follows: laparoscopic cholecystectomy (254 surgeries, 8.8%), partial colectomy (244 surgeries, 8.4%), partial mastectomy (167 surgeries, 5.8%), laparoscopic appendectomy (166 surgeries, 5.7%) and open appendectomy (102 surgeries, 3.5%). Tables V, VI and VII describe the patient population.

Table V: Characteristics of age of the NSQIP patient population

	Minimum	Maximum	Mean
Age	18	95	61

Table VI: Characteristics of gender of the NSQIP patient population

	Number of patients	Percentage
Male	1468	50.5
Female	1437	49.5

Table VII: Most frequently performed surgeries of the NSQIP database

Type of surgery	Number of surgeries	Percentage
Partial mastectomy	167	5.8
Partial colectomy	244	8.4
Appendectomy	102	3.5
Laparoscopic appendectomy	166	5.7
Laparoscopic cholecystectomy	254	8.8

Note: All surgeries that constitute more than 3% of total surgeries were included in this table.

Concerning SSI outcome, 5.2% (148) of the patients developed a superficial incisional SSI, 0.3% (9) of the patients acquired a deep incisional SSI and 3.9% (111) of patients developed an organ/space SSI. Overall, Table VIII shows that 9.2% (268) of the 2907 patients developed any type of surgical site infection.

Table VIII: Frequency distribution of SSIs (any type, superficial incisional, deep incisional and organ/space)

Type of SSI	Number of infections	Percentage
Any type of SSI	268	9.2
Superficial incisional SSI	148	5.2
Deep incisional SSI	9	0.3
Organ/space SSI	111	3.9

Table IX describes the distribution of the 37 studied risk factors and Table X describes the SSI incidence for each of the risk factors. The highest difference in the SSI was observed for inpatients compared to outpatients (90.20%), followed by those who obtained general anesthesia (87.90%), who underwent general surgery (85.30%), those treated by a resident with less than 4 years of experience (82.80%), who had an abnormal BMI (64.70%) and who underwent an additional procedure by the same surgical team under the same anesthestic (61.50%).

Table IX: Frequency distribution of the 37 studied risk factors

Risk factor	Count	Percentage
Male	1468	50.5
Inpatient status	1982	68.2
Emergent surgery	1188	40.9
Transfer from other location or inpatient (not admitted from home)	168	5.8
General anesthesia	2416	83.1
General surgery	2326	80
Under/overweight (BMI below 18.5 or above 25)	1133	39
Diabetic	455	15.7
Smoker	443	15.2
Alcohol abuse	34	1.2
Dyspnea (upon moderate exertion or at rest)	176	6.1
Partially or totally dependent	141	4.9
Ventilator usage	29	1
COPD (severe)	90	3.1
Pneumonia	13	0.4
Congestive heart failure	38	1.3
Myocardial infarction	29	1
History of angina	23	0.8
Hypertension	1264	43.5
PVD	185	6.4
Gangrene	138	4.7
Renal failure	11	0.4
Dialysis	42	1.4
Disseminated cancer	132	4.5
Open wound	147	5.1
Steroid use	92	3.2
Weight loss >10%	123	4.2
Bleeding disorder	197	6.8
Preoperative transfusion	11	0.4

Chemotherapy	87	3
Radiotherapy	49	1.7
Sepsis (or SIRS or septic shock)	283	9.7
Resident with less than 4 years of residency	2200	75.7
Wound classification III or IV (contaminated or dirty/ infected)	592	20.4
ASA class 3 or 4 (severe disturb or life threat)	1109	38.1
Other procedures	1353	46.5
Concurrent procedures	117	4

Table X: SSI incidence (any type, superficial incisional and organ/space) according to risk factor presence and absence

Risk factor category	Variables	SSI outcome (any type)				Postop Superficial Incisional SSI				Postop Organ Space SSI			
		No #	No %	Yes #	Yes %	No #	No %	Yes #	Yes %	No #	No %	Yes #	Yes %
Gender	Female	1325	50.20%	112	42.30%	1365	49.50%	72	48.30%	1395	50.10%	42	35.30%
	Male	1315	49.80%	153	57.70%	1391	50.50%	77	51.70%	1391	49.90%	77	64.70%
Patient status	Outpatient	898	34.00%	26	9.80%	905	32.80%	19	12.80%	917	32.90%	7	5.90%
	Inpatient	1743	66.00%	239	90.20%	1852	67.20%	130	87.20%	1870	67.10%	112	94.10%
Surgery Status	Elective	1117	51.40%	114	46.70%	1166	51.00%	65	48.50%	1183	51.30%	48	42.50%
	Emergent	1058	48.60%	130	53.30%	1119	49.00%	69	51.50%	1123	48.70%	65	57.50%
Tobacco Use	No	2242	84.90%	222	83.80%	2346	85.10%	118	79.20%	2357	84.50%	107	89.90%
	Yes	400	15.10%	43	16.20%	412	14.90%	31	20.80%	431	15.50%	12	10.10%
Alcohol Abuse	No	2614	98.90%	259	97.70%	2727	98.90%	146	98.00%	2758	98.90%	115	96.60%
	Yes	28	1.10%	6	2.30%	31	1.10%	3	2.00%	30	1.10%	4	3.40%
Ventilator Usage	No	2614	98.90%	264	99.60%	2729	98.90%	149	100.00%	2760	99.00%	118	99.20%
	Yes	28	1.10%	1	0.40%	29	1.10%	0	0.00%	28	1.00%	1	0.80%
COPD	No	2560	96.90%	257	97.00%	2673	96.90%	144	96.60%	2700	96.80%	117	98.30%
	Yes	82	3.10%	8	3.00%	85	3.10%	5	3.40%	88	3.20%	2	1.70%
Pneumonia	No	2634	99.70%	260	98.10%	2747	99.60%	147	98.70%	2778	99.60%	116	97.50%
	Yes	8	0.30%	5	1.90%	11	0.40%	2	1.30%	10	0.40%	3	2.50%

Congestive Heart Failure	No	2608	98.70%	261	98.50%	2722	98.70%	147	98.70%	2752	98.70%	117	98.30%
	Yes	34	1.30%	4	1.50%	36	1.30%	2	1.30%	36	1.30%	2	1.70%
Myocardial Infarction	No	2614	98.90%	264	99.60%	2729	98.90%	149	100.00%	2760	99.00%	118	99.20%
	Yes	28	1.10%	1	0.40%	29	1.10%	0	0.00%	28	1.00%	1	0.80%
History of Angina	No	2621	99.20%	263	99.20%	2736	99.20%	148	99.30%	2766	99.20%	118	99.20%
	Yes	21	0.80%	2	0.80%	22	0.80%	1	0.70%	22	0.80%	1	0.80%

Risk factor category	Varia-bles	SSI outcome (any type)				Postop Superficial Incisional SSI				Postop Organ Space SSI			
		No #	No %	Yes #	Yes %	No #	No %	Yes #	Yes %	No #	No %	Yes #	Yes %
Hypertension	No	1506	57.00 %	137	51.70 %	1565	56.70 %	78	52.30%	1581	56.70%	62	52.10%
	Yes	1136	43.00 %	128	48.30 %	1193	43.30 %	71	47.70%	1207	43.30%	57	47.90%
PVD	No	2474	93.60 %	248	93.60 %	2586	93.80 %	136	91.30%	2607	93.50%	115	96.60%
	Yes	168	6.40%	17	6.40%	172	6.20%	13	8.70%	181	6.50%	4	3.40%
Gangrene	No	2517	95.30 %	252	95.10 %	2629	95.30 %	140	94.00%	2654	95.20%	115	96.60%
	Yes	125	4.70%	13	4.90%	129	4.70%	9	6.00%	134	4.80%	4	3.40%
Renal Failure	No	2632	99.60 %	264	99.60 %	2747	99.60 %	149	100.00 %	2778	99.60%	118	99.20%
	Yes	10	0.40%	1	0.40%	11	0.40%	0	0.00%	10	0.40%	1	0.80%
Dialysis	No	2605	98.60 %	260	98.10 %	2719	98.60 %	146	98.00%	2748	98.60%	117	98.30%
	Yes	37	1.40%	5	1.90%	39	1.40%	3	2.00%	40	1.40%	2	1.70%
Disseminated Cancer	No	2531	95.80 %	243	91.70 %	2636	95.60 %	138	92.60%	2666	95.70%	108	90.80%
	Yes	110	4.20%	22	8.30%	121	4.40%	11	7.40%	121	4.30%	11	9.20%

Open Wound	No	2520	95.40 %	239	90.20 %	2632	95.50 %	127	85.20%	2643	94.80%	116	97.50%
	Yes	121	4.60%	26	9.80%	125	4.50%	22	14.80%	144	5.20%	3	2.50%
Steroid Use	No	2563	97.00 %	251	94.70 %	2673	97.00 %	141	94.60%	2700	96.90%	114	95.80%
	Yes	78	3.00%	14	5.30%	84	3.00%	8	5.40%	87	3.10%	5	4.20%
Weight Loss >10%	No	2537	96.10 %	246	92.80 %	2642	95.80 %	141	94.60%	2676	96.00%	107	89.90%
	Yes	104	3.90%	19	7.20%	115	4.20%	8	5.40%	111	4.00%	12	10.10%
Bleeding Disorder	No	2462	93.20 %	247	93.20 %	2570	93.20 %	139	93.30%	2598	93.20%	111	93.30%
	Yes	179	6.80%	18	6.80%	187	6.80%	10	6.70%	189	6.80%	8	6.70%
Preoperative Transfusion	No	2549	99.60 %	254	99.60 %	2659	99.60 %	144	100.00 %	2690	99.60%	113	99.10%
	Yes	10	0.40%	1	0.40%	11	0.40%	0	0.00%	10	0.40%	1	0.90%
Chemotherapy	No	2561	96.90 %	259	97.70 %	2674	97.00 %	146	98.00%	2704	97.00%	116	97.50%
	Yes	81	3.10%	6	2.30%	84	3.00%	3	2.00%	84	3.00%	3	2.50%

Risk factor category	Variables	SSI outcome (any type)				Postop Superficial Incisional SSI				Postop Organ Space SSI			
		No #	No %	Yes #	Yes %	No #	No %	Yes #	Yes %	No #	No %	Yes #	Yes %
Radio-therapy	No	2598	98.30%	260	98.10%	2712	98.30%	146	98.00%	2741	98.30%	117	98.30%
	Yes	44	1.70%	5	1.90%	46	1.70%	3	2.00%	47	1.70%	2	1.70%
Diabetes	Non-diabetic	2239	84.70%	213	80.40%	2340	84.80%	112	75.20%	2347	84.20%	105	88.20%
	Diabetic	403	15.30%	52	19.60%	418	15.20%	37	24.80%	441	15.80%	14	11.80%
Dyspnea	No dyspnea	2480	93.90%	251	94.70%	2589	93.90%	142	95.30%	2620	94.00%	111	93.30%
	Dyspnea	162	6.10%	14	5.30%	169	6.10%	7	4.70%	168	6.00%	8	6.70%
Functio-nal Status	Independent	2529	95.70%	237	89.40%	2634	95.50%	132	88.60%	2660	95.40%	106	89.10%
	Partially or totally dependent	113	4.30%	28	10.60%	124	4.50%	17	11.40%	128	4.60%	13	10.90%
Highest Level of Resident	5 to 8 years of residency	606	23.40%	45	17.20%	625	23.10%	26	17.80%	632	23.10%	19	16.00%
	0 to 4 years of residency	1983	76.60%	217	82.80%	2080	76.90%	120	82.20%	2100	76.90%	100	84.00%
Wound Classifi-cation	Class I or II	2135	80.90%	178	67.20%	2198	79.80%	115	77.20%	2249	80.70%	64	53.80%
	Class III or IV	505	19.10%	87	32.80%	558	20.20%	34	22.80%	537	19.30%	55	46.20%
ASA Class	ASA 1 or 2	1587	61.90%	129	49.60%	1653	61.70%	63	43.20%	1649	60.90%	67	57.30%
	ASA 3 or 4	978	38.10%	131	50.40%	1026	38.30%	83	56.80%	1059	39.10%	50	42.70%

BMI	Normal BMI	627	38.00%	60	35.30%	656	37.90%	31	35.60%	657	37.80%	30	35.70%
	Under/ overweight	1023	62.00%	110	64.70%	1077	62.10%	56	64.40%	1079	62.20%	54	64.30%

Risk factor category	Variables	SSI outcome (any type)				Postop Superficial Incisional SSI				Postop Organ Space SSI			
		No #	No %	Yes #	Yes %	No #	No %	Yes #	Yes %	No #	No %	Yes #	Yes %
Transfer Origin	Not transferred, admitted directly from home	2488	94.20%	251	94.70%	2597	94.20%	142	95.30%	2629	94.30%	110	92.40%
	Transfer from other or inpatient	154	5.80%	14	5.30%	161	5.80%	7	4.70%	159	5.70%	9	7.60%
Sepsis	No sepsis	2110	89.80%	179	80.60%	2187	89.10%	102	87.20%	2210	89.70%	79	73.10%
	SIRS, sepsis or septic shock	240	10.20%	43	19.40%	268	10.90%	15	12.80%	254	10.30%	29	26.90%
Surgical Subspe-cialty	Vascular	542	20.50%	39	14.70%	559	20.30%	22	14.80%	565	20.30%	16	13.40%
	General	2100	79.50%	226	85.30%	2199	79.70%	127	85.20%	2223	79.70%	103	86.60%
Concur-rent Proce-dures	No	2539	96.10%	251	94.70%	2647	96.00%	143	96.00%	2679	96.10%	111	93.30%
	Yes	103	3.90%	14	5.30%	111	4.00%	6	4.00%	109	3.90%	8	6.70%
Other Proce-dures	No	1227	50.30%	89	38.50%	1265	49.80%	51	39.20%	1279	49.80%	37	36.30%
	Yes	1211	49.70%	142	61.50%	1274	50.20%	79	60.80%	1288	50.20%	65	63.70%
Anesthesia Technique	Spinal, local, epidural,	459	17.40%	32	12.10%	469	17.00%	22	14.80%	482	17.30%	9	7.60%

regional or MAC													
General	2183	82.60%	233	87.90%	2289	83.00%	127	85.20%	2306	82.70%	110	92.40%	

Significant Risk Factors in Chi-Square analyses. The data in Table XI summarizes the odds ratios for all risk factors that had a significant ($p<0.05$) association with any type of SSI according to the bivariate analysis. The highest odds ratio was observed for preoperative pneumonia followed by inpatient status.

Table XI: Significant risk factors predisposing patients to any type of SSI

Risk factor	Odds Ratio	p-value
Male gender	1.376	0.014
Inpatient status	4.736	<0.001
Preoperative pneumonia	6.332	0.004
Disseminated cancer	2.083	0.005
Open wound	2.266	0.001
Preoperative weight loss >10%	1.884	0.023
Partially or totally dependent	2.644	<0.001
Level of resident from 0 to 4 years	1.474	0.021
Class III or IV wound	2.066	<0.001
ASA class of 3 or 4	1.648	<0.001
Preoperative sepsis	2.112	<0.001
General anesthesia	1.531	0.031
General surgery	1.496	0.024
Other procedures	1.617	0.001

Tables XII and XIII summarize the significant risk factors ($p<0.05$) that predispose patients to acquire a superficial incisional and an organ/space SSI, respectively, as well as their odds ratios and p-values. For superficial incisional SSIs, the highest odds ratios were

observed for open wound and inpatient status whereas for organ/space SSIs, the highest odds ratios were observed for inpatient status, preoperative pneumonia, Class III or IV wound, alcohol abuse and preoperative sepsis. Due to the low number of deep incisional SSIs, no risk factors were found to be significant in predisposing patients for this type of infection.

Table XII: Significant risk factors predisposing patients to superficial incisional SSIs

Risk factor	Odds Ratio	p-value
Inpatient status	3.343	<0.001
Open wound	3.647	<0.001
Diabetes	1.849	0.003
Partially or totally dependent	2.736	0.001
ASA class of 3 or 4	2.133	<0.001
Other procedures	1.538	0.019

Table XIII: Significant risk factors predisposing patients to organ/space SSIs

Risk factor	Odds Ratio	p-value
Male gender	1.839	0.002
Inpatient status	7.846	<0.001
Alcohol abuse	3.198	0.048
Preoperative pneumonia	7.184	0.014
Disseminated cancer	2.244	0.021
Preoperative weight loss >10%	2.704	0.004
Partially or totally dependent	2.549	0.007
Class III or IV wound	3.599	<0.001

Preoperative sepsis	3.194	<0.001
General anesthesia	2.555	0.004
Other procedures	1.744	0.008

Overall, inpatient status, dependence for everyday activities (partial or total dependence) and other procedures performed by the same surgical team under the same anesthetic are common significant risk factors for the development of SSIs in general, superficial incisional SSI and organ/space SSI. Moreover, male gender, preoperative pneumonia, disseminated cancer, preoperative weight loss of more than 10% of the patient's body mass, a wound classification of III (contaminated) or IV (dirty/ infected), preoperative sepsis, SIRS or septic shock and general anesthesia can predispose patients to an SSI in general or to an organ/space SSI. Furthermore, an open wound and a patient's ASA class of 3 (severe disturb) or 4 (life threat) are common significant risk factors for SSIs in general and superficial incisional SSIs. Nonetheless, diabetes is only significant in the development of a superficial incisional SSI whereas alcohol abuse can predispose a patient to develop an organ/space SSI. Even though the resident's level and the surgical subspecialty (general surgery) of the procedure were not found to predispose a patient for superficial incisional and organ/space SSI, they were found to be significant risk factors for SSIs in general.

Table XIV shows all the p-values obtained from bivariate analyses of the 37 studied risk factors. (All significant risk factors are in bold.)

Table XIV: Significance (p-values) of all risk factors in bivariate analyses

Risk factor	Any type of SSI	Superficial incisional SSI	Deep incisional SSI	Organ/ space SSI
Gender	**0.014**	0.801	0.179	**0.002**
Patient status	**<0.001**	**<0.001**	0.065	**<0.001**
Surgery status	0.177	0.594	0.335	0.068
Transfer origin	0.890	0.718	0.415	0.418
Anesthesia technique	**0.031**	0.574	1.000	**0.004**
Surgical subspecialty	**0.024**	0.114	0.698	0.078
BMI	0.507	0.734	0.717	0.731
Diabetes	0.076	**0.003**	0.155	0.302
Tobacco use	0.654	0.061	1.000	0.119
Alcohol abuse	0.121	0.252	1.000	**0.048**
Dyspnea	0.685	0.597	1.000	0.695
Functional status prior to surgery	**<0.001**	**0.001**	1.000	**0.007**
Ventilator usage	0.512	0.399	1.000	1.000
COPD	1.000	0.807	0.247	0.585
Pneumonia	**0.004**	0.141	1.000	**0.014**
Congestive heart failure	0.774	1.000	1.000	0.668
Myocardial infarction	0.512	0.399	1.000	1.000
History of angina	1.000	1.000	1.000	0.619
Hypertension	0.104	0.309	0.515	0.345
PVD	1.000	0.226	1.000	0.246
Gangrene	0.879	0.427	1.000	0.658
Renal failure	1.000	1.000	1.000	0.369
Dialysis	0.584	0.474	0.123	0.690
Disseminated cancer	**0.005**	0.102	0.060	**0.021**
Open wound	**0.001**	**<0.001**	0.374	0.282

Steroid use	0.062	0.141	0.252	0.425
Weight loss >10%	**0.023**	0.408	1.000	**0.004**
Bleeding disorder	1.000	1.000	0.469	1.000
Preoperative transfusion	1.000	1.000	1.000	0.366
Chemotherapy	0.573	0.625	1.000	1.000
Radiotherapy	0.800	1.000	1.000	1.000
Sepsis	**<0.001**	0.544	0.607	**<0.001**
Highest level of resident	**0.021**	0.156	1.000	0.074
Wound classification	**<0.001**	0.465	0.400	**<0.001**
ASA class	**<0.001**	**<0.001**	0.167	0.440
Other procedures	**0.001**	**0.019**	0.125	**0.008**
Concurrent procedures	0.253	1.000	1.000	0.146

Significant Risk Factors in logistic regression analyses. Table XV summarizes the results of the multivariate logistic regression analysis. These data show that the highest independent association of any SSI was observed for inpatient status.

Table XV: Significant independent risk factors predisposing patients to any type of SSI

Risk factor	Odds Ratio	p-value
Male gender	1.854	0.005
Inpatient status	9.491	<0.001
Hypertension	2.464	<0.001
Steroid use	2.485	0.042
Partially or totally dependent	2.577	0.047

Tables XVI and XVII show the significant independent risk factors for superficial incisional and organ/space SSIs ($p<0.05$). These results show that inpatient status had the highest independent odds ratios for superficial incisional and organ/space SSIs. Moreover, partial or total dependence and weight loss more than 10% of body mass prior to surgery are independent predictors for superficial incisional SSIs and organ/space SSIs, respectively.

Inpatient status and hypertension were found to be significant for all three SSI categories (SSI in general, superficial incisional SSI and organ/space SSI). Furthermore, the male gender is a common risk factor that predisposes patients to SSIs in general and organ/space SSIs whereas steroid use and dependence (partial or total) for everyday activities were found to be significant for SSIs in general and superficial incisional SSIs. Moreover, preoperative weight loss more than 10% of the patient's body mass and a wound classification of 3 or 4 were found to be significant only for organ/space SSIs.

Table XVI: Significant independent risk factors predisposing patients to superficial incisional SSIs

Risk factor	Odds Ratio	p-value
Inpatient status	6.592	0.002
Hypertension	2.098	0.017
Steroid use	2.971	0.049
Partially or totally dependent	3.703	0.031

Table XVII: Significant independent risk factors predisposing patients to organ/space SSIs

Risk factor	Odds Ratio	p-value
Male gender	2.097	0.015
Inpatient status	15.067	0.009
Hypertension	2.597	0.002
Preoperative weight loss >10%	3.057	0.013
Class III or IV wound	2.637	0.006

Table XVIII describes the significance values (p-values) of all risk factors studied obtained from multiple logistic regression analyses. (All independent significant risk factors are in bold.)

Table XVIII: Significance (p-values) of all risk factors in logistic regression

Risk factor	Any type of SSI	Superficial incisional SSI	Deep incisional SSI	Organ/ space SSI
Gender	**0.005**	0.224	0.228	**0.015**
Patient status	**<0.001**	**0.002**	0.988	**0.009**
Surgery status	0.713	0.845	0.798	0.960
Transfer origin	0.990	0.908	0.997	0.563
Anesthesia technique	0.134	0.379	0.673	0.199
Surgical subspecialty	0.777	0.523	0.775	0.583
BMI	0.676	0.324	0.437	0.852
Diabetes	0.694	0.627	0.993	0.819
Tobacco use	0.640	0.414	0.980	0.847
Alcohol abuse	0.806	0.916	0.999	0.285

Dyspnea	0.761	0.729	0.998	0.884
Functional status prior to surgery	**0.047**	**0.031**	0.997	0.292
Ventilator usage	0.999	0.999	0.999	0.999
COPD	0.465	0.586	0.986	0.998
Pneumonia	0.197	0.387	0.999	0.433
Congestive heart failure	0.639	0.998	0.999	0.471
Myocardial infarction	0.999	0.998	1.000	0.998
History of angina	0.999	0.999	1.000	0.999
Hypertension	**<0.001**	**0.017**	0.342	**0.002**
PVD	0.542	0.518	0.996	0.505
Gangrene	0.155	0.180	0.998	0.346
Dialysis	0.538	0.090	0.999	0.998
Disseminated cancer	0.682	0.910	0.996	0.851
Open wound	0.949	0.847	1.000	0.756
Steroid use	**0.042**	**0.049**	0.671	0.725
Weight loss >10%	0.228	0.928	0.994	**0.013**
Bleeding disorder	0.174	0.520	0.999	0.254
Preoperative transfusion	0.999	0.999	0.999	0.999
Chemotherapy	0.169	0.498	0.998	0.218
Radiotherapy	0.521	0.998	0.998	0.103
Sepsis	0.344	0.878	0.418	0.159
Highest level of resident	0.767	0.859	0.908	0.786
Wound classification	0.090	0.616	0.726	**0.006**
ASA class	0.779	0.903	0.989	0.625
Other procedures	0.068	0.085	0.409	0.207
Concurrent procedures	0.515	0.742	0.673	0.384

Since logistic regression calculates adjusted results while bivariate tests present crude results (Antonio, Zanolli, Carniel, & Morcillo, 2009) (Dode & Santos, 2009), it is logical that fewer risk factors were found to be significant with logistic regression than in the bivariate analyses. Three of the five significant risk factors found to be significant in multiple logistic regression were also significant in the bivariate results. These risk factors were: male gender, inpatient status and dependence (partial or total) for everyday activities prior to surgery.

Overall, the risk factors included in the final scoring tool were male gender, inpatient status, hypertension, steroid use and partial or total dependence for everyday activities.

Risk factors included in risk-index tool. Fifty and a half percent (1468) of the patients were male, 68.2% (1982) were inpatients, 43.5% (1264) of the patients were hypertensive, 3.2% (92) of the patients had a condition that required corticosteroid use and 4.9% (141) of the patients were partially or totally dependent prior to surgery.

Individual patient scores. According to the risk factors' respective odds ratios, a specific weight was calculated and assigned to each significant variable. These, as well as the relative weights and scores, are summarized in Table XIX.

Table XIX: Variables and SSI weights in final SSI logistic regression model

Significant risk factor	Negative (0)	Positive (risk factor) (1)	Odds Ratio (OR)	Relative SSI weight	Variable score value
Gender	Female	Male	1.854	0.0982	10
Patient status	Outpatient	Inpatient	9.491	0.5029	50
Hypertension	No	Yes	2.464	0.1306	13
Steroid use	No	Yes	2.485	0.1317	13
Functional status	Indepen-dent	Partially or totally dependent	2.577	0.1366	14
Total			18.871	1	100

If the patient possesses the risk factor, his/her individual patient score would increase by the value in the last column. Patient status is the most influential risk factor in the model. If an individual was an inpatient, his/her score would increase by fifty points. Hypertension, steroid use and functional status prior to surgery have similar odds ratios and therefore add a similar value to the patient's score if the risk factor is present. Hypertension and steroid use add thirteen points each to the score whereas a dependent patient (partially or totally) for everyday activities would have a value of fourteen added to his/her score. Nonetheless, male gender is the least influential risk factor included in the model with an addition of ten points to the patient's score. Clearly, the patients who possess all five of the risk factors in the risk-index tool have a score of one hundred and those who possess none of them have a score of zero. Table XX presents the frequency distribution of the scores in the study cohort.

Table XX: Frequency distribution representing individual patient SSI scores

Patient score	Frequency	Percentage
0	324	11.1
10	196	6.7
13	228	7.9
14	1	0.0
23	172	5.9
26	2	0.1
27	1	0.0
36	1	0.0
50	454	15.6
60	558	19.2
63	345	11.9
64	30	1.0
73	451	15.6
74	33	1.1
77	52	1.8
86	18	0.6
87	34	1.1
90	2	0.1
100	5	0.2
Total	2907	99.9%

Note: The three categories that have a frequency of 1 patient have a percentage between 0 and 0.049%, increasing the overall percentage to 100%.

The majority of patients (63.3%) have a score between 50 and 73 suggesting that they possess between one and three risk factors. Five patients who presented at the time of surgery with all five risk factors included in the model have a score of one hundred.

Moreover, 324 patients (11.1%) possess none of the five risk factors in the model, therefore presenting with a score of zero.

ROC curve. The sensitivity and specificity of the SSI scoring tool was assessed using an ROC curve (Receiver Operating Characteristic). The sensitivity and specificity of the SSI scoring tool are 75.5% and 49.8%, respectively. The false positive rate is 50.2% and the false negative rate is 24.5% for estimating the development of an SSI in surgical patients in the study cohort.

The ROC curve is presented in Figure 1 and has an area under the curve of 0.660 ($p<0.001$, 95% CI= 0.628-0.692). Three sections can be distinguished on the curve. The first has the highest slope representing an exponential relationship, the second has a moderate slope (linear relationship) and the last has the lowest slope and also presents with a linear relationship. Thusly, two cutoff points were established. The first has a value of 43.17 and presents with a sensitivity of 90.2% and a value of 66.0% for 1-specificity (specificity= 34.0%). The second cutoff value is 63.40 and coincides with a sensitivity of 38.1% and 1-specificity of 20.4% (specificity= 79.6%). These cutoffs were used to define patients at low, moderate and high risk for an SSI.

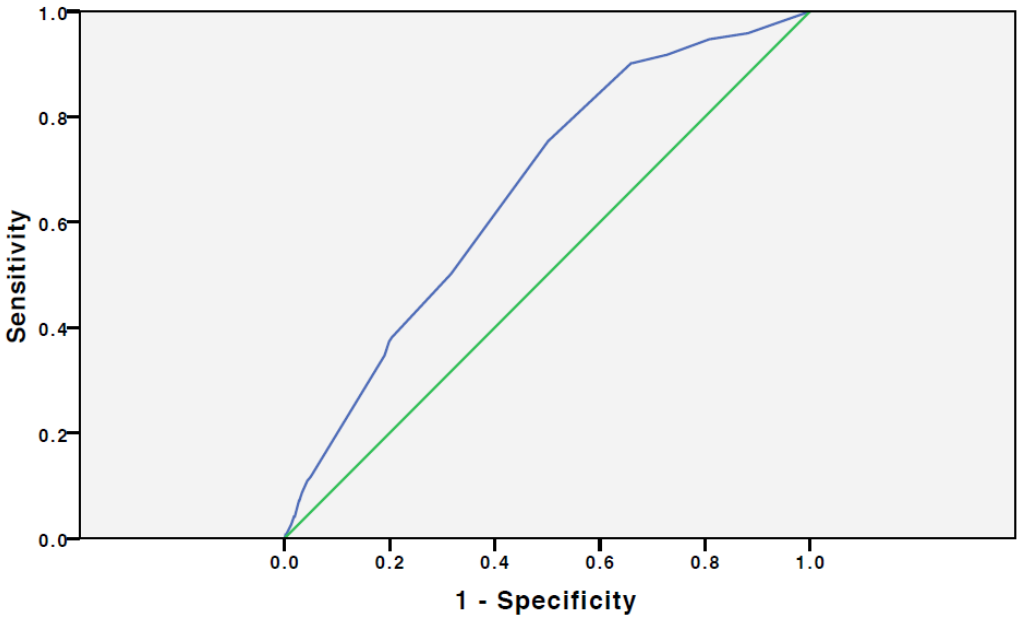

Figure 1: Receiver operating curve analysis for surgical site infection (SSI) risk scoring tool for the NSQIP database at the JGH in Montreal

General SSI outcomes for low-, moderate- and high-risk patients. After establishing the cutoff points, we created three groups according to the risk of developing an SSI. Patients with an individual SSI score below 43.17 have a low risk of developing an SSI, patients with a score between 43.171 and 63.40 have a moderate risk of acquiring this postsurgical infection and patients with a score above 63.401 are high-risk SSI surgical patients. In the NSQIP database, 31.8% (925), 46.2% (1342) and 22.0% (640) of the patients had a low, moderate and high risk of developing any type of SSI, respectively.

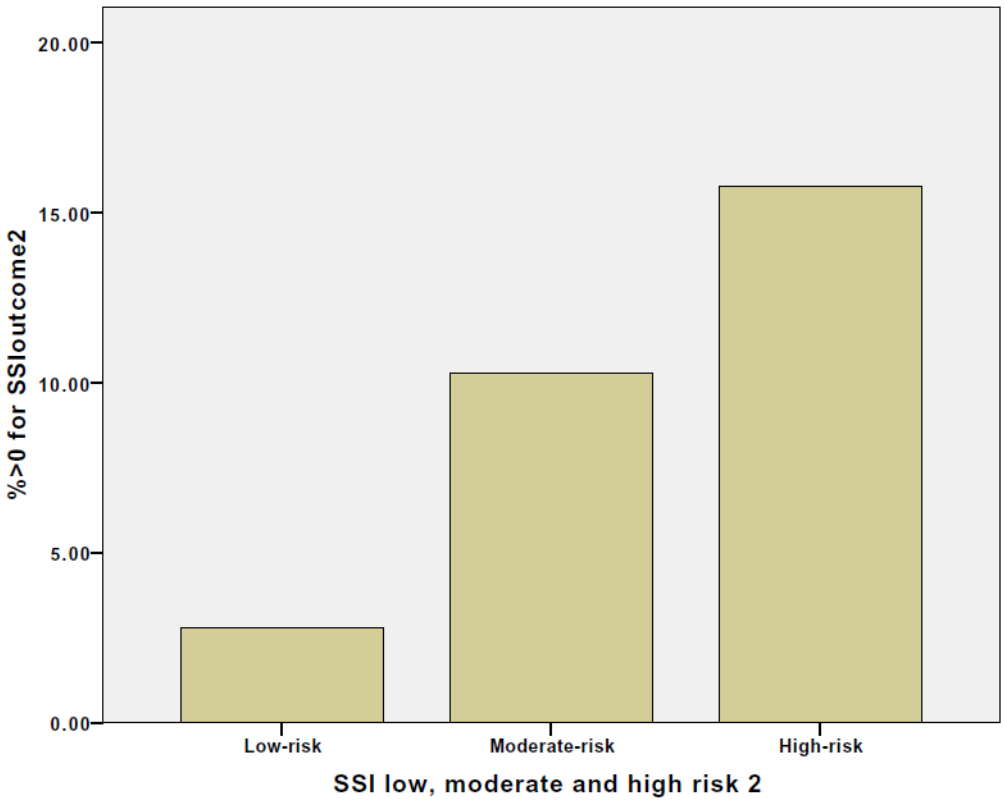

Figure 2: Simple bar chart representing the percentage of SSI outcomes (all types) for low-risk, moderate-risk and high-risk groups

Figure 2 presents the percentages of low-risk, moderate-risk and high-risk patients who develop any type of SSI. Approximately 3% of low-risk patients, 10% of moderate-risk patients and 16% of high-risk patients develop any type of SSI postoperatively.

Binary logistic regression analyses were used to determine each group's odds ratio of developing an SSI. Compared to the low-risk group, the moderate-risk group has an OR of 3.963 ($p<0.001$, 95% CI= 2.584-6.079) and the high-risk group has an OR of 6.479 ($p<0.001$, 95% CI= 4.156-10.101) (Table XXI). The moderate-risk group has an increased

risk of 3.963 compared to the low-risk group. The high-risk group has an OR of 3.255 ($p<0.001$, 95% CI= 2.407-4.400) when compared to the moderate-risk group (Table XXII).

Table XXI: Odds Ratios (ORs) and 95% CI of moderate and high-risk patients compared to low-risk patients in the development of any type of SSI

	OR	95% CI lower extremity	95% CI higher extremity
Moderate-risk	3.963	2.584	6.079
High-risk	6.479	4.156	10.101

Note: All p-values are below 0.001.

Table XXII: Odds Ratios (ORs) and 95% CI of moderate and high-risk patients compared to low-risk and moderate-risk patients, respectively, in the development of any type of SSI

	OR	95% CI lower extremity	95% CI higher extremity
Moderate-risk	3.963	2.584	6.079
High-risk	3.255	2.407	4.400

Note: All p-values are below 0.001.

Superficial incisional SSI outcomes for low-, moderate- and high-risk patients. Figure 3 represents the percentages of patients who acquire a superficial incisional SSI. Approximately 2%, 5.5% and 8.5% of low-risk, moderate-risk and high-risk patients develop a superficial incisional SSI, respectively.

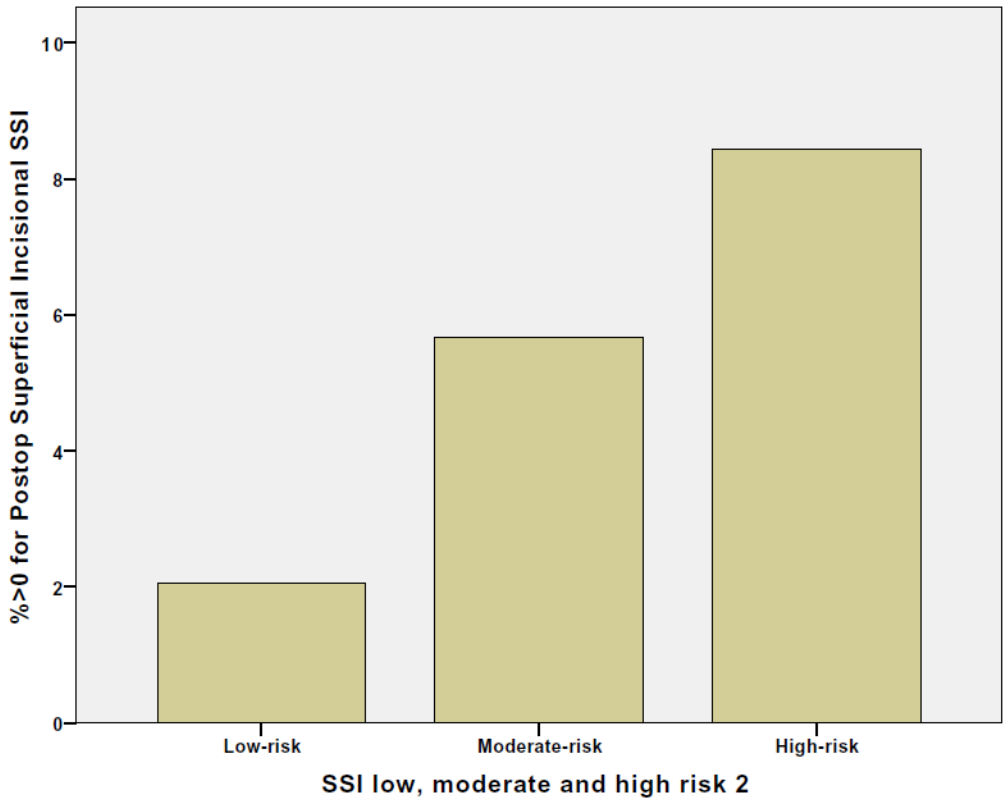

Figure 3: Simple bar chart representing the percentage of superficial incisional SSI outcomes for low-risk, moderate-risk and high-risk groups

Compared to low-risk patients, moderate-risk SSI patients have an OR of 2.863 ($p<0.001$, 95% CI= 1.719-4.767) and high-risk patients have an OR of 4.394 ($p<0.001$, 95% CI= 2.579-7.488) of developing a superficial incisional SSI (Table XXIII).

Compared to low-risk patients, moderate-risk patients have an OR of 2.863 ($p<0.001$, 95% CI= 1.719-4.767) and, compared to moderate-risk patients, high-risk patients have an OR of 2.597 ($p<0.001$, 95% CI= 1.780-3.789) (Table XXIV).

Table XXIII: Odds Ratios (ORs) and 95% CI of moderate and high-risk patients compared to low-risk patients in the development of superficial incisional SSIs

	OR	95% CI lower extremity	95% CI higher extremity
Moderate-risk	2.863	1.719	4.767
High-risk	4.394	2.579	7.488

Note: All p-values are below 0.001.

Table XXIV: Odds Ratios (ORs) and 95% CI of moderate and high-risk patients compared to low-risk and moderate-risk patients, respectively, in the development of superficial incisional SSIs

	OR	95% CI lower extremity	95% CI higher extremity
Moderate-risk	2.863	1.719	4.767
High-risk	2.597	1.780	3.789

Note: All p-values are below 0.001.

Organ/space SSI outcomes for low-, moderate- and high-risk patients.

Figure 4 shows that less than 1% of low-risk patients develop an organ/space SSI. Furthermore, approximately 4.5% and 8% of moderate-risk and high-risk patients acquire an organ/space SSI, respectively.

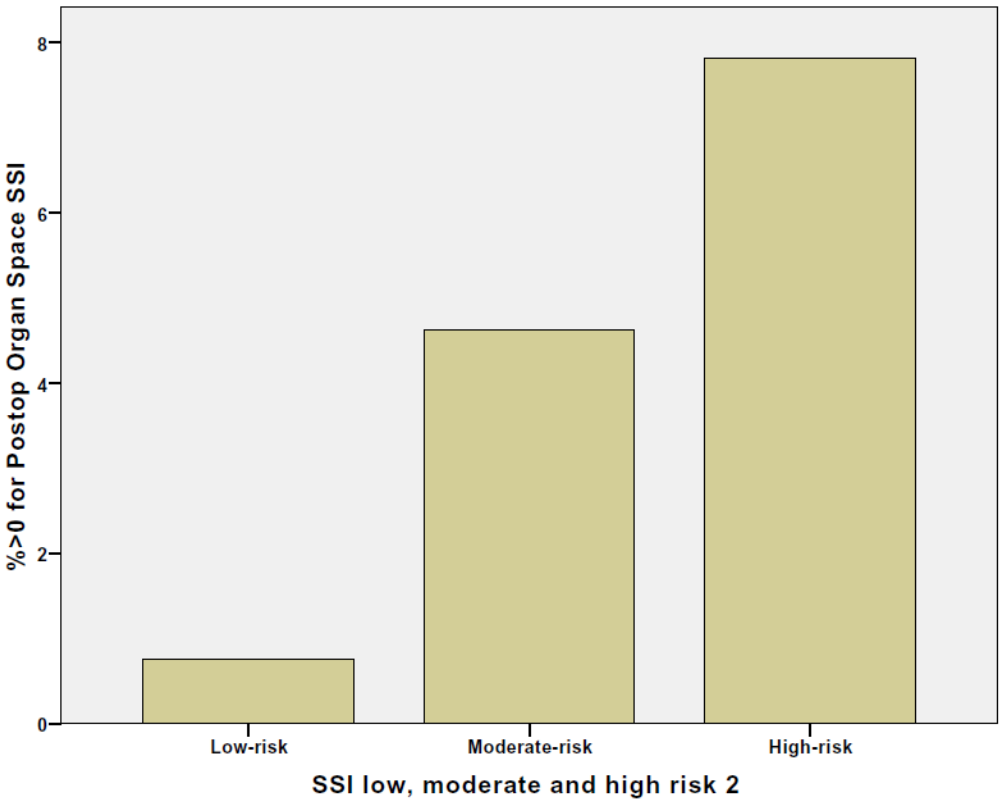

Figure 4: Simple bar chart representing the percentage of organ/space SSI outcomes for low-risk, moderate-risk and high-risk groups

Moderate-risk patients have an OR of 6.352 ($p<0.001$, 95% CI= 2.894-13.942) and high-risk patients have an OR of 11.114 ($p<0.001$, 95% CI= 5.005-24.677) of developing an SSI when compared to low-risk patients (Table XXV).

The results in table XXVI show that, when compared to the low-risk group, moderate-risk patients have an OR of 6.352 ($p<0.001$, 95% CI= 2.894-13.942), and high-risk patients have an OR of 4.410 ($p<0.001$, 95% CI= 2.708-7.181) when compared to moderate-risk patients for developing an SSI.

Table XXV: Odds Ratios (ORs) and 95% CI of moderate and high-risk patients compared to low-risk patients in the development of organ/space SSIs

	OR	95% CI lower extremity	95% CI higher extremity
Moderate-risk	6.352	2.894	13.942
High-risk	11.114	5.005	24.677

Note: All p-values are below 0.001.

Table XXVI: Odds Ratios (ORs) and 95% CI of moderate and high-risk patients compared to low-risk and moderate-risk patients, respectively, in the development of organ/space SSIs

	OR	95% CI lower extremity	95% CI higher extremity
Moderate-risk	6.352	2.894	13.942
High-risk	4.410	2.708	7.181

Note: All p-values are below 0.001.

V. Discussion

Surgical site infections are the second most common surgical complication causing significant burden of illness due to increased hospital stay, morbidity, mortality and healthcare costs. (Kirkland, Briggs, Trivette, Wilkinson, & Sexton, 1999) Due to the increasing prevalence of resistant bacteria, it is important to focus on prevention rather than developing new antibiotics that bacteria will eventually become resistant to as well. (Barie, Nichols, & Wilson, 2006) Given limited financial resources, it is also necessary that preventive interventions are applied in a focused and cost-efficient manner. The use of an SSI screening tool will allow the identification of high-risk patients for whom more intensive and aggressive prevention measures should be applied.

In the current study, the following factors were found to have a significant and independent association with the risk of an SSI: male gender, inpatient status, hypertension, preoperative corticosteroid use and partial or total dependence for everyday activities prior to surgery.

These results concur with those reported in the literature. For instance, Miki et al., Korinek et al., Jeong et al., Tang et al. and Askarian et al. have found that male gender is a significant predictor of SSIs. (Miki, Inoue, Mohri, Kobayashi, & Kusunoki, 2006) (Korinek, et al., 2005) (Jeong, et al., 2012) (Tang, et al., 2001) (Askarian, Yadollahi, & Assadian, 2012)

Although no conclusion has been made concerning the reason why males have an increased risk of SSI, it is possible that bacterial skin colonization could be associated to this since differences between males and females have been found concerning skin pH, serum production and skin thickness. (Jeong, et al., 2012)

There is little evidence of a direct association between inpatient status and development of SSI. Hennessey et al. do however state that the duration of inpatient stay is negatively correlated with preoperative albumin levels which is an independent risk factor for SSI. (Hennessey, Burke, Ni-Dhonochu, Shields, Winter, & Mealy, 2010) On the other hand, one can presume that a preoperative stay in the hospital has many effects on the patient. Firstly, it has been shown that preoperative mobility decreases the risk of postoperative complications. (Valkenet, van de Port, Dronkers, de Vries, Lindeman, & Backx, 2011) (Simunovic, Devereaux, & Bhandari, 2011) (Hirsch, 1995) Secondly, a longer preoperative stay can increase the patient's risk of acquiring bacteria circulating in the hospital which are not typically present in his/her flora. This can include resistant bacteria since these types of microorganisms survive in hospital settings by transmitting to individuals with a weakened immune system (for instance surgical patients). (Lipsitch, Bergstrom, & Levin, 2000)

There is evidence in the literature to support that hypertension is an independent risk factor for SSIs although the precise mechanism has not been demonstrated. Cardoso Del Monte et al. presume that the "chronic alteration in peripheral blood supply as a result of increased vascular resistance" could explain the increased infection rates among hypertensive surgical patients. (Cardoso Del Monte & Pinto Neto, 2010)

Moreover, it is logical that corticosteroid use in the 30 days prior to surgery is a significant risk factor for the development of SSIs since these drugs diminish the patient's immune function and therefore increases risk of opportunistic infections, including SSI. This hypothesis also concurs with the scientific literature. Lee et al. and Malone et al. found that steroid use is an independent risk factor for SSI development. (Lee, et al., 2011) (Malone, Genuit, Tracy, Gannon, & Napolitano, 2002)

The link between functional status prior to surgery and the risk of SSI has not yet been established and this is a new finding for this analysis. However, this could be related to reduced mobility in patients with lower functional status. Anderson et al. showed that a partially or totally dependent patient prior to surgery has an increased risk of developing an SSI caused by MRSA, but this has not been proven not for any other type of pathogenic microorganism. (Anderson, et al., 2008)

Other risk factors have been shown to be significant in the development of SSIs including obesity, diabetes mellitus, tobacco use, alcohol abuse, COPD, disseminated cancer, chemotherapy, radiotherapy and patient ASA score. However, none of these risk factors were found to be independently associated with the SSI risk in our analyses. One possible explanation of this is the low number of patients with these risk factors in our database. Another explanation could be that the effect of these factors is captured by the variables that were identified as significant predictors of SSIs in our study. The low number of SSIs could also affect these statistical results. It is important to remember that the low number of nine deep incisional SSIs most probably caused the absence of significant risk factors

for this type of infection. Only 5.2% (148 out of 2907 patients) and 3.9% (111 out of 2907 patients) developed a superficial incisional SSI and an organ/space SSI, respectively.

The SSI risk tool is user-friendly and easy to interpret. A presence of a risk factor would add the specific score value to the patient score. One must simply calculate the patient score by adding the values of each of the risk factors present for the patient. The final score varies from 0 to 100 where 0 indicates that the patient does not have any risk factor in the model and where a score of 100 indicates that the patient has all the risk factors included in the model. The final patient score would permit the classification of the patient in one of three groups: low-risk, moderate-risk or high-risk of developing any type of SSI. The decision whether additional or more aggressive prophylactic care (preoperative and intraoperative) is to be administered to the patient should be assessed according to the overall risk-benefit ratio. In general, high-risk patients would receive additional prophylactic SSI care. It is the surgical staff's discretion, according to their expertise, whether additional care is necessary and should be provided to moderate-risk patients. This decision would have important financial and resource utilization implications since the majority of surgical patients (46.2%) have a moderate risk of developing an SSI.

Table XXVII: Frequency distribution representing the number of risk factors of each patient

Number of risk factors	Frequency	Percent	Cumulative %
0	324	11.1	11.1

1	879	30.2	41.4
2	1108	38.1	79.5
3	537	18.5	98
4	54	1.9	99.8
5	5	0.2	100
Total	2907	100	

The SSI risk tool was developed using the logistic regression parameters standardized to a range from zero to one hundred with higher values indicating greater risk of an SSI. Although 324 patients had an SSI risk tool score of zero (Table XXVII), the overall distribution showed important variance with respect to the score value and the number of combination of risk factors. This is an important observation showing that the risk score can adequately summarize the effects of several risk factors and their combination in homogeneous groups of similar SSI risk. It is interesting to note that although 324 patients (11.1%) did not possess any risk factors in the model, only 31.8% (925) patients had a low risk of developing an SSI. The majority of the population was moderate-risk patients who possessed more than one risk factor in the model.

As previously mentioned, we produced an ROC curve to determine the cutoff values for low-risk, moderate-risk and high-risk patients in the development of SSIs. The area under the curve of 0.660, though not ideal, still confirms the validity of the model. The sensitivity and specificity of the curve are 75.5% and 49.8%, respectively, signifying that 75.5% of

the positives are true positives and 50.2% of the negatives are true negatives. Also, the two cutoff values that were determined are as follows: 43.17 and 63.40. Therefore, a patient with a score below 43.17 is considered a low-risk patient, between 43.17 and 63.399 is considered a moderate-risk patient and above 63.40 is considered a high-risk patient.

The increase from the first to the third category is similar in all three SSI types. Approximately the same percentage of high-risk patients develop superficial incisional and organ/space SSIs even though the odds ratio are quite different. High-risk patients have an OR of 4.394 ($p<0.001$, 95% CI= 2.579-7.488) for superficial incisional SSI development whereas the same category of patients have an OR of 11.114 ($p<0.001$, 95% CI= 5.005-24.677) for organ/space SSI. This can be explained by the higher incidence of superficial incisional SSIs.

Concerning low-risk and moderate-risk patients, higher proportions can be found in the superficial incisional SSI graph compared to the amount of low-risk and moderate-risk patients who develop an organ/space SSI. Two percent of low-risk patients develop a superficial incisional SSI whereas less than 1% of the low-risk patients develop an organ/space SSI. Similarly, nearly 6% patients and approximately 4.5% of moderate-risk patients acquire a superficial incisional SSI and an organ/space SSI, respectively. Even though patients have higher ORs in the development of organ/space SSIs, higher percentages can be found on the superficial incisional SSI graphs since these infections are the most common type of SSI.

The results of the study agree in general with the scientific literature, although some risk factors evaluated in this project were not previously assessed. Some of these risk factors include inpatient status and partial or total dependence for everyday activities prior to surgery. On the other hand, certain risk factors known to independently predict SSIs were not found to be significant in this study, for example, diabetes mellitus, BMI, tobacco use, alcohol abuse, COPD and ASA score. Case-mix and patient profile differences between studies and patient populations may explain this. Even though this project included nearly 3000 patients, a larger population will be required to validate these findings and the SSI scoring tool. The strengths of the study include the following: the NSQIP database analysis is prospective, non-biased and comprehensive. Consequently, selection bias is eliminated. The only disadvantage is the generalization of patients. Overall, we can state that NSQIP is a valid database which eliminates many types of biases and constitutes a very appropriate choice for this project. This can be observed in the results of this study. For example, since the majority of the significant risk factors in the logistic regression results were present for all three categories (any type of SSI, superficial incisional and organ/space SSI) and simply by observing the relative increase in the incidence of SSIs between specific risk group, we can conclude that our results are internally valid.

VI. Final Conclusion and Summary

Surgical site infections are one of the most common complications following surgery. Due to the increasing emergence of resistant bacteria and since currently available antibiotics are becoming less effective against these microorganisms, more attention should be provided preoperatively and intraoperatively to prevent SSIs rather than focusing on postoperative treatments.

The SSI risk tool developed in this study using the JGH patient population is a valid first version of a tool that, through further research and validation, can be expanded and generalized to other institutions. For instance, the risk factor of inpatient status is a newly presented risk factor in the literature and one of the highest odds ratios in the study (OR= 4.736 lower only to preoperative pneumonia in predisposing patients to an SSI). For the above reasons, inpatient status should be further assessed in a sensitivity analysis to establish if it is a high predisposing risk factor in the development of SSIs.

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11.3 Appendix 3: Description of Variables Assessed

Variable	Definition
Age	Age of patient with patients over 89 coded as 90. No patients under 15 were included.
Gender	• Male; • Female.
BMI	Calculated from the patient's height and weight as follows: BMI = (Weight / Height^2) x 703.
Race	• American Indian or Alaska Native; • Asian; • Black or African American; • Native Hawaiian or Pacific Islander; • Unknown/ Not reported; • White.
Hispanic Race	• Yes; • No.
In/Outpatient Status	Hospital's definition of inpatient and outpatient status. • Inpatient; • Outpatient.
Transfer/ Origin Status	Patient's transfer status which includes the following options: • Not transferred, admitted directly from home; • Acute care hospital (inpatients); • Nursing home/ chronic care facility/ intermediate care unit; • Transfer from other; • Transfer from outside Emergency Department.
Principal Anesthesia Technique	Principal anesthesia administered during the principal operative procedure, as reported by the anesthesia provider. • General; • Epidural; • Spinal; • Regional; • Local; • Monitored Anesthesia Care (MAC); • Other; • None.

Variable	Definition
Surgical Specialty	Surgical specialty area that best characterizes the principal operative procedure. If a surgeon is privileged to perform cases within multiple specialties (regardless of board certification), the service line/ specialty most closely related to the principal operative procedure was assigned. • Cardiac surgery; • General surgery; • Gynecologic surgery; • Neurosurgery; • Orthopedic surgery; • Otolaryngology (ENT) surgery; • Plastic surgery; • Thoracic surgery; • Urologic surgery; • Vascular surgery; • Interventional radiology.
Diabetes Mellitus with Oral Agents or Insulin	• No diabetes or diabetes controlled by diet alone; • Diabetes requiring therapy with a non-insulin anti-diabetic agent; • Diabetes requiring daily insulin therapy. ○ If a patient required non-insulin and insulin therapy, he/she was to be assigned the insulin classification.
Current Smoker within One Year (Cigarette Use Only)	Current smoking in the year prior to admission for surgery. Patients who smoked cigars or pipes, used chewing tobacco or smoked mechanical/ electronic cigarettes were not included.
Dyspnea within the 30 Days prior to Surgery	Dyspnea may have been symptomatic of numerous disorders that interfered with adequate ventilation or perfusion of the blood with oxygen and was defined as difficult, painful or labored breathing. The intent of this variable was to capture the usual or typical level of dyspnea (patient's baseline) within the 30 days prior to surgery. The intent was not to include patients solely because of an acute respiratory condition leading to intubation prior to surgery, but rather to reflect a chronic disease state. The patients' dyspnea status when they were in their usual state of health, prior to the onset of acute illness, within the 30 days prior to surgery, was characterized:

Variable	Definition
	• No dyspnea; • Dyspnea upon moderate exertion (for example was unable to climb one flight of stairs without shortness of breath); • Dyspnea at rest (for example could not complete a sentence without needing to take a breath).
Functional Health Status within the 30 Days prior to Surgery	This variable focused on the patient's abilities to perform activities of daily living (ADLs) in the 30 days prior to surgery. ADLs were defined as the activities usually performed in the course of a normal day in a person's life. ADLs include bathing, feeding, dressing, toileting and mobility. The best functional status demonstrated by the patient within the 30 days prior to surgery was reported. • Independent: the patient does not require assistance from another person for any activities of daily living. This includes a person who is able to function independently with prosthetics, equipment, or devices; • Partially dependent: The patient requires some assistance from another person for activities of daily living. This includes a person who utilizes prosthetics, equipment, or devices but still requires some assistance from another person for daily activities; • Totally dependent: The patient requires total assistance for all activities of daily living.
Ventilator Dependence at Any Time during the 48 Hours Preceding Surgery	This does not include the treatment of sleep apnea with Continuous Positive Airway Pressure.
History of Severe Chronic Obstructive Pulmonary Disease (COPD)	Emphysema and/or chronic bronchitis/ bronchiectasis/ bronchiolitis obliterans organizing pneumonia is a progressive disease that increases difficulty in breathing. The medical record was to confirm a historical or current diagnosis of COPD and at least one of the following within 30 days prior to the principal operative procedure or at the time the patient is being considered as a candidate for surgery: • Functional disability from COPD; • Requires chronic bronchodilator therapy with oral or inhaled agents or other medication specifically targeted to this disease;

Variable	Definition
	• Hospitalization in the past for treatment of COPD; • A forced expiratory volume-1 (FEV1) of < 75% of predicted on a prior pulmonary function test.
Ascites within 30 Days prior to Surgery	The presence of fluid accumulation in the peritoneal cavity noted on physical examination, abdominal ultrasound, or abdominal CT/ MRI within 30 days prior to the operation.
Congestive Heart Failure within 30 Days prior to Surgery	Congestive heart failure (CHF) is the inability of the heart to pump a sufficient quantity of blood to meet the metabolic needs of the body or can do so only at increased ventricular filling pressure. Only newly diagnosed CHF within the previous 30 days or a diagnosis of chronic CHF with new signs or symptoms in the 30 days prior to surgery fulfilled this definition. Common manifestations are: abnormal limitation in exercise tolerance due to dyspnea or fatigue; orthopnea (dyspnea on lying supine); paroxysmal nocturnal dyspnea; increased jugular venous pressure; pulmonary rates on physical examination; cardiomegaly; pulmonary vascular engorgement; pulmonary edema.
Hypertension Requiring Medication within 30 Days of Surgery	Hypertension was defined as blood pressure of 140/ 90 mmHg or above most of the time. The diagnosis of hypertension must have been documented in the patient's medical record and the condition was severe enough that it required antihypertensive medication within 30 days prior to the principal operative procedure or at the time the patient was being considered as a candidate for surgery. The patient must have been receiving or required long-term treatment of chronic hypertension for > 2 weeks.
Acute Renal Failure	The patient must have met one of the following (A or B) scenarios within 24 hours of the operation: A: An increase in BUN based on two measurements and two creatinine results above 3 mg/dL. There must have been two measurements per laboratory value, the most recent of which was to be within 24 hours prior to surgery; the second was to be within 90 days of surgery. B: The surgeon or attending physician documented acute renal failure in the medical record and the patient demonstrated one of the following: • An increase in BUN based on at least two measurements, the most recent which was to be within 24 hours prior to surgery and the second was to be within 90 days prior to surgery and one

Variable	Definition
	creatinine above 3 mg/dL, which was to be within 24 hours of the operation; • Two creatinine results above 3 mg/dL, the most recent of which was to be within 24 hours of surgery, the second was to be within 90 days of surgery and one abnormal BUN (based on each hospital's reference range for BUN), which was to be within 24 hours of surgery.
Currently Requiring or on Dialysis	The patient had acute or chronic renal failure requiring treatment with peritoneal dialysis, hemodialysis, hemofiltration, hemodiafiltration or ultrafiltration within 2 weeks prior to the principal operative procedure.
Disseminated Cancer	The patient must have primary cancer that has metastasized or disseminated to a major organ and met at least one of the following criteria within one year of surgery: • The patient received or was indicated to receive active treatment for the cancer; • The case was deemed untreatable.
Open Wound (with or without Infection)	Breach in the integrity of the skin or separation of skin edges and included open surgical wounds, with or without cellulitis or purulent exudate.
Steroid Use for a Chronic Condition in the 30 Days prior to Surgery	The patient had required the regular administration of oral or parenteral corticosteroid use medications or immunosuppressant medications within 30 days of surgery or at the time the patient was being considered as a candidate for surgery for a chronic medical condition.
Decrease of more than 10% in Body Weight within 6 Months of Surgery	Intentional weight loss as part of a weight reduction program was excluded.
Bleeding Disorder	Any chronic, persistent, active condition that placed the patient at risk for excessive bleeding.
Red Blood Cell Preoperative Transfusion	Preoperative loss of blood necessitating any transfusion (minimum of 1 unit) of whole blood/ packed red cells transfused during the 72 hours prior to surgery, including any blood transfused in the emergency room.
Sepsis within 48 Hours prior to Surgery	Including systemic inflammatory response syndrome (SIRS), sepsis and septic shock.

Variable	Definition
	• SIRS was diagnosed by the presence of two or more of the following criteria: temperature > 38°C or < 36°C; heart rate > 90 bpm; respiratory rate > 20 breaths/ minute or $PaCO_2$ < 32 mmHg (< 4.3 kPA); white blood cell count > 12,000 cells/mm^3, < 4,000 cells/mm^3 or > 10% immature (band) forms; anion gap acidosis; • Sepsis is defined as the systemic response to infection and was diagnosed by the presence of SIRS with one of the following criteria: positive blood culture or clinical documentation of purulence or positive culture from any site of sepsis; suspected pre-operative clinical condition of infection or bowel infarction which led to surgery; • Septic shock was diagnosis by the presence of sepsis and documented organ and/or circulatory dysfunction.
Emergent Case	An emergency case was usually performed within a short interval of time between patient diagnosis or the onset of related preoperative symptomatology. It was implied that the patient's well-being and outcome was potentially threatened by unnecessary delay and the patient's status could have deteriorated unpredictably or rapidly.
Elective Case	Patient is brought to the hospital or facility for a scheduled (elective) surgery from their home or normal living situation on the day that the procedure was performed.
Wound Classification	Wound classification was assigned based on the primary principal procedure performed. • Clean: an uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered; • Clean/ contaminated: an operative wound in which the respiratory, alimentary, genital or urinary tracts are entered under controlled conditions and without unusual contamination; • Contaminated: open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered including necrotic

Variable	Definition
	tissue without evidence of purulent drainage are included in this category; • Dirty/ infected: old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera.
American Society of Anesthesiology (ASA) Classification	The American Society of Anesthesiology (ASA) Physical Status Classification of the patient's present physical condition on a scale from 1-5 as it appears on the anesthesia record: • ASA 1: normal healthy patient; • ASA 2: patient with systemic disease; • ASA 3: patient with severe systemic disease; • ASA 4: patient with severe systemic disease that is a constant threat to life; • ASA 5: moribund patient who is not expected to survive without the operation
Operative Times	Procedure duration > 3 hours.
Other Procedure	Additional operative procedure performed by the same surgical team under the same anesthetic.
Concurrent Procedure	Additional operative procedure performed by a different surgical team under the same anesthetic.
Discharge Destination	• Skilled care, not home; • Unskilled facility, not home; • Facility which was home; • Home; • Separate acute care; • Rehabilitation center.

11.4 Appendix 4: Final JSS-SSI Risk Scoring Tool Patient-Level Assessment

Risk Factor	SSI Score based on Yes/ No Assessment. If 'Yes' Answered, Add Point Value Below	SSI Risk Classification
Discharge destination: facility, acute care center, rehab center or other	+16	Low: 0-42 points Moderate: 43-58 points High: 59-100 points
Surgery duration >3 hours	+19	
Inpatient prior to surgery	+24	
General, gynecologic, ENT, thoracic, urologic surgery	+22	
Class III contaminated or Class IV dirty/ infected wound class	+19	
Individualized Patient Assessment	Score	Low/ moderate/ high risk

Example: Patient is an outpatient who will undergo a general surgery planned to last 4 hours. The patient presents with a class II clean-contaminated wound and is to return home following discharge.

Risk Factor	SSI Score based on Yes/ No Assessment. If 'Yes' Answered, Add Point Value Below	SSI Risk Classification
Discharge destination: facility, acute care center, rehab center or other	0	Low: 0-42 points Moderate: 43-58 points High: 59-100 points
Surgery duration >3 hours	+19	
Inpatient prior to surgery	0	
General, gynecologic, ENT, thoracic, urologic surgery	+22	
Class III contaminated or Class IV dirty/ infected wound class	0	
Individualized Patient Assessment	**41**	**Low risk**