University of KwaZulu-Natal

Surgical site infections at a quaternary South African Hospital – Epidemiology and impact on healthcare resources

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ABSTRACT

Background: Studies focused on the epidemiology of surgical site infection (SSI) and its impact on healthcare resource utilisation in resource-constrained African settings are rare. This information is important for two reasons: 1) It facilitates the development of setting-specific risk stratification tools for identifying patients who might benefit from additional preventative interventions, and 2) It can guide public health specialists' decisions around resource and budget allocations to surgical units and the degree to which this can be optimised through SSI prevention. The research comprising this PhD thesis sought to address these gaps in the knowledge.

Methodology: This research is comprised of five stand-alone analyses involving surgical patient data obtained from a South African quaternary hospital. The data was collected through patient medical chart review, as well as accessing the hospital's and service laboratory's administrative systems. Study designs used in this research include cohort, trend analysis, geospatial analysis, case-control, and prognostic study designs.

Results: The incidence of SSI in high-risk laparotomy patients was 16.6%. Risk factors for SSI in this group included infectious indication for surgery, preoperative non-steroidal anti-inflammatory use, preoperative hypoalbuminemia, Bogota bag use, and perioperative blood transfusion. A 10-year trend analysis of all surgeries performed at the hospital found no change in admissions for post-discharge SSI. Mortality in elderly SSI admissions declined. The geospatial analysis found that most post-discharge SSI admissions originated from urban areas. Analysis of the laparotomy dataset showed that SSI resulted in an additional 1.06 days of hospitalisation (additional cost of ZAR8900/ $1180), but only in patients who already had short hospital stays. While preoperative hypoalbuminemia demonstrates a similar prognostic performance to the more complex SENIC/NNIS risk stratification methods (C-statistic 0.677 versus 0.652/0.634), preoperative serum sodium is unlikely to have the same prognostic utility.

Conclusions: SSI is common among South African patients undergoing high-risk surgery. A setting-specific, multifactorial risk stratification tool might be of benefit in this population. Inpatient and post-discharge SSIs contribute to unnecessary healthcare utilisation a expenditure in this resource-constrained setting. There is also great potential for certain routine preoperative laboratory tests to be used as simple, cost-effective SSI risk stratification tools in African settings.

Isizinda: Ucwaningo lugxile ekwakhiwenisimo sendawo ehlinziwe yokutheleleka (SSI) nomthelela wakho wokusetshenziswa komthombo wokunakekela ngokokwelapha ezizindeni esivaleleke e-Afrika nokungavamile. Lolu lwazi lubalulekile ngezizathu ezimbili: 1) Kusebenzisa intuthuko yamathuluzi okuchaza ingcuphe egxile esizindeni esiqondile sokuhlonza iziguli ezingazuza emizamweni eyongeziwe yokuvimbela, nokuthi 2) ingahola izinqumo zongoti bezempilo yomphakathi ngomthombo nokwabiwa kwezimali kuya ezikhungweni zokuhlinzwa kanye nezinga lapho enganyuswa khona ngokuvimbela nge-SSI. Ucwaningo okusekelwe kuyo le PhD kuhloswe ngalo ukubhekana nalezi zikhala olwazini.

Indlelakwenza: Lolu cwaningo lunohlaziyo oluyisihlanu oluzimele olufaka imininingo yesigulo esihlinziwe olutholakele esibhedlela esisezingeni lesine. Imininingo iqoqwe ngokubuyekeza ishathi lokwelapha lesiguli, kanjalo nokufinyelela ezinhlelweni zesibhedlela kanjalo nezinsiza zaselabhorethri. Uhlelosakhiwo locwaningo olusetshenziswe kulolu cwaningo lufaka ikhohothi, ukuhlaziya okwenziwa kuleso sikhathi, ukuhlaziya umumomhlaba, ukulawula ucwaningonto, nohlelosakhiwo locwaningo oluyinhlonzasifo.

Imiphumela: Ukwenzeka kwe-SSI ezigulini ezisengcupheni yelapharathomi ingama-16.6%. Izizathu zengcuphe ze-SSI kuleli qembu elifakwe izinkomba zokutheleleka, isidambisikuvuvukala okunganasteroydi angesikhathi sokuhlinzwa. Ukuhlaziya okwenzeka eminyakeni eyi-10 kokuhlinza okwenziwa esibhedlela akutholanga shintsho ekungenisweni esibhedlela emva kokukhishwa. Ukufa kwabadala ekufakweni esibhedlela nge-SSI kusukela ezindaweni zasemadolobheni. Ukuhlaziya kwedathasethi yelapharothomi ikhombise ukuthi i-SSI inomphumela wezinsuku ezi-1.06 ezongeziwe zokulaliswa esibhedlela (izindleko ezongeziwe zama-ZAR8900/$1180), kodwa yiziguli esezike zahlala kafushane esibhedlela. Ngesikhathi i-hypoalbuminemia ngaphambi kokuhlinzwa ikhombisa ukusebenza kokuhlonzwa kwesifo ezindlelenikwenza zokuchaza ingcuphe eyinkimbi ye-SENIC/NNIS (istathistikhi i-C0677 uma siqhathaniswa ne-0.652/0.634), isiramu yesodiyamu yangaphambi kokuhlinzwa okungenzeka ibe nenhlonzasifo efanayo.

Iziphetho: I-SSI ivamile ezigulini zaseNingizimu Afrika ezisezingcupheni ezinkulu. Isizinda esiqondile, ithuluzi lokucacisa ingcuphe enezizathu eziningi zokuzuza eqoqwenibantu. Iziguli ezelashelwa esibhedlela nama-SSI emva kokukhishwa esibhedlela kufaka ukusetshenziswa kokunakekelwa ngokwezempilo nokusetshenziswa kulesi sizinda esincishelwe yimithombo. Kuphinde kube nokukwazi okusezingeni ngokwezivivinyo ezilungiswe ngaphambi kwesikhathi elabhorethri ukuba zisetshenziswe, njengamathuluzi alula, nashibhile okuchaza ingcuphe yama-SSI ezizindeni zase-Afrika.

ATTESTATION

I declare that:

- (i) The research reported in this thesis is my original research.
- (ii) This thesis has not been submitted for any degree or examination at any other university.
- (iii) This thesis does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.
- (iv) This thesis does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then their words have been re-written but the general information attributed to them has been referenced.
- (v) This thesis does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the thesis and in the References section.

My contribution to each manuscript includes:

- (a) Conception or design of the work; and the acquisition, analysis, and interpretation of data for the work.
- (b) Drafting the work or revising it critically for important intellectual content.
- (c) Final approval of the version to be published.

Student's signature: [redacted] **Date:** 5 July 2021

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LIST OF ABBREVIATIONS

Abstract

NNIS	National Nosocomial Infections Surveillance
SENIC	Study of the Efficacy of Nosocomial Infection Control
SSI	Surgical site infection
ZAR	South African Rands

Chapter 1: Literature review

ASA	American Society of Anesthesiologists
ASOS	African Surgical Outcomes Study
CDC	Centers for Disease Control
HDI	Human development index
HIC	High-income country
ISOS	International Surgical Outcomes Study
LMIC	Low- and middle-income country
LoS	Length of stay
NNIS	National Nosocomial Infections Surveillance System
SENIC	Study on the Efficacy of Nosocomial Infection Control
SSI	Surgical site infection
WHO	World Health Organisation

Chapter 2: Introduction

SASOS	South African Surgical Outcomes Study
SSI	Surgical site infection

Chapter 3: Incidence of surgical site infection and associated risk factors in patients undergoing high-risk surgery at a South African quaternary hospital

95%CI	95% confidence interval
ASOS	The African Surgical Outcomes Study
CDC	The Centers for Disease Control
ISOS	International Surgical Outcomes Study
OR	Odds ratio
SPSS	Statistical Package for the Social Sciences
SSI	Surgical site infection

Chapter 4: The impact of surgical site infection on healthcare utilisation and healthcare expenditure at a South African quaternary hospital

95%CI	95% confidence interval
ASOS	African Surgical Outcomes Study
ENT	Ear, nose, and throat
IALCH	Inkosi Albert Luthuli Central Hospital
ICD-10	International Classification of Disease 10th Revision
IQR	Interquartile range
LoS	Length of stay
SPSS	Statistical Package for the Social Sciences
SSI	Surgical site infection
WHO	World Health Organisation
ZAR	South African Rands

Chapter 5: Prognostic relevance of routinely performed laboratory tests for surgical site infection in a South African setting

95%CI	95% confidence interval
ASA	American Society of Anesthesiologists
CDC	Centers for Disease Control
IALCH	Inkosi Albert Luthuli Central Hospital
IQR	Interquartile range
KS	Kolmogorov-Smirnov
NHLS	National Health Laboratory Service
NNIS	National Nosocomial Infections Surveillance
NPV	Negative predictive value
PPV	Positive predictive value
OR	Odds ratios
SANAS	South African National Accreditation System
SD	Standard deviation
SENIC	Study of the Efficacy of Nosocomial Infection Control
SSI	Surgical site infection
ROC	Receiver-operator-characteristic
WHO	World Health Organisation

Chapter 6: Conclusions

NNIS	National Nosocomial Infections Surveillance
SSI	Surgical site infection
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LIST OF MANUSCRIPTS

#	**Manuscript title**	**Page**
1	Naidoo N, Madiba TE, Moodley Y. Incidence and risk factors for surgical site infection following laparotomy at a South African quaternary hospital. Surg Chron. 2019;24(4):179-184.	38
2	Naidoo N, Madiba TE, Moodley Y. Admissions for post-discharge surgical site infection at a quaternary South African public sector hospital. S Afr J Surg. 2019;57(4):13-17.	57
3	Naidoo N, Madiba TE, Moodley Y. Impact of surgical site infection on postoperative length of stay and hospitalization costs at a quaternary South African hospital. Surg Chron. 2020; 25(4):311-314.	73
4	Naidoo N, Madiba TE, Moodley Y. A comparison of preoperative hypoalbuminaemia with the NNIS and SENIC risk scores for the prediction of surgical site infection in a South African setting. The Journal of Medical Laboratory Science & Technology South Africa 2020;2(1):36-40.	88
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Chapter 1

Literature review

1.1 Nosocomial infections

Over 200 million people worldwide undergo surgical procedures each year.[1] Inevitably, a proportion of these surgical patients will suffer a complication shortly after their procedure. Nosocomial infections, also referred to as healthcare-associated infections, are "infections occurring in patients during the process of care in a hospital or other health care facility which were not present or incubating at the time of admission to that health facility".[2] Nosocomial infections are amongst the most frequently encountered complications in hospitalised patients, affecting 5-15% of patients admitted to general wards and up to 51% of patients admitted to critical care units.[3, 4] As shown in Figure 1, the most common sites of nosocomial infection are the urinary tract, surgical wounds, the lung, and the bloodstream.[5]

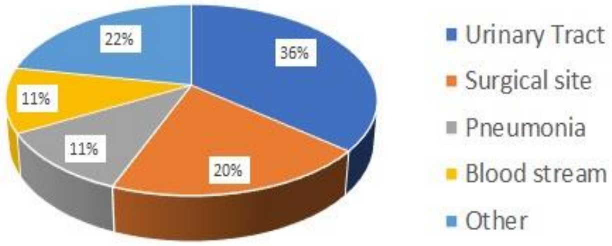

Figure 1. Common sites of nosocomial infection*
*Adapted from: McFee (2009)[5]

Most of the robust data on nosocomial infections come from high-income settings such as the United States or Europe. Mortality from nosocomial infection can be high, particularly in patients admitted to critical care units. It is estimated that, in the United States alone, 1.7 million patients suffer from nosocomial infections each year, of which 99000 will die.[5] A study of data from England reported that 22800 patients died from nosocomial infections during 2016/2017.[6] Furthermore, in Europe there are an estimated 45 million nosocomial infections annually, with 37000 deaths attributed to nosocomial infections every year. [7] Nosocomial infections are also a significant economic burden, costing healthcare systems between $17 billion and $20 billion annually in the United States.[5]

In the European Union, the annual economic burden of nosocomial infections amounts to €7 billion.[7] Thus, the prevention of infectious complications in hospitalised patients has implications for patient outcomes and healthcare expenditure.

1.2 Definition of surgical site infection

Surgical site infections (SSIs) are the most important infectious complications in surgical patients. As per Table I, The Centers for Disease Control (CDC) define SSIs as infections associated with a surgical incision which occur within 30 days of surgery, where surgery does not involve the insertion of implant devices, or within one year in the case of surgery involving the insertion of implant devices.[8]

Table I. Criteria for defining SSIs*

Superficial Incisional SSI	Infection occurs within 30 days after the operation *and* infection involves only skin or subcutaneous tissue of the incision *and* at least *one* of the following: 1. Purulent drainage, with or without laboratory confirmation, from the superficial incision. 2. Organisms isolated from an aseptically obtained culture/fluid/tissue from superficial incision. 3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat *and* superficial incision is deliberately opened by surgeon, *unless* incision is culture-negative. 4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.
Deep Incisional SSI	Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation *and* infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision *and* at least *one* of the following: 1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site. 2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative. 3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination. 4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.
Organ Space SSI	Infection occurs within 30 days after the operation if no implant† is left in place or within 1 year if implant is in place and the infection appears to be related to the operation *and* infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation *and* at least *one* of the following: 1. Purulent drainage from a drain that is placed through a stab wound‡ into the organ/space. 2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space. 3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination. 4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

*From: Mangram et al., (1999)[8]

The CDC further stratifies SSIs into three categories (Superficial, deep incisional, or organ space) according to the extent of the infection in relation to the level of the skin. This is outlined in Figure 2.[8]

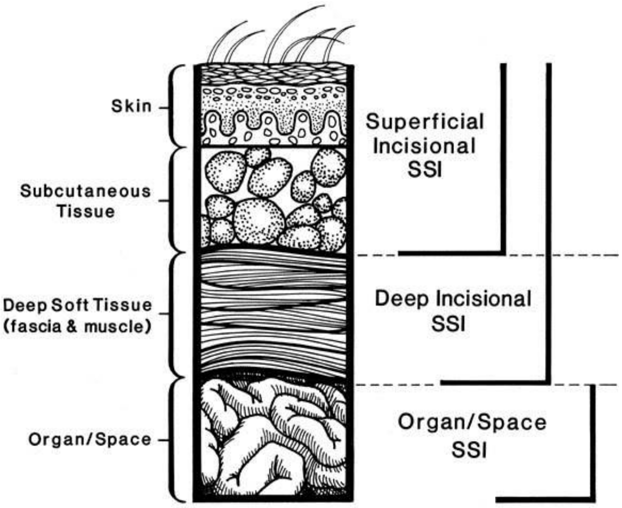

Figure 2. Categorisation of SSI*
*From: Mangram et al., (1999)[8]

1.3 Incidence of surgical site infection

1.3.1 Incidence when compared with other nosocomial infections

It is estimated that SSI accounts for up to 20% of all healthcare-associated infections.[5, 9] While SSIs account for one-fifth of all nosocomial infections amongst combined medical and surgical patient populations, they account for 38% of all nosocomial infections in surgical patient populations.[10]

1.3.2 Incidence according to the extent of infection

The International Surgical Outcomes Study (ISOS) found that SSI incidence differs according to the extent of infection, with superficial infection being the most common (incidence: 2.9%), followed by deep-incisional (incidence: 1.3%), and organ-space (incidence: 0.8%) infection.[11] A collaborative multinational cohort study of postoperative outcomes in several African countries, the African Surgical Outcomes Study (ASOS), also reported superficial infection to be the most common SSI (incidence: 3.5%), followed by deep-incisional (incidence: 0.7%), and organ-space SSI (incidence: 0.2%) infection.[12]

1.3.3 Incidence according to geographic locale

The incidence of SSI varies by geographic locale. A 2014 systematic review by Fan et al., summarised the incidence of SSI in various countries around the world, although this did not include South Africa.[13] Figure 3 presents the findings of this review.

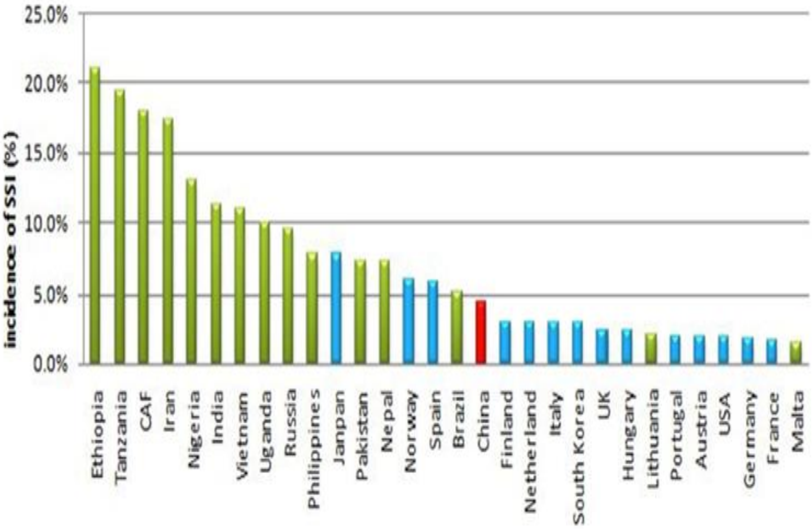

Figure 3. Incidence of SSI by country*
*From: Fan et al., (2014)[13]

The 2014 systematic review by Fan et al., reported that the incidence of SSI was highest in sub-Saharan African countries, ranging from 10% in Uganda to over 20% in Ethiopia.[13] This is much higher than the reported incidence of <5% in high-income countries.[13] ASOS reported the rate of SSI in African settings to range between 0.2% and 3.5%.[12] A potential explanation for the discrepancy in SSI incidence in African settings reported in ASOS and the review of Fan et al., was that the ASOS study did not include post-discharge SSI, while some of the studies included in the review conducted by Fan et al., measured SSI incidence up to 30 days postoperatively.[12, 13]

A global observational study of SSI outcomes following abdominal surgery, the GlobalSurg-2 study, reported the 30-day postoperative incidence of SSI to be 12.3%.[14] The inpatient SSI incidence was estimated at only 6.7%, highlighting the fact that almost half of all SSIs reported at 30 days following surgery were post-discharge SSIs. Furthermore, the GlobalSurg-2 study showed that the incidence of SSI appeared to be inversely related to human development index (HDI), with the incidence of SSI in high-HDI countries estimated at 9.4%, middle-HDI countries estimated at 14.0%, and low-HDI countries estimated at 23.2%.[14] Lastly, ISOS estimated the crude incidence of SSI in elective surgery patients from 27 low-, middle-, and high-income countries at 5%.[11]

1.3.4 Incidence according to surgical specialty

A systematic review of the published literature conducted by Korol et al., summarised the median incidence of SSI by surgical specialty.[15] The review reported tumour-related surgery to be associated with the highest incidence of SSI (Median incidence: 17.0%), followed by transplant surgery (Median incidence: 6.8%), neurosurgery (Median incidence: 4.2%), gastric surgery (Median incidence: 4.0%), cardiothoracic surgery (Median incidence: 2.8%), and orthopaedic surgery (Median incidence: 2.7%). The median incidence of SSI was lowest in mixed surgical populations (1.9%).[15] It is possible that the difference in SSI incidence between the various surgical specialties is a reflection of the differing SSI risk factor burden (including procedural risk) amongst the patients in these different surgical specialties.

1.4. Pathophysiology of surgical site infection

1.4.1 Impaired wound healing and wound dehiscence

The skin, considered a component of the innate immunity, is an initial defence mechanism against microorganisms. It serves as physical barrier, preventing colonisation of the underlying tissues by microorganisms which can originate either from the patients themselves (i.e. commensal microorganisms on the skin or those from the gastrointestinal tract) or from the environment (i.e. surgical staff or surgical equipment).[16, 17] When the integrity of the intact skin is compromised through surgical insult, the underlying tissues become susceptible to microbial colonisation.[16, 17]

The initial process of wound healing occurs when the surgical site is infiltrated by leukocytes, such as macrophages, in response to the surgical insult.[18] These immune cells debride the wound, dispose of microbes in the wound, and release cytokines at the site of surgical incision which promote recruitment and differentiation of mesenchymal cells to collagen-producing fibroblasts. Apart from its structural function within wounds, collagen stimulates cellular migration and contributes to new tissue development.[18] Given that the final step of wound healing is dependent on the preceding steps, any disruption at the preceding steps will inevitably lead to impaired wound healing. In turn, closure of the surgical wound is delayed, during which time the wound surface is susceptible to colonization by microorganisms. Although immune cells play a crucial role in promoting wound healing, their actions during an infection can lead to separation of the edges of a surgical incision, commonly known as wound dehiscence. In response to bacterial endotoxins, macrophages release enzymes (such as collagenase) into the wound environment. Collagenase degrades collagen in the wound, leading to structural instability and splitting of the wound edges. This creates an entry point for other microorganisms into the surgical wound.[19]

1.4.2 Immunosuppression

The role that neutrophils play in controlling the bacterial colonisation of surgical wounds must be acknowledged.[20] Clearance of bacterial infections is primarily mediated by these innate immune cells,[21] which comprise up to 80% of the peripheral mononuclear cell buffy coat.[22] They exert their bactericidal action through phagocytosis and the production of reactive oxygen/nitrogen species.[20, 23] During phagocytosis, the neutrophil engulfs bacteria and kills these through intracellular enzyme activity. Reactive oxygen and nitrogen species are bactericidal through the damage they cause to bacterial genetic material. Surgical, anaesthetic, or patient-related factors might interfere with intracellular processes in neutrophils, thereby blunting their function.[19, 24] This would enable early bacterial colonisers to persist and multiply in the surgical wound.

1.4.3 Hypoxia

Adequate blood supply and oxygenation of the surgical site is crucial for the wound healing process and the bactericidal activity of neutrophils. More specifically, molecular oxygen is required for collagen deposition during wound healing and the production of reactive oxygen species by neutrophils.[18, 23] Inadequate perfusion might cause tissue hypoxia at the surgical site. Hypoxia is influenced by various factors, including comorbidity and intraoperative events such as bleeding.[19] These factors increase vasoconstriction through modulation of the sympathetic nervous system, resulting in reduced oxygen tension at the surgical site.[25]

1.5 Risk factors for surgical site infection

There are various risk factors associated with the development of SSI, broadly grouped as host (patient), surgical, and microbial factors. As shown in Figure 4, there are often interactions between risk factors, hinting at the multifactorial nature of SSI.[26] Interestingly, evidence has shown that risk factors for perioperative outcomes differ in clinical importance between high-income countries (HICs), such as those in Europe and North America, and low- or middle-income countries (LMICs) in Africa.[27, 28] This might also hold true for SSI, but while there is sufficient high-quality data on this topic from HICs, the data from LMICs are far less robust and this hinders comparisons between settings.

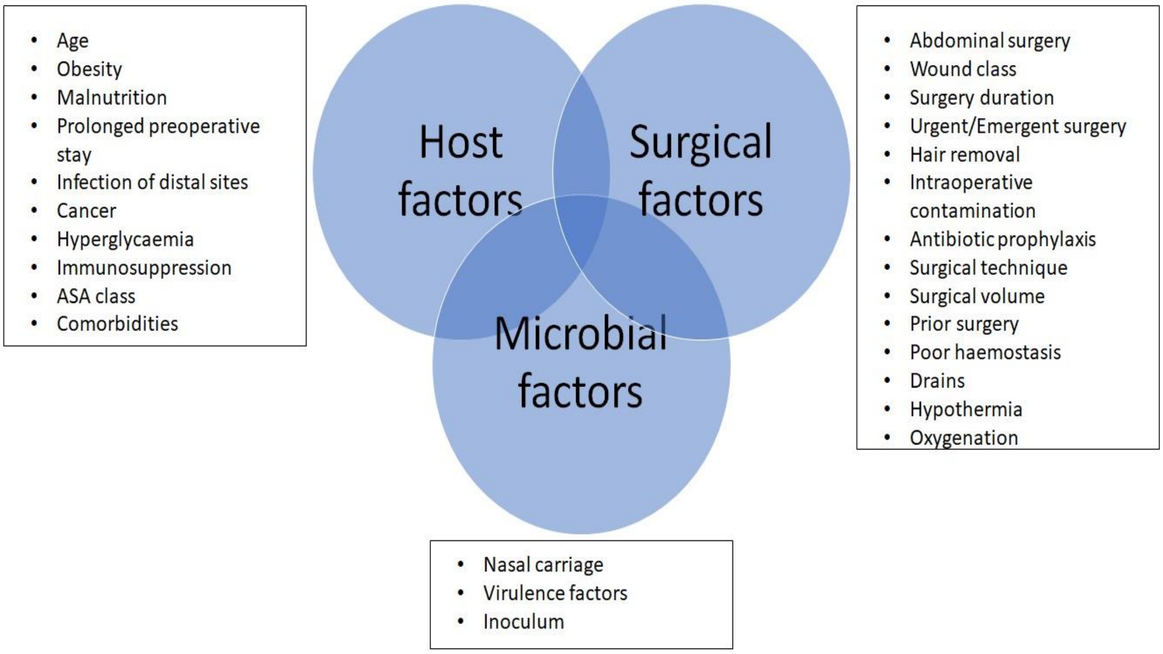

Figure 4. Risk factors for SSI*
Adapted from: Johns Hopkins University (2010)[26]

1.6 Microbiology of surgical site infection

The causative agents of SSI are usually identified through microbiological culture techniques, which involves seeding microbiological growth media with pus or tissue exudate collected from surgical wounds suspected of being infected, and incubating these between 25-45°C for several days.[29, 30] Antimicrobial therapy resistance testing can also be performed on bacteria isolated from pure cultures.[30] This information improves clinicians' decision-making around antimicrobial therapy in patients with SSI.

There are some instances when microbiological culture fails to yield a medically significant organism after several days, a result also referred to as "culture-negative" result.[31] This might be a result of a slow growing organism or atypical organisms that are not traditionally associated with SSI.[31] However, a culture-negative result in the presence of signs and symptoms suggestive of SSI should not be a reason to delay or withhold antimicrobial chemoprophylaxis in a patient with possible/probable SSI.[8]

Table II presents a list of pathogens commonly isolated from surgical wounds. Bacteria comprise the majority of microorganisms cultured from the pus or tissue exudate collected from infected surgical wounds.[8] Staphylococcal bacterial species are among the most important SSI pathogens.[8] Staphylococcal species (e.g. *Staphylococcus aureus and Staphylococcus epidermidis*) are considered part of the normal flora of the human skin, and usually do not pose a threat when the skin is intact. However, these microorganisms might become pathogenic when introduced through breaks in the skin, as would be the case with a surgical incision.[32] Variants of *S. aureus* which are resistant to the antibiotic methicillin and are associated with increased healthcare resource utilisation, including increased financial costs.[33] Gram-negative bacilli are also important pathogenic bacteria isolated from infected surgical wounds (Table II).[8] This group includes *Escherichia coli*, a bacterium which is part of the normal flora of the human gastrointestinal tract.[34] One would therefore expect that this group of microorganisms would predominate in microbiological cultures of infected surgical wounds in patients who have undergone open abdominal surgery.[8, 35]

Table II. Common pathogens isolated from surgical wounds, by surgical specialty*

Type of operation	**Predominant microorganisms cultured from pus or tissue exudate collected from infected surgical wounds**
Abdominal surgery	Gram-negative bacilli, anaerobes, streptococci
Breast surgery	*Staphylococcus aureus*, coagulase-negative staphylococci
Cardiothoracic surgery	*S. aureus,* coagulase-negative staphylococci
Head and neck surgery	*S. aureus,* coagulase-negative staphylococci
Neurosurgery	*S. aureus,* coagulase-negative staphylococci
Obstetric and gynaecologic surgery	Gram-negative bacilli, enterococci, anaerobes, group B streptococci
Orthopaedic surgery	*S. aureus,* coagulase-negative staphylococci
Vascular surgery	*S. aureus*, *S. epidermidis*, gram-negative bacilli

*Adapted from: Mangram et al., (1999)[8]

1.7 Consequences of surgical site infection

1.7.1. Postoperative mortality

The GlobalSurg-2 Study estimated the worldwide 30-day postoperative mortality of patients with SSI to be 4.7%.[14] When settings were stratified according to HDI, SSI mortality was highest in low HDI countries (4.8%), followed by middle HDI countries (1.6%) and high HDI countries (1.5%).[14] ISOS reported that postoperative mortality in patients with SSI ranged between 1.3% and 7.0%.[36] With regard to African settings, ASOS reported inpatient mortality in patients with SSI to be 5.2% in patients with superficial SSI, 13.1% in patients with deep incisional SSI, and 22.4% in patients with organ space SSI.[12] Superficial SSI, deep incisional SSI, and organ space SSI were present in 2.0%, 3.8%, and 4.8% of all elective surgery patients who died.[12]

Some studies have gone on to demonstrate that SSI is a predictor of postoperative mortality, even after the analyses were adjusted for other factors which are known to be associated with postoperative mortality. An analysis of data from an SSI surveillance network in France found an adjusted 1.6-fold higher odds of postoperative mortality in patients who had SSI.[37] Coello et al., used data from hospitals across England to demonstrate an adjusted 1.8-fold higher odds of mortality in hip surgery patients who had SSI when compared with patients who did not have a SSI.[38] Furthermore, Coello et al., were also able to demonstrate a higher odds of mortality in vascular surgery, large bowel surgery, and hip surgery patients who had a deep-incisional/organ-space SSI when compared to patients who did not have any SSI (Odds ratios of 6.8, 1.8, and 2.5).[38]

1.7.2 Length of hospital stay

The GlobalSurg-2 Study reported a median length of stay (LoS) of just over three times longer for patients with SSI when compared to patients who did not have SSI (7.0 days versus 2.0 days, $p<0.001$).[14] The same study did not, however, present specific LoS data associated with SSI for the different HDI settings. LoS data for patients with and without SSI were not reported in ASOS. However, a systematic review of studies from across the world found that the mean additional LoS in patients with SSI was between 4.9 and 32.2 days longer than for patients who did not have SSI .[39]

1.7.3 Healthcare expenditure

The published literature suggests that there are significantly higher healthcare costs associated with SSI.[39] In mixed surgical populations, patients with SSI incur mean additional healthcare costs ranging between $3859 and $11087 when compared with patients who do not have SSI. In patients undergoing cardiothoracic surgery, there are estimated mean additional healthcare costs of between $7992 and $35354.[39] The mean additional healthcare costs of SSI in orthopaedic surgery patients has been estimated at $20573, while in head and neck cancer surgery patients this is estimated at $18738. Breast surgery patients with SSI are estimated to incur additional healthcare costs of $10897.[39] Unfortunately, published SSI cost data from Africa are lacking, despite their relevance in the resource-constrained healthcare facilities in this region.

1.7.4 Quality of life in afflicted patients

SSIs also impact the overall quality of life in afflicted patients. Important aspects to consider in this respect are physical morbidity and pain from SSI as well as psychological morbidity.[40] Patients may experience severe distress, which can persist for many months following discharge from hospital.[41] In patients who suffer severe physical morbidity, their roles within families might change with them turning from “providers” to requiring assistance with daily activities of living. Family members might be required to take a leave of absence from work to care for patients with SSI once they are discharged from hospital.[40] Thus, SSI can also have implications for the families of afflicted patients.

1.8 Prevention, prediction, and management of surgical site infection

1.8.1 Prevention

The World Health Organisation (WHO) guidelines on SSI prevention provide a comprehensive range of evidence-based recommendations that consider various factors related to the impact of SSI including the global perspective, the balance between benefits and harms, the quality of evidence, cost and resource implications, and patient values and preferences.[42] A summary of these recommendations is provided in Table III.

The WHO strongly advocates for nine recommendations made as part of their SSI prevention guidelines.[42] Surgical patients who are identified as nasal carriers of *S. aureus* should be given 2% intranasal mupirocin, with or without additional chlorhexidine gluconate-based body wash. Mechanical bowel preparation without oral antibiotic therapy is not recommended for adults undergoing elective colorectal surgery.[42] Preoperative hair removal should be avoided, but if this is necessary, hair should be trimmed with a pair of clippers rather than using a razor blade. Antibiotic chemoprophylaxis should be administered in patients without contraindications. Furthermore, antibiotic chemoprophylaxis should be given at least 2 hours prior to surgical incision being made.[42] Preoperative handwashing by surgeons and other operating room staff should be performed using water and antibacterial soap or an alcohol-based hand disinfectant prior to sterile gloves being donned. Preparation of the surgical site should be done using a chlorhexidine gluconate-based antiseptic.[42]

Patients having their procedures performed under general anaesthesia with endotracheal intubation should be given 80% fraction of inspired oxygen intraoperatively, which should be extended 2-6 hours postoperatively if possible. Lastly, the WHO discourages the use of postoperative antibiotic chemoprophylaxis.[42]

Table III. Recommendations for the prevention of SSI*

Recommendation	**Strength of recommendation**	**Level of evidence**
Preoperative showers	Conditional	Moderate
S. aureus decolonisation (nasal and body)	Conditional-strong	Moderate
Extended-spectrum beta-lactamase screening	N/A	Lacking
Preoperative antibiotic prophylaxis (within 2 hours of surgical incision)	Strong	Low-moderate
Mechanical bowel preparation with oral antibiotics (colorectal surgery)	Conditional	Moderate
Remove hair only when necessary	Strong	Moderate
Alcohol-based surgical site preparation	Strong	Low-moderate
Avoid using antimicrobial skin sealants	Conditional	Very low
Surgical hand preparation (hand washing)	Strong	Moderate
Nutritional support	Conditional	Very low
Continuation of immunosuppressive agents during perioperative period	Conditional	Very low
Perioperative supplemental oxygen	Strong	Moderate
Maintaining perioperative normothermia	Conditional	Moderate
Perioperative glucose control	Conditional	Low
Maintaining perioperative normovolemia	Conditional	Low
Drapes and gowns	Conditional	Very low-moderate
Wound protector devices	Conditional	Very low
Incisional wound irrigation (aqueous PVP-I solution before closure, particularly in clean/clean-contaminated wounds; avoid antibiotic incisional wound irrigation).	Conditional	Low
Prophylactic negative pressure wound therapy	Conditional	Low
Surgical gloves	N/A	Lacking
New set of surgical instruments for each surgery	N/A	Lacking
Antimicrobial sutures	Conditional	Moderate
Unnecessary laminar flow ventilation in operating room	Conditional	Very low-low
Unnecessary continuation of surgical antibiotic prophylaxis	Strong	Moderate
Unnecessary use of advanced dressings	Conditional	Low
Avoid antimicrobial prophylaxis in the presence of a drain	Conditional	Low

*Adapted from: World Health Organisation guideline[42]

1.8.2 Prediction

There are two widely used methods for establishing the probability of SSI, namely the Study on the Efficacy of Nosocomial Infection Control (SENIC) score and the National Nosocomial Infections Surveillance System (NNIS) score.[8, 43, 44]

The SENIC score, shown in Figure 5, is comprised of the following variables: abdominal operation, operation lasting >2 hours, a surgical site with a wound classification of either contaminated or dirty/infected, and an operation performed on a patient having 3 or more discharge diagnoses.[8, 44] The SENIC score is unweighted, with each variable allocated a single point. Cumulative point scores for the SENIC score range between 0 points and 4 points, which corresponds to a predicted SSI risk of between <1% and almost 30%.[8, 44]

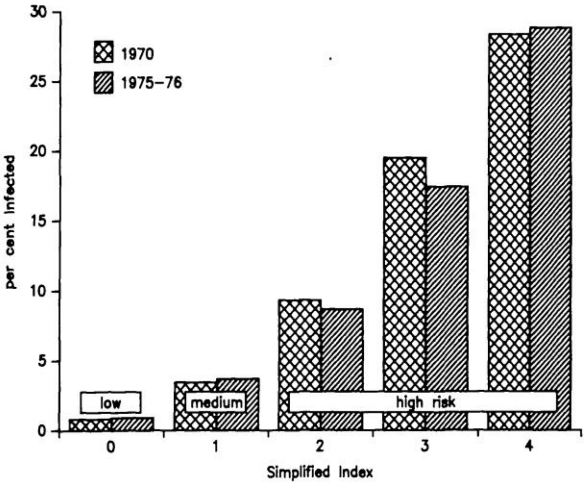

Figure 5. Cumulative SENIC score and predicted risk of SSI
*From: Hayley et al., (1985)[44]

The NNIS score, shown in Figure 6, was developed in the United States during the early 1990's as an improvement over the SENIC score.[45] It is procedure-specific and is most accurate when applied to prospectively collected patient data. It is an unweighted score comprised of three variables - American Society of Anesthesiologists (ASA) Physical Status Classification of >2, either contaminated or dirty/infected wound classification, and length of operation >T hours (where T is the approximate 75th percentile of the duration of the specific operation being performed).[8, 43, 45] One point is allocated for each variable that is present in a patient. Cumulative point scores for the NNIS score range between 0 points and 3 points, which corresponds to a predicted SSI risk of between 1.5% and 13.0%.[45]

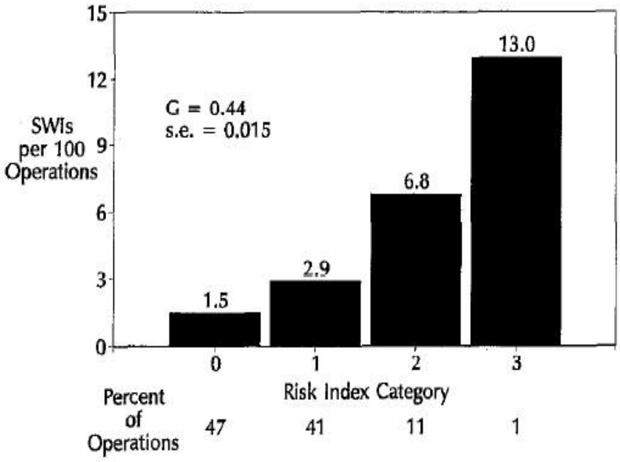

Figure 6. Cumulative NNIS score and predicted risk of SSI
*From: Culver et al., (1991)[45]

The probability of SSI extrapolated from a cumulative NNIS or SENIC score can be used to identify specific high-risk patients, and guide perioperative decision-making around whether additional, resource-intensive preventative strategies are required for SSI risk-reduction strategies in these high-risk patients. While these two scores remain popular, their performance varies between surgical populations in different countries, as well as by surgical specialty. This suggests that adaptations of the SENIC and NNIS scores might be required to improve SSI prediction in certain surgical populations and settings.

Although the SENIC and NNIS scores provide a way forward in terms of SSI prediction, there are several shortcomings with these methods which must be considered. A Turkish study in colorectal surgery patients reported that the predictive performance of the SENIC and NNIS scores were acceptable, but still far from perfect.[46] In fact, when the SENIC and

NNIS scores were “combined” the predictive accuracy achieved was superior when compared with each individual score alone. The authors of the Turkish study also pointed out that there are several factors involved in the development of SSI, some of which may not be included in the SENIC or NNIS scores.[46] This would imply that one would need to recalibrate the SENIC and NNIS scores to the various settings and patient populations in which they will be applied. The potential difference in performance of these risk prediction methods between countries is highlighted by the findings of another study of colorectal surgery patients conducted in the United States.[47] In that research, the NNIS score was found to perform poorly, with a predictive accuracy that was well below the accepted thresholds for prognostic tests.[47] Furthermore, a study involving Brazilian orthopaedic surgical patients also found poor predictive performance of the NNIS when compared with a locally-derived risk prediction model.[48] Other possible shortcomings of the NNIS and SENIC scores are that they require collection of additional data and might be time consuming in resource-limited settings.

1.8.3 Management

A simplified algorithm for the management of SSI is presented in Figure 7.[49]

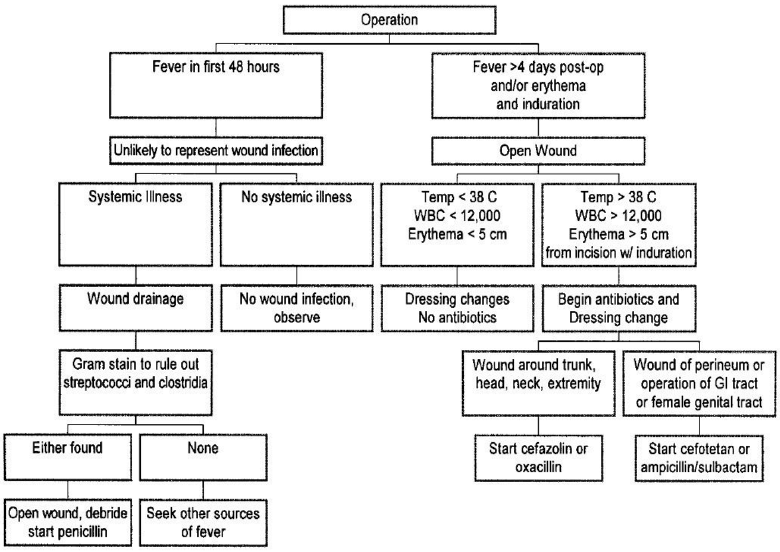

Figure 7. Simplified algorithm for management of SSI*
*From: Nichols et al., (2000)[49]

Briefly, the initial steps of the algorithm involve establishing whether there are any signs or symptoms associated with SSI. This might include examining the surgical wound, and assessing the patient's vital signs and routine laboratory test reports.[49] If a superficial SSI is suspected, based on the findings of this initial assessment, dressing changes with or without oral antibiotic therapy might be warranted. Broad-spectrum antibiotics can be prescribed while the results of the microbiological culture and antimicrobial susceptibility testing are pending. If the results of the antimicrobial susceptibility testing suggest that the causative microorganism is resistant to broad-spectrum antibiotics, antibiotic therapy can be changed to include antibiotics to which the microorganism is susceptible.[49] The site of the infection must be taken into account, as this too can dictate which antibiotics must be administered. Deep-incisional and organ-space infections are likely to be preceded by systemic illness. Furthermore, deep-incisional and organ-space SSIs are more difficult to manage and often require that wounds be surgically opened and debrided, followed by appropriate antibiotic therapy.[49]

1.9 Gap in the literature

There is a wealth of literature from high-income countries which reports on the epidemiology of SSI, its consequences on patient outcomes, healthcare resource utilisation, and methods to predict this common postoperative complication. However, reports on these aspects of SSI from African settings are scarce, and very little robust data exist to improve our understanding of this complication in this resource-constrained setting where intrabdominal sepsis is common, there is a lack of treatment modalities, and a lack of SSI recognition or knowledge thereof. Access to surgical care in Africa has traditionally been limited, but there is a growing commitment to scale up this access by the year 2030.[50] If surgical rates are to increase across Africa, it is likely that SSI will be become an important challenge in this setting. This highlights the need for additional research aimed at improving our understanding of SSI epidemiology, its impact on healthcare resource utilisation (including healthcare expenditure), and preoperative risk stratification approaches in African surgical populations.

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Chapter 2

Introduction

2.1 South Africa's disease profile

South Africa currently faces a quadruple burden of disease. This includes communicable disease conditions, non-communicable disease conditions, maternal-child conditions, and injury from trauma or violence.[1, 2] Although communicable diseases have traditionally accounted for most of the morbidity and mortality in South Africa prior to the early 1990's, a steadily increasing burden of non-communicable disease conditions has heralded the beginning of an epidemiological transition in the country.[2] As evidenced by the attributed mortality rates in Figure 1, this increasing trend in non-communicable conditions is most profound in the black African population group, who constitute the majority of the South African population.[2]

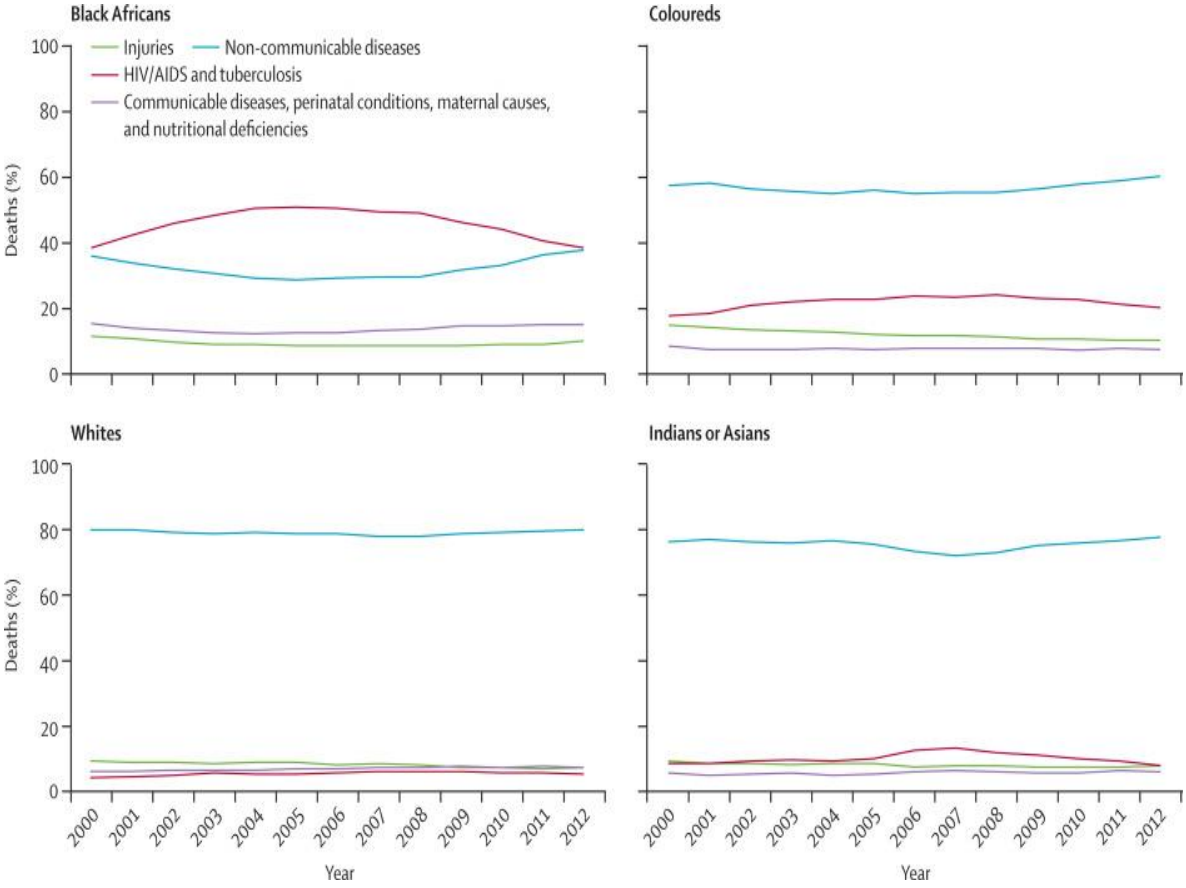

Figure 1. Mortality trends in South Africa (2000-2012), stratified by population group and disease condition*
*From: Pillay-van Wyk et al., (2016)[2]

Possible explanations for the increase in non-communicable disease burden relative to the communicable disease burden include: Rollout of antiretroviral therapy and strengthened tuberculosis control initiatives,[1] well-organised childhood vaccination programmes,[3] improved living conditions for all the country's citizens following the end of Apartheid,[4] increased urbanisation and adoption of unhealthy westernised-lifestyles by the black African population; and overall increased life expectancy of the country's population.[1]

If the theory of epidemiologic transition is applied, the burden of non-communicable conditions in South Africa will exceed that of communicable conditions in the coming years and the country's disease profile will begin to resemble that of high-income countries in Europe or North America.[5]

2.2 Surgical burden of disease in South Africa

It is estimated that 11% of the global burden of disease can be addressed through surgical intervention.[6] With regard to sub-Saharan Africa, studies from Sierra Leone and Mozambique report a surgical burden of disease in the range of 25-60%.[7, 8] Although there are no studies from South Africa which have sought to establish the surgical burden of disease in this setting, it is likely that this estimate would be slightly higher than the global estimate but far less than that reported in countries such as Senegal and Mozambique, which are more resource-constrained and have different disease profiles.[9]

Surgery is a key component of the public health system's response to the quadruple burden of disease that South Africa faces, and is often necessary to reduce morbidity and/or mortality and improve the quality of life in patients suffering from acute or chronic disease conditions.[10-13]

2.3 Surgical services in South Africa

Healthcare in South Africa is available through government-funded facilities (public-sector facilities) or "user pays" facilities (private-sector facilities). An estimated 84% of the South African population access healthcare via public-sector facilities.[14] As per Figure 2, a tiered system of hospitals is currently used to cope with the large volume of patients accessing healthcare in the public-sector.

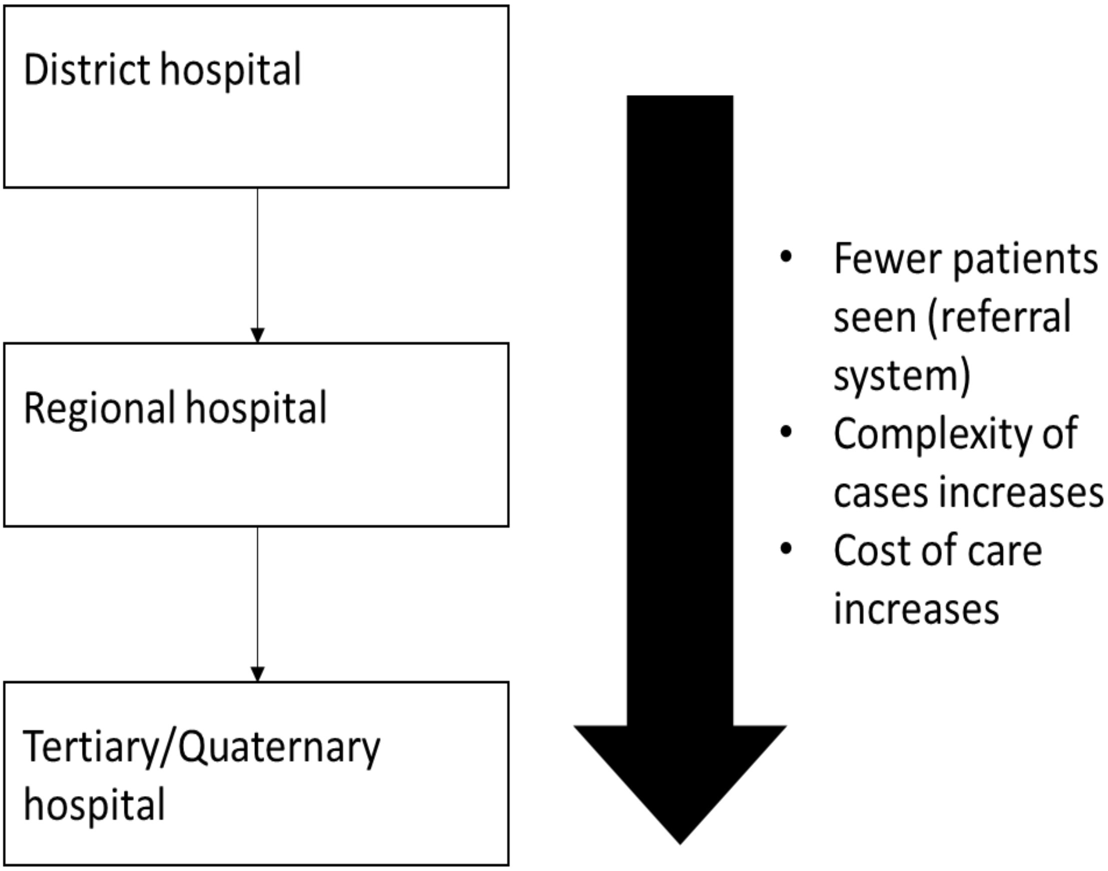

Figure 2. Structure of the public-sector hospital system in South Africa

District hospitals are the first port of call for most patients entering the South African public healthcare system. They are staffed by general surgeons and perform a limited number of acute procedures.[15] Regional hospitals represent the second tier of the South African public healthcare system. These hospitals are staffed by specialist surgeons, have considerably more resources than a district hospital, and are thus able to perform more complex procedures. District hospitals will often refer patients to a regional hospital for surgical procedures.[15] Likewise, regional hospitals might refer very complex surgical cases to higher-level tertiary or quaternary (“central”) hospitals.[16] Tertiary and quaternary hospitals are a scarce resource in South Africa, as there are only a few of these facilities in the country. These hospitals are staffed by sub-specialists and care at these facilities is very costly when compared with the cost of care offered at district and regional hospitals.[17] Resource limitations have made assessing national trends in the numbers of patients having surgery at public-sector hospitals difficult. However, the South African Surgical Outcomes Study (SASOS) reported that 4021 patients aged ≥16 years old had surgery at public-sector hospitals during a single week in 2014.[18] Based on these data, it is likely that >200000 patients undergo surgery at public-sector hospitals each year.

2.4 Surgical site infection in South African settings

Despite the potential implications of surgical site infection (SSI) for patient morbidity/mortality, healthcare resource utilisation and expenditure, this preventable complication has not received much attention in South Africa from an epidemiological study perspective. There are only two recently published studies reporting SSI incidence as a primary endpoint. One study was conducted at an urban trauma centre in the Western Cape Province,[19] and the other was conducted at tertiary hospital in the rural Northern Cape Province.[20] The overall incidence rates for SSI reported in these studies vary widely (0.03% and 4.6%, respectively).[19, 20] The two studies form the Western Cape and Northern Cape Provinces are not directly comparable given the differences in case mix and resource availability between these two settings; however they do provide important information regarding the magnitude of SSI in South African surgical populations. The predictors of SSI in South African patients are also poorly described. This hinders our understanding of the underlying mechanisms of SSI pathogenesis in this setting, and the development of novel setting-specific clinical risk stratification tools for identifying high-risk patients who might benefit from additional preventative interventions. The importance of differences in risk factors for SSI between various countries should not be ignored, with research on other postoperative outcomes revealing a discordance in risk factors between South African patients and those in other countries.[21, 22] Similarly, there have been no attempts to validate existing SSI risk stratification tools developed in other countries in South African surgical patients, nor have there been attempts to test the utility of widely accessible and low-cost preoperative laboratory tests as SSI risk stratification tools in this setting. Lastly, studies investigating the resource and economic impact of SSI in South Africa are lacking. These studies are needed to guide public health specialists with decision-making, specifically decisions around resource and budget allocations to surgical units and the degree to which these can be optimised through SSI prevention. Moreover, if SSIs do have significant resource and economic consequences in South African hospitals, these consequences are likely to be amplified at scarce quaternary-level facilities where costs of care are already high.[17] Thus, there is a need to address the identified gaps in the knowledge around SSIs at South African public-sector facilities, particularly high-level quaternary facilities.

2.5 Research questions and hypotheses

a). What is the incidence of SSI in a quaternary-level setting?

Hypothesis **–** The incidence of SSI in a quaternary-level hospital setting is high, given the complexity of the surgical cases attending quaternary hospitals and the existing risk profile of these cases.

b). What are the risk factors for SSI in a quaternary-level setting?

***Hypothesis* –** SSI in patients attending quaternary South African hospitals is multifactorial, and there are some SSI risk factors which might be shared or different between South Africa and other countries.

c). What implications do SSIs have on healthcare utilisation at quaternary hospitals?

***Hypothesis* –** SSIs increase utilisation of quaternary-level healthcare services through unnecessary rehospitalisation and additional days stayed in hospital.

d). What implications do SSIs have on healthcare expenditure at quaternary hospitals?

***Hypothesis* –** SSI is associated with a crude increase in healthcare expenditure in a quaternary hospital environment.

e). Do routine preoperative laboratory tests have a role in SSI risk stratification at quaternary hospitals?

***Hypothesis* –** In quaternary settings, routine preoperative laboratory tests are a cost-effective and accurate method of identifying patients who are at higher risk of developing SSI such that preventative measures can be initiated in these specific patients.

2.6 Research aim

The overarching aim of this research was to contribute toward improving the management of SSI in South Africa, in the context of a quaternary-level hospital.

2.7 Research objectives

The objectives of this research were to -

a). To determine the incidence of SSI and associated risk factors in patients undergoing high-risk surgery at a quaternary South African hospital.

b). To determine the impact of SSI on healthcare utilisation and healthcare expenditure at a quaternary South African hospital.

c). To evaluate the prognostic relevance of routinely performed laboratory tests for SSI at a quaternary South African hospital.

Each objective has been addressed through peer-reviewed journal manuscripts (Chapters 3-5 of this PhD thesis).

2.8 Novelty of this research

Firstly, the analysis performed under Objective 1 has contributed to the existing limited literature on SSI incidence in South African public-sector hospitals, as well as its associated risk factors. The analysis performed under Objective 1 was also a deviation from prior research on SSI from South Africa, in that it involved a large sample size and a robust multivariate statistical analysis which was used to identify risk factors for SSI. Objective 2 of the research involved a “big data” approach and unique information from an electronic hospital admissions system to investigate trends in post-discharge admissions for SSI. A novel geospatial analysis (also performed under Objective 2) was also used to identify locales where post-discharge SSI are common. The use of technology to address aspects of Objective 2 is in keeping with the South African Government’s National Health Insurance Policy, which promotes the use of technology in its endeavour to improve the health of all citizens.[23] An analysis done under Objective 2 also provided some of the first evidence of the resource and economic impact that SSI can have in a South African setting, information which local hospitalists have no doubt been eagerly awaiting. Lastly, Objective 3 embraces the largely ignored topic of risk stratification for SSI at public-sector hospitals in South African. Two important features of the analyses done under Objective 3 were that it was the first to validate two widely used SSI risk stratification tools in South African surgical patients, and that it was the first to investigate the concept of using ubiquitous preoperative laboratory tests for SSI risk stratification at a public-sector hospital in South Africa.

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Chapter 3

Incidence of surgical site infection and associated risk factors in patients undergoing high-risk surgery at a South African quaternary hospital

Preamble

This chapter relates to Objective 1 of the PhD research project and is comprised of a single manuscript (Manuscript 1). The manuscript details a retrospective chart review study in a sample of 439 high-risk laparotomy patients who underwent their surgical procedures at a South African quaternary hospital. An adjusted/multivariate statistical analysis was used to identify risk factors for surgical site infection (SSI) in these patients. Several clinical and laboratory risk factors were identified. Overall, the findings reported in this manuscript have furthered our understanding of SSI aetiology in high-risk South African surgical patients. Furthermore, the findings on the laboratory risk factors were used to inform the analyses done as part of Chapter 3 of this PhD research project.

3.1 Manuscript 1

Published in final form as:

Naidoo N, Madiba TE, Moodley Y. Incidence and risk factors for surgical site infection following laparotomy at a South African quaternary hospital. Surg Chron. 2019;24(4):179-184.

3.2 Manuscript abstract

Background: A published report of surgical site infection (SSI) incidence and risk factors following laparotomy in a South African setting is lacking. This information would have important implications for SSI clinical prediction rules in South African patients undergoing this common surgical procedure.

Objective: This study sought to determine the incidence and associated risk factors for SSI following laparotomy in a South African setting.

Methods: This was a retrospective chart review study of 439 patients who underwent laparotomy at a South African quaternary hospital over a 5-year period. Data collected for each patient included demographic information, comorbidities, medication use, and surgery-related variables. The Centers for Disease Control definition of SSI was used in this study. The incidence of SSI was determined using conventional epidemiological methods. Logistic regression was used to identify risk factors for SSI.

Results: The incidence of SSI was 16.6% (95% Confidence Interval, 95%CI: 13.4-20.4%). Risk factors for SSI included infectious indication for surgery (Odds Ratio, OR: 3.32, 95%CI: 1.16-9.47; p=0.025), preoperative non-steroidal anti-inflammatory use (OR: 2.82, 95%CI: 1.33-5.95; p=0.007), preoperative hypoalbuminemia (OR: 2.47, 95%CI: 1.12-5.42; p=0.025), Bogota bag use (OR: 2.23, 95%CI: 1.05-4.74; p=0.036), and perioperative blood transfusion (OR: 2.51, 95%CI: 1.33-4.75; p=0.004).

Conclusion: The incidence of SSI in South African patients undergoing laparotomy is higher than that reported for mixed surgical populations. Several risk factors for SSI were identified. The prognostic relevance of these risk factors and the reduction in SSI risk when these factors are addressed requires further investigation.

3.3 Introduction

Over 234 million people undergo surgery around the world each year.[1] A proportion of these patients will suffer postoperative complications, with surgical site infection (SSI) being amongst the most commonly encountered of these postoperative complications.[2] Findings from the International Surgical Outcomes Study (ISOS) suggest that the global incidence of SSI is between 0.8% for organ space SSI and 2.9% for superficial SSI.[2] ISOS also reported that mortality in patients with SSI was between 1.3% for patients with superficial SSI and 7.0% for patients with organ space SSI.[2]

The African Surgical Outcomes Study (ASOS) reported a higher incidence of SSI in African settings, ranging from 0.2% for organ space SSI to 3.5% for superficial SSI.[3] Mortality in patients with SSI was also higher in ASOS when compared with ISOS, and ranged between 5.2% for superficial SSI to 22.4% for organ space SSI.[3] Healthcare expenditure data related to SSIs in African settings are not readily available. However, it is likely that there is an association between SSIs and increased healthcare expenditure in African settings, as is the case in other countries around the world.[4, 5]

The morbidity, mortality, and potentially increased healthcare expenditure associated with SSIs in African settings highlights the importance of identifying individual patients who might be at risk for this complication in these settings. These patients can then be targeted for additional preventative interventions for SSI which are over and above those interventions that are instituted as standard of care, in order to mitigate some of this risk. Targeting individual high-risk patients for additional SSI prevention interventions rather than all surgical patients would also ensure that this process would not be too resource intensive. This point is relevant in African settings, where public healthcare systems are often under-resourced. Clinical prediction rules are one possible method which can be used to identify high-risk patients for SSI.[6, 7] This method involves the identification of high-risk patients based on the number of risk factors for a specific complication. Every risk factor carries a point score, and a total point score is computed for each patient.[8] A total point score threshold is determined which is then used to classify patients as high-risk or low-risk for the complication.[8] Studies for other postoperative outcomes suggest that some clinical prediction rules might not perform equally well in African surgical settings and in overseas surgical settings where these methods were originally developed.[9] This can be attributed to the difference in the general health profiles between surgical populations in these different settings, which might then impact the relative importance of a risk factor between these different settings.[9] Risk factors for SSI following common major surgical procedures, such as laparotomy, in a South African setting have not yet been identified. This information would have great importance with regard to the development of a setting-specific clinical prediction rule for SSI.

Therefore, the objective of this study was to determine the incidence and associated risk factors for SSI following laparotomy at a South African quaternary hospital.

3.4 Methods

3.4.1 Ethical approval

This study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, and the KwaZulu-Natal Provincial Department of Health (Protocol number: BCA208/18).

3.4.2 Study design

This was a retrospective chart review study.

3.4.3 Study setting

The study was conducted at a quaternary hospital located in Durban, South Africa. The 850-bed quaternary hospital is a public-sector facility and provides various healthcare services to the residents of KwaZulu-Natal province, which is on the east coast of South Africa. Admission to the hospital is strictly by referral from lower-level healthcare facilities. The population served by the hospital is predominantly of black African ethnicity.

3.4.4 Study sample

The study sample consisted of 439 adult laparotomy patients. These patients were retrospectively identified from the hospital theatre lists. All 439 patients had their surgical procedures performed between 1 January 2006 and 31 December 2010. The sample size was based on the assumed incidence of SSI in our setting (between 15-20%) and widely accepted statistical rules of thumb for conducting regression analyses to determine possible associations between independent variables and a dichotomous dependent variable (i.e. the "10 events per variable rule", which would ensure that between 7 and 9 independent variables could have been tested in our regression analysis to identify risk factors for SSI). There were nearly 700 laparotomies performed during the specified time period, however only 439 were adults (aged >18 years old). The patients were identified from the operative room lists at the hospital during the specified time period. Laparotomy patients are considered high-risk for surgical site infection, as any open abdominal surgery is considered to carry additional risk for surgical site infection.

3.4.5 Data sources and definitions

Data were collected during a retrospective chart review process using an electronic spreadsheet. Data collected for each patient included demographic information, comorbidities, medication use, and surgery-related variables. Demographic information was collected from the patient’s hospital admission notes. A comorbidity was considered present if there was a physician’s diagnosis attesting to this in the patient’s admission notes or progress notes. Obesity was defined as BMI >30. The indication for surgery was established from the operative notes. Medication use was ascertained from the patient’s admission notes or from the list of medications administered to the patient while he or she was admitted to hospital. Preoperative non-steroidal anti-inflammatory drug (NSAID) use was defined as use of NSAIDs (for example ibuprofen or indomethacin) within 3 days prior to surgery. Information for surgery-related variables were obtained from the operative notes and anaesthetic record of each patient. Peri-operative blood transfusion was defined as the receipt of at least 1 unit of packed red cells intra- or postoperatively. The study outcome was SSI following laparotomy. The Centers for Disease Control (CDC) definition of SSI requires the evidence of clinical signs and symptoms of infection and is not solely based on microbiological evidence of infection.[10] Clinical signs and symptoms of infection can include the following: swelling and redness, pain at the site of surgical incision, presence of pus, fever, surgical wound dehiscence, or histopathological or radiological evidence of infection. The CDC further categorises SSI according to the extent of the infection (Superficial incisional, deep incisional, and organ space infection).[10] The CDC definition of SSI was used in this study, however there was no additional categorisation according to the extent of the infection as all SSIs in this study were deemed to be of importance, irrespective of the extent of the infection. The SSI outcome was measured up to 30 days postoperatively.

3.4.6 Statistical analysis

Patients with missing data were excluded from the analysis. Descriptive statistical methods were used to determine the distribution of various characteristics in the study sample. Results for the descriptive statistical analysis are presented as frequencies and percentages. The incidence of SSI in the study sample was calculated using conventional epidemiological equations. Results for this aspect of the data analysis are presented as a percentage along with a 95% confidence interval (95%CI).

Potential statistical associations between the various characteristics and SSI were initially tested using bivariate statistical analysis (χ^2 test or Fishers Exact test). Results for the bivariate statistical analysis are presented as frequencies and percentages, along with a corresponding p-value. Characteristics with $p<0.10$ from the bivariate statistical analysis were then selected for inclusion as independent variables in a logistic regression analysis, with SSI being the dependent variable. This "purposeful" selection of characteristics for inclusion in the logistic regression analysis was performed to ensure that the subsequent regression model was parsimonious.[11] The fit of the regression model was evaluated using the Hosmer-Lemeshow test, with $p>0.05$ indicative of appropriate model fit. Results for the regression analysis are presented as odds ratios (OR) with 95%CI, and a corresponding p-value. Characteristics with an OR >1.00 and $p<0.05$ were classified as risk factors for SSI. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp, USA).

3.5 Results

The characteristics of the study sample are described in Table I. The majority of patients were ≤60 years old (357 patients, 81.3%). One-third of the study sample (145 patients) were males.

Table I. Characteristics of the study sample and results of the analysis investigating bivariate associations between these characteristics and SSI

Characteristic	**Category**	**All (N=439), n (% N)**	**SSI (N=73), n (% N)**	**No SSI (N=366), n (% N)**	**p**
Median age in years (Interquartile range)	-	42.0 (31.0-56.0)	40 (31.8-56.3)	43.0 (30.0-56.0)	0.772
Age>60	>60 years	82 (18.7)	11 (15.1)	71 (19.4)	0.386
	≤60 years	357 (81.3)	62 (84.9)	295 (80.6)	
Gender	Male	145 (33.0)	26 (35.6)	119 (32.5)	0.607
	Female	294 (67.0)	47 (64.4)	247 (67.5)	
Indication for surgery	Bleed	12 (2.7)	2 (2.8)	10 (2.7)	<0.001*
	Cancer	183 (41.7)	19 (26.0)	164 (44.8)	
	Infection	36 (8.2)	19 (26.0)	17 (4.6)	
	Other	151 (34.4)	19 (26.0)	132 (36.1)	
	Trauma	57 (13.0)	14 (19.2)	43 (11.8)	
American Society of Anesthesiologists Score	>2	207 (47.2)	44 (60.3)	163 (44.5)	0.014*
	≤2	232 (52.8)	29 (39.7)	203 (55.5)	
Preoperative non-steroidal anti-inflammatory	Yes	62 (14.1)	17 (23.3)	45 (12.3)	0.014*
	No	377 (85.9)	56 (76.7)	321 (87.7)	
Preoperative statin	Yes	25 (5.7)	6 (8.2)	19 (5.2)	0.280
	No	414 (94.3)	67 (91.8)	347 (94.8)	
Obesity	Yes	152 (34.6)	31 (42.5)	121 (33.1)	0.302
	No	105 (23.9)	15 (20.5)	90 (24.6)	
	Missing	182 (41.5)	27 (37.0)	155 (42.3)	
Hypertension	Yes	140 (31.9)	26 (35.6)	114 (31.1)	0.454
	No	299 (68.1)	47 (64.4)	252 (68.9)	
Diabetes	Yes	57 (13.0)	13 (17.8)	44 (12.0)	0.179
	No	382 (87.0)	60 (82.2)	322 (88.0)	
Cardiovascular disease	Yes	50 (11.4)	5 (6.8)	45 (12.3)	0.181
	No	389 (88.6)	68 (93.2)	321 (87.7)	
HIV	Yes	30 (6.8)	2 (2.7)	28 (7.7)	0.200
	No	409 (93.2)	71 (97.3)	338 (92.3)	
Metastatic cancer	Yes	86 (19.6)	9 (12.3)	77 (21.0)	0.087*
	No	353 (80.4)	64 (87.7)	289 (79.0)	
Obstructive airway disease	Yes	25 (5.7)	6 (8.2)	19 (5.2)	0.280
	No	414 (94.3)	67 (91.8)	347 (94.8)	
Gastric ulcers	Yes	17 (3.9)	4 (5.5)	13 (3.6)	0.502
	No	422 (96.1)	69 (94.5)	353 (96.4)	
Current smoker	Yes	44 (10.0)	7 (9.6)	37 (10.1)	0.892
	No	395 (90.0)	66 (90.4)	329 (89.9)	
Preoperative leukopenia	Yes	35 (8.0)	6 (8.2)	29 (7.9)	0.932
	No	404 (92.0)	67 (91.8)	337 (92.1)	
Preoperative thrombocytosis	Yes	47 (10.7)	7 (9.6)	40 (10.9)	0.735
	No	392 (89.3)	66 (90.4)	326 (89.1)	
Preoperative renal impairment	Yes	67 (15.3)	18 (24.7)	49 (13.4)	0.014*
	No	372 (84.7)	55 (75.3)	317 (86.6)	
Preoperative anaemia	Yes	314 (71.5)	62 (84.9)	252 (68.9)	0.005*
	No	125 (28.5)	11 (15.1)	114 (31.1)	
Preoperative hyponatremia	Yes	54 (12.3)	14 (19.2)	40 (10.9)	0.050*
	No	385 (87.7)	59 (80.8)	326 (89.1)	
Preoperative hypoalbuminemia	Yes	159 (36.2)	48 (65.8)	111 (30.3)	<0.001*
	No	280 (63.8)	25 (34.2)	255 (69.7)	
Emergency procedure	Yes	150 (34.2)	36 (49.3)	114 (31.1)	0.003*
	No	289 (65.8)	37 (50.7)	252 (68.9)	
Contaminated procedure	Yes	88 (20.0)	31 (42.5)	57 (15.6)	<0.001*
	No	351 (80.0)	42 (57.5)	309 (84.4)	
Surgery duration >2 hours	Yes	153 (34.9)	20 (27.4)	133 (36.3)	0.143
	No	286 (65.1)	53 (72.6)	233 (63.7)	
Bogota bag	Yes	70 (15.9)	322 (88.0)	47 (64.4)	<0.001*
	No	369 (84.1)	44 (12.0)	26 (35.6)	
Antibiotic prophylaxis	Yes	366 (83.4)	55 (75.3)	311 (85.0)	0.044*
	No	73(16.6)	18 (24.7)	55 (15.0)	
Perioperative blood transfusion	Yes	157 (35.8)	46 (63.0)	111 (30.3)	<0.001*
	No	282 (64.2)	27 (37.0)	255 (69.7)	
Patient-controlled analgesia postoperatively	Yes	33 (7.5)	3 (4.1)	30 (8.2)	0.227
	No	406 (92.5)	70 (95.9)	336 (91.8)	

SSI: Surgical site infection. *Selected for inclusion in the logistic regression model, based on bivariate p-value <0.10.

Most patients' surgeries were cancer-related (183 patients, 41.7%). Just over half of the study sample had American Society of Anesthesiologists Score ≤2 (232 patients, 52.8%). Around one in every seven patients (62 patients, 14.1%) was taking a non-steroidal anti-inflammatory drug prior to surgery. Only 25 patients (5.7%) were taking statin drugs prior to surgery. Obesity and hypertension were the two most prevalent comorbidities (152 patients, 34.6% and 140 patients, 31.9%). The two most common laboratory abnormalities were anaemia (314 patients, 71.5%) and hypoalbuminemia (159 patients, 36.2%). Only a small proportion of the study sample had their surgical wounds closed with a Bogota bag (70 patients, 15.9%). The vast majority of patients received antibiotic prophylaxis (366, patients, 83.4%). A total of 157 patients (35.8%) required a blood transfusion during or shortly after their surgery. Patient-controlled analgesia was rarely used following surgery (33 patients, 7.5%). A total of 150 patients (34.2%) had emergency surgery. The duration of surgery was ≤2 hours for almost two-thirds of the study sample (286 patients, 65.1%).

The results of the bivariate statistical analysis are also presented in Table I. Out of the 439 patients undergoing laparotomy in the study sample, 73 patients were identified as having SSI following their procedure. This equated to an estimated SSI incidence of 16.6% (95%CI: 13.4-20.4%) in the study sample.

Variables with p<0.10 subsequently included in the logistic regression analysis included: indication for surgery, American Society of Anesthesiologists score, preoperative non-steroidal anti-inflammatory use, metastatic cancer, preoperative renal impairment, preoperative anaemia, preoperative hyponatremia, preoperative hypo-albuminemia, emergency procedure, contaminated procedure, Bogota bag use, antibiotic prophylaxis, and blood transfusion. The results of the logistic regression analysis are shown in Table II. The Hosmer-Lemeshow test indicated appropriate model fit (p=0.381).

Table II. Findings of the logistic regression analysis investigating independent risk factors for SSI

Characteristic	**Category**	**OR (95%CI)**	**p**
Indication for surgery	Bleed	0.44 (0.08-2.57)	0.361
	Cancer	1.03 (0.34-3.10)	0.961
	Infection	3.32 (1.16-9.47)	0.025*
	Other	0.78 (0.31-1.94)	0.588
	Trauma/injury	1.00 (Reference)	-
American Society of Anesthesiologists Score	>2	1.36 (0.75-2.48)	0.313
	≤2	1.00 (Reference)	-
Preoperative non-steroidal anti-inflammatory	Yes	2.82 (1.33-5.95)	0.007*
	No	1.00 (Reference)	-
Metastatic cancer	Yes	0.46 (0.20-1.10)	0.080
	No	1.00 (Reference)	-
Preoperative renal impairment	Yes	0.99 (0.45-2.17)	0.970
	No	1.00 (Reference)	-
Preoperative anaemia	Yes	1.25 (0.57-2.75)	0.582
	No	1.00 (Reference)	-
Preoperative hyponatremia	Yes	1.35 (0.61-3.00)	0.458
	No	1.00 (Reference)	-
Preoperative hypoalbuminemia	Yes	2.47 (1.12-5.42)	0.025*
	No	1.00 (Reference	-
Emergency procedure	Yes	0.59 (0.26-1.31)	0.194
	No	1.00 (Reference)	-
Contaminated procedure	Yes	1.22 (0.58-2.55)	0.599
	No	1.00 (Reference)	-
Bogota bag	Yes	2.23 (1.05-4.74)	0.036*
	No	1.00 (Reference)	-
Antibiotic prophylaxis	Yes	0.66 (0.32-1.34)	0.247
	No	1.00 (Reference)	-
Perioperative blood transfusion	Yes	2.51 (1.33-4.75)	0.004*
	No	1.00 (Reference)	-

OR: Odds ratio, 95%CI: 95% Confidence interval. *Statistically significant result at $p<0.05$.

Statistically significant results were noted for infectious indication for surgery (OR: 3.32, 95%CI: 1.16-9.47; p=0.025), preoperative non-steroidal anti-inflammatory use (OR: 2.82, 95%CI: 1.33-5.95; p=0.007), preoperative hypoalbuminemia (OR: 2.47, 95%CI: 1.12-5.42; p=0.025), Bogota bag use (OR: 2.23, 95%CI: 1.05-4.74; p=0.036), and perioperative blood transfusion (OR: 2.51, 95%CI: 1.33-4.75; p=0.004).

3.6 Discussion

The incidence of SSI in this study was far higher than that reported for ISOS and ASOS.[2, 3] It is possible that this finding is due to one crucial difference between the current study and ISOS and ASOS, which is that the current study was performed solely in a high-risk major surgery group while ISOS and ASOS were performed in surgical populations which were a mix of major and minor surgical procedures.[2, 3] Open intra-abdominal surgery itself is associated with an increased risk of developing SSI.[12] It is likely that the SSI incidence in ISOS and ASOS was “diluted” by the inclusion of lower risk surgical procedures in these two studies. Our study findings are more in line with a 2014 systematic review by Fan et al., which reported that the incidence of SSI was highest in African countries, and ranged between 10% in Uganda to over 20% in Ethiopia. Furthermore, the incidence of SSI in our study fell between the estimates reported for high-income and low-income countries which contributed data to ISOS.[2] This suggests that there is still room for improvement in reducing SSI rates in our South African setting.

Several risk factors for SSI were identified in this study. These were infectious indication for surgery, preoperative non-steroidal anti-inflammatory use, preoperative hypoalbuminemia, Bogota bag use, and perioperative blood transfusion. These characteristics were associated with an approximately two- to four-fold increase in risk for SSI. The finding for infectious indication for surgery being associated with a higher risk of SSI is probably reflective of underlying immune dysfunction in patients with pre-existing infection. Nonsteroidal anti-inflammatory medications are often prescribed for pain control during the perioperative period.[13] As the name implies, these medications control pain by reducing inflammation.[14] This might contribute to an impaired immune response in surgical patients, resulting in a predisposition to SSI. The link between hypoalbuminemia and a higher risk of SSI is well established.[15, 16] Hypoalbuminemia is often considered a sign of malnutrition.[17] Besides impairment of the immune response, malnutrition might also cause impaired wound healing.[18] The intact integument acts as a physical barrier against infection and surgical incisions, which represent disruptions in the integumentary system,[19] would remain open for far longer in malnourished individuals. During this time period the disrupted integument at the site of the surgical incision might be susceptible to bacterial colonisation.[19] Similarly, the use of a Bogota bag would also leave the disrupted integument susceptible to bacterial colonisation.[20] Some blood loss is inevitable during open intra-abdominal surgery.[21, 22] Perioperative transfusion might be proposed to address perioperative blood loss. However, transfusion itself has been found to be associated with an increased risk of several postoperative complications, including SSI.[23] In agreement with the pathophysiology of other risk factors identified in this study, it has been postulated that perioperative transfusion might impair the immune response. This appears to be supported by the findings of a recent study involving patients undergoing gastrointestinal surgery, wherein there was an immunosuppressive gene expression profile exhibited by patients who had received a perioperative blood transfusion.[24] The study had specifically found that that this gene expression profile could have a profoundly negative impact on cells of innate immune response,[24] which would therefore make patients who received blood transfusions at higher risk for postoperative infectious complications.

The prognostic performance of the SSI risk factors identified in this study should be investigated in future research as components of a new clinical prediction rule. This would assist with the preoperative identification of patients who are at high-risk for SSI following their procedures. It might also be worth considering the potential benefits of trying to address some of the modifiable risk factors identified in this study. This could mitigate some of the risk for SSI in high-risk patients. For instance, pain in surgical patients could be managed using other analgesics.[25] Malnourished patients should be offered adequate nutritional support.[26] Optimising surgical technique and the use of anti-fibrinolytic agents are strategies which can be used to prevent excess perioperative blood loss.[27] This could reduce the need for a perioperative blood transfusion. Where there is no option for patients other than blood transfusion, then these patients should have their surgical incisions reviewed more often during the postoperative period for SSI. One cannot mitigate the risk of SSI associated with the indication for surgery. Furthermore, one cannot completely mitigate for the risk of SSI associated with the use of a Bogota bag. These risk factors can be used to identify high-risk patients for more stringent postoperative monitoring.

There were limitations to this research. This study involved patient data from a single, quaternary level hospital. The patient profile is that of very complex cases which cannot be managed at lower-level healthcare facilities. Therefore, the findings of this research might not necessarily be generalisable to other hospitals or other surgical populations. Information regarding the use of over-the-counter and herbal medications, which might have an immune boosting effect in surgical patients, was not collected as part of this study as it was difficult to retrospectively establish the use of these medications from the patients' medical chart. There were also some variables for which a significant amount of data was missing, for example the composition of suture material used to close the surgical incision in the patients operative notes. These variables could not be reliably investigated in this study and were excluded from the data analysis. The study outcome was only measured until 30 days postoperatively, which is in keeping with the CDC definition for SSI. However, there might possibly have been some patients with delayed SSI, in that they presented with SSI at a time point which fell outside the 30-day postoperative period. These patients would have been considered as SSI-negative in the statistical analysis. Lastly, we did not stratify the SSI according to the extent of the infection. Therefore, the local incidence of superficial, deep-incisional, and organ space SSI could not be determined and compared with the international literature.

3.7 Conclusion

The incidence of SSI observed in the study sample of South African patients undergoing laparotomy was much higher than that reported in larger studies involving mixed surgical populations. This is in keeping with other studies which report that patients undergoing intra-abdominal surgery are a high-risk surgical population for SSI.[12] Several risk factors for SSI were identified in this study. These risk factors were infectious indication for surgery, preoperative non-steroidal anti-inflammatory use, preoperative hypoalbuminemia, Bogota bag use, and perioperative blood transfusion. This finding confirms the established view of SSI as being multifactorial.[28] The prognostic relevance of the SSI risk factors identified in this study and the reduction in risk when these factors are addressed requires further investigation.

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Chapter 4

The impact of surgical site infection on healthcare utilisation and healthcare expenditure at a South African quaternary hospital

Preamble

Chapter 4, comprised of 2 manuscripts (Manuscript 2 and Manuscript 3), addresses Objective 2 of the PhD research project. Manuscript 2 is a report of post-discharge surgical site infection (SSI) admissions at a quaternary/teaching South African hospital. Data for 1240 post-discharge SSI admissions was obtained from the hospital's admissions database for the period 2006-2015. A trend analysis performed over the 10-year study period suggested that SSI prevention requires strengthening at the inpatient and outpatient level. In addition, a semi-quantitative geospatial analysis of the admissions data showed a disparity in post-discharge SSI admissions between urban and rural areas, which requires further investigation. Manuscript 3 used the data from laparotomy patients collected as part of Objective 1 of the PhD research study to investigate inpatient healthcare utilisation and costs associated with SSI following major surgery. The results of the adjusted statistical analysis suggested that a reduction in inpatient SSI incidence might yield potential benefits for healthcare utilisation and financial expenditure in our resource-limited setting.

4.1.1 Manuscript 2

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4.1.2 Manuscript abstract

Background: Reports of post-discharge admissions for surgical site infection (SSI) in African settings are lacking. This information could assist with allocating resources within hospitals, as well as developing targeted interventions aimed at reducing post-discharge SSI.

Objective: The primary objective of this study was to determine trends in admissions for post-discharge SSI at a South African quaternary/teaching hospital. The secondary objective was to determine trends in mortality rates for these admissions.

Methods: This was a retrospective review of adult admissions for post-discharge SSI at a South African quaternary/teaching hospital between 2006 and 2015. Admissions for post-discharge SSI were identified using the hospital administrative database and appropriate International Classification of Disease, 10th Revision codes. Mortality was determined from the discharge disposition for each admission. Data were analysed with simple regression and trend line statistics. The geospatial distribution of post-discharge SSI, based on the residential postal codes recorded on the hospital administrative database for each admission, was determined using the Power Map® software program.

Results: There was no change in admissions for post-discharge SSI over the study period (p=0.17). Mortality in elderly admissions declined during the study period (p=0.03). Most admissions for post-discharge SSIs originated from urban areas.

Conclusion: Despite the implementation of universal SSI prevention methods, admissions for post-discharge SSI remained consistent during the study period. Urban areas appeared to be more severely affected by post discharge SSI than rural areas. Additional prevention methods for post discharge SSI are required.

4.1.3 Introduction

Surgical site infection (SSI) is an important postoperative complication,[1,2] and contributes towards increased healthcare expenditure and resource utilisation at healthcare facilities.[3] Post-operative surgical site infection can occur as an in-hospital event or a post-discharge event.[4,5] Furthermore, the incidence of inpatient and post-discharge SSI differs according to surgical procedure.[4]

Inpatient data from the African Surgical Outcomes Study (ASOS) has highlighted the importance of SSI in African settings.[6] However, loss to follow-up once the patient is discharged from hospital is a challenge,[7] and most studies from African settings are usually investigations of inpatient outcomes only. Even ASOS did not extend investigations of most post-operative complications beyond hospital discharge.[6]

There is a gap in the literature regarding post-discharge SSI in an African setting. Addressing this deficiency could be important for three reasons. Firstly, it could assist public health specialists and surgeons in deciding how resources should be allocated within healthcare facilities for SSI-related admissions. Secondly, it could assist with the development of interventions aimed at reducing post-discharge SSI. Lastly, the demand for surgical procedures is increasing on the African continent,[8] and some of these surgical cases are at risk for SSI.[6]

The primary objective of this study was to determine trends in admissions for post-discharge SSI at a South African quaternary/teaching hospital. The secondary objective of this study was to determine trends in mortality for these admissions.

4.1.4 Methods

4.1.4.1 Ethical approval

This study was part of a larger healthcare utilisation project approved by the Biomedical Research Ethics Committee at University of KwaZulu-Natal, South Africa (Protocol BE595/16).

4.1.4.2 Study design

This study was a retrospective review of data from a hospital admissions database.

4.1.4.3 Study setting

The study setting was the Inkosi Albert Luthuli Central Hospital (IALCH), located in Durban, South Africa. This quaternary/teaching hospital has 850 beds and offers specialised medical and surgical services to the populace of the KwaZulu-Natal. Surgical procedure rates at IALCH are shown in Table I. Cardiac surgeries were defined as procedures performed on the heart by cardiac surgeons. Noncardiac surgeries were defined as all other procedures which did not meet the definition of cardiac surgery.

4.1.4.4 Study sample

The study sample was comprised of all adult admissions at IALCH between 1 January 2006 and 31 December 2015, with a primary International Classification of Disease 10th Revision (ICD-10) diagnosis code indicative of SSI (Table II). In addition, ICD-10 codes were broadly classified as SSIs not involving grafts/prostheses (T81.4) and SSIs involving grafts/prostheses (All remaining ICD-10 codes listed in Table II). The decision to include all adult admissions during the specified study period was based on conventional methods for assessing trends data (i.e all eligible patients must be included in order to provide an unbiased estimate of trends for SSI-related admissions and its consequences).

Table I. Surgical procedure rates at IALCH (2006-2015)*

Specialty	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Cardiac	93.1 (87.2-99.0)	89.2 (83.6-94.8)	86.6 (81.2-92.0)	78.4 (73.3-83.5)	73.9 (68.8-78.9)	82.7 (78.0-87.5)	72.5 (68.1-76.8)	70.7 (66.5-74.9)	76.2 (71.9-80.5)	74.0 (69.5-78.5)
Noncardiac	906.9 (912.6-900.8)	910.8 (905.0-916.2)	913.4 (907.9-918.0)	921.6 (916.3-926.6)	926.1 (920.9-930.9)	917.3 (912.4-921.9)	927.5 (923.0-931.8)	929.3 (925.0-933.4)	923.8 (919.3-928.0)	926.0 (921.4-930.4)
ENT	58.7 (53.9-63.5)	57.8 (53.2-62.4)	68.1 (63.3-72.9)	83.7 (78.4-89.0)	70.1 (65.3-75.0)	67.2 (62.9-71.5)	70.4 (66.1-74.7)	72.8 (68.5-77.0)	79.5 (75.1-83.9)	69.1 (64.8-73.5)
Gynaecology	54.4 (49.8-59.0)	50.2 (45.9-54.5)	35.4 (31.9-38.9)	49.1 (45.0-53.2)	56.7 (52.3-61.1)	61.9 (57.7-66.0)	58.3 (54.3-62.2)	61.1 (57.2-65.0)	51.8 (48.2-55.4)	55.0 (51.1-59.0)
Neurosurgery	229.6 (221.1-238.1)	252.6 (244.0-261.1)	258.1 (249.7-266.5)	222.7 (214.8-230.6)	240.0 (231.9-248.2)	227.8 (220.6-235.0)	216.2 (209.3-223.2)	218.8 (212.1-225.5)	215.1 (208.5-221.8)	211.7 (204.6-218.7)
Obstetric	1.7 (0.9-2.6)	3.2 (2.1-4.3)	38.5 (34.9-42.2)	34.5 (31.0-38.0)	36.0 (32.4-39.5)	42.9 (39.4-46.4)	45.3 (41.8-48.8)	44.9 (41.5-48.2)	46.3 (42.9-49.7)	37.7 (34.4-41.0)
Eye	83.8 (78.2-89.5)	73.5 (68.4-78.6)	77.8 (72.6-82.9)	83.2 (78.0-88.5)	83.0 (77.7-88.3)	87.7 (82.8-92.6)	98.0 (93.0-103.0)	104.4 (99.5-109.4)	102.3 (97.4-107.2)	103.4 (98.1-108.6)
Orthopaedic	59.2 (54.4-64.0)	63.4 (58.6-68.2)	55.8 (51.4-60.2)	60.1 (55.6-64.7)	71.4 (66.5-76.3)	84.4 (79.6-89.2)	98.1 (93.1-103.2)	96.4 (91.6-101.2)	100.8 (95.9-105.7)	118.7 (113.1-124.3)
Plastic surgery	100.2 (94.1-106.3)	96.3 (90.5-102.1)	98.0 (92.3-103.7)	93.7 (88.2-99.3)	79.1 (74.0-84.3)	83.5 (78.7-88.3)	86.0 (81.3-90.8)	86.6 (82.1-91.2)	88.5 (83.9-93.1)	79.2 (74.5-83.8)
Specialised surgery	49.3 (44.9-53.7)	48.4 (44.2-52.6)	40.0 (36.2-43.7)	36.6 (33.0-44.2)	40.0 (36.3-43.6)	48.7 (45.0-54.2)	45.3 (41.8-48.8)	52.8 (49.1-56.4)	55.3 (51.6-59.0)	52.7 (48.9-56.6)
Thoracic	106.6 (100.4-112.9)	96.2 (90.4-102.0)	90.6 (85.1-96.1)	102.9 (97.1-108.7)	106.8 (100.9-112.6)	81.7 (77.0-86.5)	75.4 (71.0-79.9)	66.2 (62.2-70.3)	60.9 (57.0-64.8)	67.6 (63.3-71.9)
Urology	70.3 (65.1-75.5)	65.1 (60.3-69.9)	65.5 (60.8-70.3)	70.3 (65.4-75.1)	68.6 (63.8-73.4)	61.3 (57.2-65.5)	68.0 (63.7-72.2)	66.3 (62.3-70.3)	71.7 (67.5-75.9)	64.2 (60.0-68.4)
Vascular	93.0 (87.1-98.9)	104.0 (98.0-110.0)	85.7 (80.3-91.1)	84.7 (79.4-90.0)	74.4 (69.4-79.4)	70.1 (65.7-74.5)	66.5 (62.3-70.7)	59.1 (55.3-62.9)	51.5 (47.9-55.1)	66.7 (62.4-71.0)

IALCH: Inkosi Albert Luthuli Central Hospital, ENT: Ear, nose, and throat.
*Expressed as rate per 1000 procedures (95% Confidence interval). Main categories are indicated by italic text.

Table II. ICD-10 diagnosis codes used to identify admissions with a post-discharge SSI

ICD-10 Code	Description
T81.4	Infection following a procedure, not elsewhere classified
T85.7	Infection and inflammatory reaction due to other internal prosthetic devices, implants and grafts
T82.6	Infection and inflammatory reaction due to cardiac valve prosthesis
T82.7	Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts
T83.5	Infection and inflammatory reaction due to prosthetic device, implant and graft in urinary system
T83.6	Infection and inflammatory reaction due to implanted penile prosthesis
T84.5	Infection and inflammatory reaction due to internal joint prosthesis
T84.6	Infection and inflammatory reaction due to internal fixation device
T84.7	Infection and inflammatory reaction due to other internal orthopedic prosthetic devices, implants and grafts

ICD: International Classification of Disease 10th Revision, SSI: Surgical site infection.

4.1.4.5 Data and definitions

The data for this study were extracted directly from the hospital admissions database and stored as a Microsoft Excel® file in preparation for statistical analysis. Beside the ICD-10 primary diagnosis code for SSI, variables contained in the database included: admission date, admission age and gender, discharge disposition, and residence postal code. Mortality was determined by reviewing the discharge disposition recorded for each admission in the hospital admissions database.

4.1.4.6 Statistical analysis

Characteristics of the entire study sample were analysed using descriptive statistical methods and are presented as frequencies and percentages, or rates with 95% confidence intervals (95%CI). Simple regression and trend line analysis was used to investigate trends in post-discharge SSI admissions and mortality in these admissions. Trends analyses were stratified according to age, gender, the nature of SSI ICD-10 code, and broad surgical category (ie. non-cardiac surgery versus cardiac surgery). The direction of a trend was determined from the slope of the trend line, with a negative slope indicating a declining trend while a positive slope would be indicative of an increasing trend.

The R^2 value from the simple regression analysis was used to interpret the strength of a trend. Trends with an R^2 value of <0.5000 were considered “weak”, trends with an R^2 value of 0.5000-0.7000 were considered “moderate”, and trends with an R^2 value of >0.7000 were considered “strong”. The descriptive statistics and simple regression/trend line analyses were performed using Microsoft Excel®. For the trends analysis, a p-value <0.05 was considered a statistically significant result.

The geospatial distribution of post-discharge SSI admissions was semi-quantitatively determined using the Power Map® add-on software for Microsoft Excel®. Briefly, the Power Map® add-on software uses postal codes in the Microsoft Excel® database and blank maps available through Microsoft Bing® to create new maps which display the geospatial distribution of a given characteristic, which in this instance would be admissions for post-discharge SSI. The display options for the map can be set such that areas with a high density of admissions for post-discharge SSI appear as red “hot spots”, while areas with a low density of admissions for post-discharge SSI would appear green. Areas with an intermediate density of admissions for post-discharge SSI would appear yellow.

4.1.5 Results

The study sample consisted of 1240 post-discharge SSI admissions which were recorded during the 10-year study period. The mean age of the study sample was 46.9 (standard deviation: 22.9) years with 15.3% (190 admissions) of the study sample aged >65 years. The median age was 46.0 (interquartile range: 32.0-60.0) years old. Six hundred and sixty-eight (53.8%) admissions in the study sample were male. A total of 808 (67.1%) admissions did not involve SSI of grafts/prostheses. Mortality across the study period was 9.5% (118 admissions).

The results of the trends analysis are shown in Figures 1 and 2. A weak, but statistically significant trend toward a reduction in mortality amongst elderly admissions with post-discharge SSI ($R^2=0.4847$, $p=0.03$) was observed (Figure 2). There were no other statistically significant trends noted for the admission and mortality outcomes.

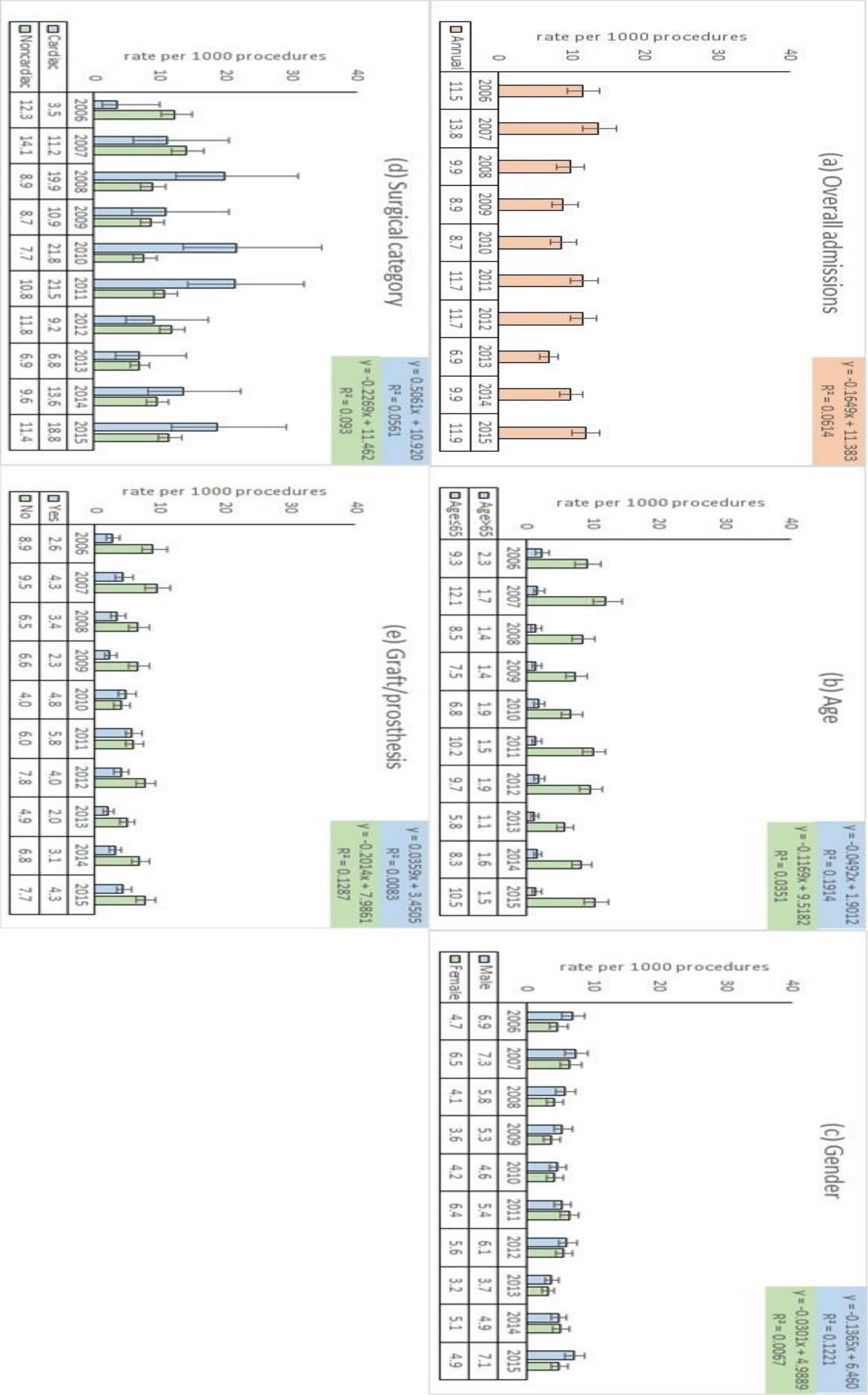

Figure 1. Overall and stratified trends in admissions for post-discharge SSI*

*Colour-coded boxes contain trend line equations and R^2 values for corresponding colour-coded variables and sub-categories. Error bars on graph indicate confidence intervals for estimates.

Figure 2. Overall and stratified trends for mortality in admissions with post-discharge SSI*

*Colour-coded boxes contain trend line equations and R^2 values for corresponding colour-coded variables and sub-categories. Error bars on graph indicate confidence intervals for estimates.

The geospatial distribution of SSI admissions in this study is shown in Figure 3. A high-density area of post-discharge SSI admissions was noted around Durban, as well as several peri-urban areas surrounding Durban. Post-discharge admissions for SSI from rural areas in the north and south, as well as the midlands of KwaZulu-Natal province were less common.

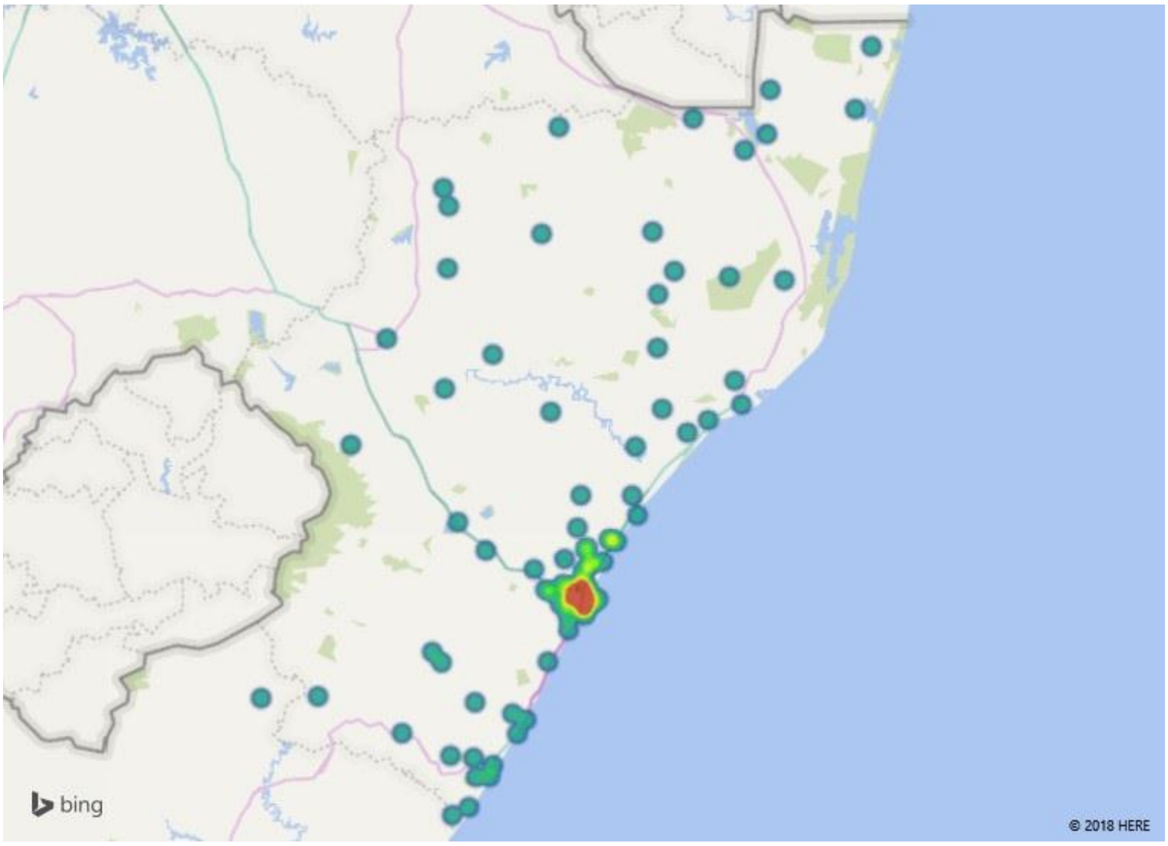

Figure 3. Geospatial distribution of post-discharge admissions for SSI in this study*

*Across entire study period (2006-2015). With reference to the density of post-discharge admissions for SSI: Green – area with low density, yellow – area with intermediate density, and red – area with high density.

4.1.6 Discussion

Along with the inpatient findings reported in ASOS,[6] this study contributes toward a better overall understanding of SSI on the African continent. Most admissions in the study sample were of younger age. There is evidence to suggest that the risk of SSI increases up to the age of 65 years of age, following which there is a decrease in risk.[9] In addition, most post-discharge SSIs were in admissions that did not have recent graft/prosthesis procedures.

Surgical procedures involving grafts or prostheses are more likely in older patients rather than younger patients, which might explain this finding. For example, while there has been an increase in knee arthroplasty amongst persons younger than 60 years of age, the majority of arthroplasties continue to be performed in persons older than 60 years.[10]

The findings of the trends analysis suggest admissions for post-discharge SSI at IALCH, irrespective of stratification level, have remained consistent during the 10-year study period. Ideally, there should have been a declining trend in post-discharge SSI during the study period. The hospital follows the World Health Organisation (WHO) recommendations for the prevention of SSI,[11] and no new policies were specifically implemented during the study period. This demonstrates that although WHO recommendations for SSI prevention have been adopted at IALCH, further efforts are required to significantly reduce admissions for post-discharge SSI.

Surgical site infection is multifactorial. Although the WHO recommendations seek to prevent SSI by addressing risk factors at the facility and healthcare worker levels, addressing risk factors at the patient level is also important. A potential method of reducing post-discharge SSI is patient empowerment through health promotion and educational initiatives. These health promotion activities and educational materials should be related to risk factor avoidance and proper wound care following discharge from hospital.[12] Health promotion materials would need to be culturally relevant to African settings to be effective. Early detection and treatment of post-discharge SSI might reduce the chances of the SSI advancing to the point where it requires patient hospitalisation for treatment. Mobile phone technology has been used in the surveillance of post-discharge SSI in some settings.[13,14] This intervention has the potential to identify post-discharge SSI at an early stage. Patients can then receive timeous treatment. As access to mobile phones in African settings is increasing,[15] post-discharge SSI surveillance through a mobile phone-based intervention in these settings should be considered.

One in ten admissions for post-discharge SSI in this study died in hospital. Overall mortality in patients with SSI in ASOS was 9.0%, but ranged between 5.2% and 22.4% depending on the extent of the SSI.[6] However, ASOS was a study of inpatient outcomes and did not investigate post-discharge complications.[6] As the mortality findings reported for this study of post-discharge SSI admissions are similar to those reported for inpatient SSI in ASOS,[6] it would appear that inpatient and post-discharge SSIs have a similar importance with regard to mortality in African settings. This once again highlights the importance of prevention of pre- and post-discharge SSI, as well as the timely diagnosis and treatment of SSI in African settings. Another finding of this study was a trend toward a reduction in mortality amongst elderly admissions with post-discharge SSI. There are two possible explanations for this finding: Firstly, the finding is artefactual, and is likely explained by factors which lie beyond the scope of the dataset used in this study; and secondly, the lower mortality amongst elderly admissions might a consequence of improved care or improved socioeconomic status in this sub-group. If the latter explanation holds true, then it generates the hypothesis that it is indeed possible to reduce fatal SSI outcomes through improving quality of postoperative care and socioeconomic status in the high-risk elderly surgical population. This hypothesis requires further testing and should form the basis of future interventional studies.

Rural patient groups have been reported as having worse postoperative outcomes (including SSI) when compared with their urban counterparts.[16] While our semi-quantitative geospatial analysis revealed high density clusters of post-discharge admissions in Durban, this finding should be interpreted with caution as it may have been influenced by our dichotomous definition of population density (whether clusters of admissions were located around a major urban centre or not), as well as the inability of the semi-quantitative analysis to account for socioeconomics, demographic group, or other potential confounders.

Strengths of this study include the large sample size and the ten-year study duration, which allowed for an appropriate trends analysis to be conducted. Another strength of this study was that the geospatial distribution of post-discharge admissions for SSI was mapped in KwaZulu-Natal.

This study also had several limitations. The data used in this study were from a single, quaternary-level South African hospital. Therefore, the findings might not necessarily be generalisable to other healthcare facilities in South Africa or other African settings. There is also a possibility that some patients, such as those patients from rural areas, may have admitted or managed for post discharge SSI at another healthcare facility much closer to their place of residence. These would represent “missed” post-discharge SSIs. There might have also been some admissions which were incorrectly coded on the hospital administrative database as having SSI. Conversely, there might have been some admissions with a primary diagnosis of SSI which were missed. The medical informatics system at IALCH has been changed several times between 2006 and 2015, during which some of the finer details related to procedures performed at the hospital were lost. Therefore, surgical procedures have been broadly classified in this study as cardiac or noncardiac (with sub-specialties) procedures. Data related to other comorbidities and medication use were not recorded on the hospital administrative database, and therefore could not be investigated in this study. The specific cause of death could not be established for those patients who died in hospital. Regrettably, the data extracted from the hospital admissions system does not provide information on the severity of the SSI. Therefore, we were unable to investigate the impact of the time between discharge and readmission on the severity of the SSI. Lastly, there was no sub-classification of SSI according to extent (superficial, deep incisional, or organ space) in this study.

4.1.7 Conclusion

Despite implementation of universal SSI prevention methods, the number of admissions for post discharge SSI at IALCH remained consistent during the study period. Additional efforts are required to reduce the number of post-discharge SSI admissions at IALCH. Such efforts would need to consider the multifactorial aetiology of SSI. A prevention package which simultaneously addresses risk factors at various levels would be best suited for reducing SSI in this setting. Patients from urban areas appear to be more affected by post discharge SSI than patients from rural areas. Further research, which accounts for socioeconomic and demographic characteristics, is required to confirm this finding. Another hypothesis generated from this research is that the reduced mortality in elderly SSI admissions might be due to improvement in care and/or improved socioeconomic status in this high-risk group. This hypothesis should be tested in future with interventional trials. While this study had strengths, it also had limitations which should be addressed in future studies on the topic.

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4.2.1 Manuscript 3

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4.2.2 Manuscript abstract

Background: Surgical site infection (SSI) is reported to increase postoperative length of stay (LoS) and hospitalisation costs in non-African settings. The impact of SSI on postoperative LoS and hospitalisation costs in an African country such as South Africa is unknown.

Objective: The primary objective of this study was to determine the impact of SSI on postoperative LoS in a sample of South African surgical patients. The secondary objective was to determine the additional costs associated with SSI in a sample of South African surgical patients.

Methods: This was a sub-analysis of data from a pre-existing laparotomy patient registry, collected at a South African quaternary hospital over a 5-year period. Demographic information, comorbidity, surgery-related variables, SSI, and other inpatient complications were collected for each patient during a retrospective chart review. Postoperative LoS was the primary study outcome. Quantile regression was used to investigate the impact of SSI across percentiles of postoperative LoS. Crude estimates of hospitalisation costs attributed to SSI were also determined.

Results: SSI was associated with an additional 1.06 days of hospitalisation at the 25th percentile of postoperative LoS. The additional cost attributed to SSI at this percentile of postoperative LoS was ZAR8900/ $1180. SSI had no significant impact at other percentiles of postoperative LoS.

Conclusion: SSI had implications for healthcare resource utilisation and hospitalisation costs in our setting, but only in patients who had shorter postoperative stays in hospital.

4.2.3 Introduction

Surgical site infection (SSI) rates range between 0.8% and 2.9%.[1] Although SSI is associated with morbidity and mortality, attention must also be given to the consequences of this complication on healthcare resource utilisation and healthcare expenditure. A systematic review by Broex et al.,[2] found that SSI contributed to a 176% mean increase and a 173% median increase in hospital length of stay (LoS). The same systematic review also found a 115% mean increase and a 110% median increase in costs.[2] All studies included in this review were predominantly from high-income, non-African settings.[2] An overall increase in healthcare resource utilisation and healthcare expenditure in cases with SSI was confirmed in a subsequent systematic review of the European literature conducted by Badia and colleagues.[3]

Both systematic reviews pointed out that the biggest driver of healthcare-associated costs in patients with SSI was additional LoS.[2, 3] There are limited studies on how SSI impacts LoS in African countries, and whether the findings for the LoS and subsequent healthcare costs associated with SSI obtained from predominantly high-income, non-African countries are applicable to a middle-income African country such as South Africa. Should SSI place a significant burden on healthcare resource utilisation and healthcare expenditure in a South African setting, then there would be an additional incentive for reducing SSI in this setting. The current study sought to address this gap in the knowledge.

The primary objective of this study was to determine the impact of SSI on postoperative LoS in a sample of South African surgical patients. The secondary objective was to determine the additional costs associated with SSI in a sample of South African surgical patients.

4.2.4 Methods

4.2.4.1 Ethical approval

This research was approved as a sub-study of a pre-existing patient registry by the Biomedical Research Ethics Committee at the University of KwaZulu-Natal, South Africa (Protocol BCA208/18).

4.2.4.2 Study design

This was a sub-analysis of data from a pre-existing registry of surgical patients.

4.2.4.3 Study setting

The pre-existing registry was compiled at a quaternary-level hospital located in the urban setting of Durban, South Africa. The hospital is a public-sector facility which offers free specialist services to residents of the KwaZulu-Natal Province on the east coast of South Africa. As the only quaternary-level hospital in this region, this facility represents a scarce healthcare resource and admission to the facility is strictly referral-based.

4.2.4.4 Study sample

The pre-existing surgical registry was comprised of adult patients who underwent laparotomy at the hospital. All patients in the registry were retrospectively identified from the hospital operating room lists for the period 1 January 2006 to 31 December 2010. The sample size was based on the assumed incidence of SSI (15-20%) and existing rules of thumb for the inclusion of variables into a regression analysis (i.e. “10 events per variable included in a regression model). Laparotomy patients were considered the most appropriate population for this study as open abdominal procedures are traditionally considered to be high-risk for the development of SSI.[4]

There were nearly 700 laparotomies performed during the specified time period; however, only 439 were adults (aged >18 years old). The patients were identified from the operative room lists at the hospital during the specified time period. Laparotomy patients are considered high-risk for SSI as any open abdominal surgery is considered to carry additional risk for SSI.

4.2.4.5 Data and definitions

The registry data were collected through a retrospective chart review. Demographic information, overall comorbidity, surgery-related variables, SSI, and other complications were collected for each patient. The source documents screened for the presence or absence of these variables included admission notes, progress notes, operation notes, anaesthetic records, laboratory reports, and hospital discharge summaries.

SSI was based on documented clinical signs and symptoms of infection which may or may not have been accompanied by a positive microbiological culture result, during the period of hospitalisation following the surgery. This definition of SSI is similar to that proposed by the Centers for Disease Control.[5] All other postoperative complications were based on a physician's diagnosis which was recorded in the relevant source documents. Postoperative LoS was determined as the number of days between the date of surgery and the date of hospital discharge as listed on the patient's hospital discharge summary.

The registry data were maintained on a password-protected electronic spreadsheet, with quality control processes being implemented at regular time points during the data collection process.

4.2.4.6 Statistical analysis

Patients with missing data were excluded from the analysis. Characteristics of the study sample were summarised using the relevant descriptive statistical methods for categorical and continuous variables. The relationship between SSI and postoperative LoS was investigated using quantile regression. This method allowed for the effects of SSI to be tested across various quantiles (also known as percentiles) of postoperative LoS, while controlling for potentially important covariates.[6] The statistical analysis in this study was stratified by three percentile values – the 25th, 50th, and 75th percentiles. SSI was the main independent variable under investigation. The analysis was controlled for patient demographics, summarised comorbidity, surgery related variables, and other complications. Results for the quantile regression are presented as regression coefficients (corresponding to a duration of postoperative LoS in days) with 95% confidence intervals (95%CIs). Where applicable, a p-value <0.050 was considered statistically significant. For the descriptive cost analysis, the unit cost per day stay at the hospital was standardised using costs reported for 2010 (8396 South African Rands – ZAR or $ 1114 per day). This unit cost per day stay at the hospital was obtained from an annual report document and is inclusive of the facility fee and healthcare professional fee. Crude hospitalisation costs specifically attributed to SSI, if any, were extrapolated from statistically significant quantile regression results for this outcome by multiplying the regression coefficients and 95%CIs obtained for SSI by the unit cost per day stay. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., USA).

4.2.5 Results

The original laparotomy patient registry consisted of 439 adult patients. It was subsequently noted that there were four patients for which the hospital discharge date could not be cross-validated with other source documents in the patient medical charts. These four patients were excluded from the final analysis, as a reliable estimate of postoperative LoS could not be calculated for them. Therefore, 435 patients were included in the final analysis. A description of important characteristics in the study sample is presented in Table I. Approximately one-third of the study sample were male (143 patients, 32.9%). The median age was 42.0 (IQR: 30.0-56.0) years old. A total of 205 patients (47.1%) had an ASA score >2. The majority of patients had surgery for treatment of a non-communicable disease condition (398 patients, 91.5%). Just over one-third of patients had emergency procedures (150 patients, 34.5%). A total of 150 patients (35.9%) received a perioperative blood transfusion. Eighty-two patients (18.9%) had a repeat laparotomy. Sixty-five patients (14.9%) experienced a SSI following their surgery, while 63 patients (14.5%) had other infectious postoperative complications. Cardiovascular, respiratory, and renal complications occurred in 24 (5.5%), 32 (7.4%), and 28 patients (6.4%), respectively. Eighty patients (18.4%) suffered postoperative mortality. The median postoperative LoS for the study sample was 7.0 (IQR: 4.0-14.0) days.

Table I. Description of the study sample

Characteristic	**Summary statistic**
Male gender, n (% of N=435)	143 (32.9)
Age in years, median (IQR)	42.0 (30.0 to 56.0)
ASA score >2, n (% of N=435)	205 (47.1)
Non-communicable disease indication for surgery, n (% of N=435)	398 (91.5)
Emergency procedure, n (% of N=435)	150 (34.5)
Perioperative blood transfusion, n (% of N=435)	156 (35.9)
Reoperation, n (% of N=435)	82 (18.9)
SSI, n (% of N=435)	65 (14.9)
Cardiovascular complications, n (% of N=435)	24 (5.5)
Respiratory complications, n (% of N=435)	32 (7.4)
Renal complications, n (% of N=435)	28 (6.4)
Other infection	63 (14.5)
Death, n (% of N=435)	80 (18.4)
Postoperative LoS in days, median (IQR)	7.0 (4.0 to 14.0)

IQR: Interquartile range, ASA: American Society of Anesthesiologists, SSI: Surgical site infection.

The impact of SSI on postoperative LoS is shown in Table II. When adjustments for important covariates were made, the impact of SSI was observed to be most profound at the 25th percentile of postoperative LoS. SSI did not have a significant impact on postoperative LoS at the 50th and 75th percentiles.

Table II. Results of the quantile regression analysis investigating the relationship between SSI and postoperative LoS

Characteristic	**Regression coefficient: 25th percentile (95%CI)**	**Regression coefficient: 50th percentile (95%CI)**	**Regression coefficient: 75th percentile (95%CI)**
Main variable			
SSI	1.06 (0.06 to 2.07)*	1.37 (-0.41 to 3.15)	3.12 (-1.52 to 7.76)
Other covariates			
Male gender	0.75 (0.01 to 1.48)*	2.71 (1.40 to 4.02)*	4.47 (1.06 to 7.88)*
Per year increase in age	0.02 (-0.01 to 0.04)	0.40 (0.01 to 0.08)*	0.01 (-0.08 to 0.11)
ASA score >2	-3.10 (-0.97 to 0.35)	0.19 (-0.97 to 1.36)	-0.58 (-3.62 to 2.46)
Noncommunicable disease indication for surgery	-0.06 (-1.30 to 1.18)	-0.92 (-3.12 to 1.28)	0.60 (-5.66 to 5.79)
Emergency procedure	1.71 (0.89 to 2.54)*	1.36 (-0.09 to 2.82)	3.81 (0.01 to 7.60)*
Perioperative blood transfusion	0.68 (-0.08 to 1.43)	1.64 (0.30 to 2.97)*	2.40 (-1.08 to 5.88)
Reoperation	2.47 (1.55 to 3.39)*	6.04 (4.41 to 7.67)*	
Cardiovascular complications	-0.20 (-1.76 to 1.37)	3.02 (0.25 to 5.80)*	2.89 (-4.35 to 10.13)
Respiratory complications	0.23 (-1.10 to 1.56)	1.55 (-0.81 to 3.91)	-0.21 (-6.36 to 5.95)
Renal complications	5.32 (3.87 to 6.77)*	6.44 (3.87 to 9.02)*	3.19 (-3.52 to 9.91)
Other infection	2.39 (1.28 to 3.50)*	3.02 (1.04 to 4.99)*	7.01 (1.86 to 12.16)*
Death	-4.44 (-5.47 to -3.42)*	-5.93 (-7.74 to -4.11)*	-5.71 (-10.44 to -0.98)*

95%CI: 95% Confidence interval, SSI: Surgical site infection, LoS: Length of stay, ASA: American Society of Anesthesiologists. Regression coefficient represents difference (either positive or negative based on sign preceding the coefficient value) in postoperative LoS days. *Statistically significant result ($p<0.050$) when compared with reference category for each characteristic.

As a crude estimate, additional hospitalisation costs associated with SSI amounted to an extra ZAR 8900 (95%CI: ZAR 504 to ZAR 17340) in the 25th percentile of postoperative LoS. This was equivalent to \$ 1180 (95%CI: \$ 67 to \$ 2300). Costs for the 50th and 75th percentiles were not calculated as SSI did not significantly impact postoperative LoS in these percentile groups ($p>0.050$ in the quantile regression analysis).

4.2.6 Discussion

SSI was associated with a minimum increase in postoperative LoS, which was most evident in the group of patients who did not stay very long in hospital (i.e. the 25th percentile group). The minimum increase in postoperative LoS of 1.06 days caused by SSI in the 25th percentile group incurred an additional healthcare expenditure of ZAR 8900 ($ 1180). The findings of this study partially confirm those from African and non-African studies which reported longer postoperative LoS in surgical patients with SSI.[2, 3] However, the extra days of hospitalisation attributed to SSI in this study was not as excessive as that in the non-African studies.[2, 3] In addition, the extra days of hospitalisation attributed to SSI in this study was not as excessive as that in a Zimbabwean study of patients undergoing abdominal surgery.[7] In the Zimbabwean study, the median LoS in patients with SSI was 10 days.[7] Furthermore, the additional days of hospitalisation attributed to SSI in our study was not generalised across all quantiles of postoperative LoS investigated. This confirms our notion that findings related to SSI and postoperative LoS derived from non-African populations might not be entirely applicable in the South African context. Our findings also highlight a potential difference in LoS attributed to SSI between African countries (South Africa and Zimbabwe), most likely due to a difference in resources between these two countries. Although the additional days of hospitalisation associated with SSI in the 25th percentile group was minimal, this could have important consequences for patient turnover in surgical wards at the hospital. Additional LoS associated with preventable conditions such as SSI can cause unnecessary delays in patient turnover. This would be further complicated by the high demand for quaternary-level healthcare services in the province of KwaZulu-Natal, South Africa. A high incidence of SSI would entail a considerable total number of extra days during which the afflicted patients would be kept in hospital. As such, SSI rates should be carefully monitored, with preventative strategies recommended for high-risk surgical populations.

The crude estimate for additional costs attributed to SSI in the 25th percentile of postoperative LoS suggests that SSI also has an economic impact in our setting. Depending on the overall incidence of SSI, treatment of this preventable condition has the potential to divert healthcare finances away from other aspects of postoperative care where such finances are most needed. Therefore, there also seems to be a financial incentive for preventing SSI at the hospital.

The association between SSI and postoperative LoS at the 25th percentile was not observed at the 50th and 75th percentiles of postoperative LoS. One must consider that the SSIs which did occur in the study population were likely minor/not severe. More severe infections would have required longer antibiotic therapy and possible surgery with recovery time. Patients who have a much shorter postoperative stay are often those who do not experience any serious complications during the immediate postoperative period. Patients who have severe complications other than SSI are unlikely to be discharged early and are given more stringent monitoring and care due to their postoperative condition. As a consequence of the more stringent monitoring, more SSIs might be detected at an early stage in development. These SSIs can then be timeously treated and will not contribute to any significant additional LoS in these patients. The potential benefits of increased postoperative monitoring in reducing postoperative complications forms the basis for an ongoing randomized controlled trial on the African continent.[8] In situations where the management of perioperative complications that are unrelated to SSI involves administration of prophylactic or therapeutic antibiotics, then this might simultaneously address an existing SSI.

There were both strengths and limitations to this research. The first strength of this study is the appropriate sample size of 435 patients which allowed for an adjusted statistical analysis to be performed. The second strength is our selection of a high-risk intra-abdominal (laparotomy) population for investigation in this study. The third strength is that this study is amongst the very few from African settings which delve into the impact of SSI on postoperative LoS and healthcare expenditure. The fourth and final strength of this study is that quantile regression was used to investigate the impact of SSI across various percentiles, rather than ordinary least squares regression which focuses on a mean value only.[6] The first limitation of this study is that it involved data from a single, urban, quaternary-level hospital. There is a possibility that the findings of this study might not be applicable to other facilities in rural areas or lower-level facilities. The second limitation is that this study did not consider the impact of post-discharge SSI. The definition of SSI used in this research did not depend solely on a positive microbiological culture result. The main clinical feature used to identify SSI in this research was the presence of pus. While it is possible that a small number of minor infections might have been missed due to a lack of pus formation, it is likely that most of the clinically meaningful infections (those where there is visible pus in the surgical site) would have been detected by the physicians. Lastly, the crudely estimated cost data does not include treatment costs for SSI.

4.2.7 Conclusion

SSI had healthcare resource and economic consequences in the group of patients who had shorter hospital stays following their surgery. The general estimates of cost in this group of patients would be directly proportional to SSI rates. The findings of this study should be interpreted with caution as it only provides a generalized estimation/exploration of costs associated with SSI, we were unable to establish the severity of the infections and could not account for this in our analysis, and no real conclusions can be truly made on healthcare utilization and economic consequences on the sole basis of this study. Nevertheless, the findings of this research serve as an added impetus for reducing SSI rates at the hospital. Future studies on this topic should be prospective, multicenter, have standardized definitions for SSI, and should also account for the severity of infection.

4.2.8 References

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Chapter 5

Prognostic relevance of routinely performed laboratory tests for surgical site infection in a South African setting

Preamble

Chapter 5 is comprised of 2 manuscripts (Manuscript 4 and Manuscript 5). This chapter sought to address Objective 3 of the PhD research project. The findings from the analysis under Objective 1 (Manuscript 1) of the PhD research project informed the analyses performed in this chapter. More specifically, this chapter investigated the possible role of preoperative serum albumin and serum sodium (which were found to be potentially associated with SSI in Manuscript 1) as predictive tests for postoperative surgical site infection (SSI) in a resource-limited South African setting. The first of the two manuscripts in this chapter (Manuscript 4) evaluated the prognostic accuracy of preoperative serum albumin for SSI and compared this with two commonly used multifactorial risk stratification tools. The findings of this analysis suggest that preoperative albumin has great promise as a simple, cost-effective tool for predicting SSI in resource-limited settings. The second of the two manuscripts in this chapter (Manuscript 5) explored the relationship between preoperative serum sodium measurements and SSI. Although this case-control analysis found a statistically significant association between lower serum sodium and a higher risk of SSI, this finding lacks clinical significance. Importantly, the two manuscripts comprising this chapter are a stepping-stone for future research on prognostic biomarkers for SSI in resource-limited settings.

5.1.1 Manuscript 4

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5.1.2 Manuscript abstract

Background: Preoperative hypoalbuminemia is a risk factor for surgical site infection (SSI) in the South African setting. However, the predictive accuracy of preoperative hypoalbuminemia has not been tested against established SSI risk stratification models in our setting, which could have important implications for SSI prevention strategies.

Objective: With reference to SSI in South African settings, the study objective was to compare the overall predictive accuracy of preoperative hypoalbuminemia with that obtained for the SENIC/NNIS risk scores.

Method: This was a sub-analysis of a pre-existing laparotomy patient registry (N=439). Variables collected as part of the registry included preoperative serum albumin measurements and all parameters of the SENIC/NNIS risk scores. Preoperative hypoalbuminemia was defined as preoperative serum albumin of <30 g/L. The study outcome was SSI up to 30 days postoperatively. Overall predictive accuracy was determined through a receiver-operator-characteristic (ROC) curve analysis, with results presented as C-statistics (95% Confidence intervals, 95%CI).

Results: The C-statistics obtained for preoperative hypoalbuminemia, the SENIC risk score, and the NNIS risk score were 0.677 (95%CI: 0.609-0.746), 0.652 (95%CI: 0.582-0.721), and 0.634 (95%CI: 0.563-0.705).

Conclusion: All three methods display similar predictive accuracy for SSI. However, preoperative hypoalbuminemia has several practical advantages over the SENIC/NNIS scores which must be considered.

5.1.3 Introduction

Surgical site infection (SSI) is recognised as an important cause of morbidity, mortality, and increased healthcare resource utilisation amongst surgical populations across the world.[1-3] The identification of surgical patients at high-risk of developing SSI and implementation of preventative strategies in these patients therefore remains an important consideration for surgeons.[4, 5] There are two commonly used risk stratification models for SSI: The Study on the Efficacy of Nosocomial Infection Control (SENIC) risk score and the National Nosocomial Infections Surveillance (NNIS) risk score.[4, 5]

The SENIC risk score was developed by Hayley et al., using data collected during 1970 for almost 59 000 American surgical patients. It is a multivariate risk model consisting of four variables, including abdominal operation, operation >2 hours in duration, contaminated-dirty wound, and having ≥3 discharge diagnoses.[4] Each variable in the model, if present, is allocated a point score of "1". Cumulative scores, which could theoretically range between 0 and 4 points, are then determined for each patient. Hayley et al., reported that the incidence of SSI in individuals with a cumulative score of ≥2 points ranged between 10% and 30%.[4]Accordingly, the cumulative score of≥2 points for the SENIC method was used as a threshold to define the "high-risk" group for SSI.[4] From their study sample of almost 59 000 surgical patients these authors determined that the high-risk group accounted for approximately 90% of all SSIs.[4] The NNIS risk score was proposed during the early 1990s as an improvement on the SENIC risk stratification for SSI.[5] Using a cohort of almost 85 000 surgical patients, Culver and colleagues were able to develop a multivariate risk model consisting of three factors: surgical wound class, operation longer than T-time (where "T" is the usual duration of a surgical procedure), and American Society of Anesthesiologists (ASA) preoperative physical status classification of ≥3.[5] The inclusion of the ASA classification in the NNIS risk score was thought to have improved the predictive accuracy of the model by accounting for intrinsic risk. Similar to the SENIC risk score, all components in the NNIS risk score are allocated a single point. Cumulative scores for the NNIS risk score can range between 0 and 3 points. Culver et al., found that the incidence of SSI was much higher in patients with cumulative NNIS scores ≥2 points (6.8-13.0%) when compared with patients who had cumulative NNIS scores <2 (1.5-2.9%).[5]

Although the SENIC and NNIS risk stratification methods represent an important leap forward in the prediction of SSI, the ability of these models to discriminate between patients with and without SSI has been questioned in recent years. Some experts have suggested that future methods aimed at SSI prediction should be based on biomarkers, as this approach might demonstrate a better ability to discriminate between patients with and without SSI.[6] Albumin is one biomarker which has been proposed for the prediction of SSI. This small, globular protein is produced in the liver and accounts for 50% of the total serum protein content in healthy individuals.[7] Hypoalbuminemia, or a serum albumin measurement below the lower limit of the normal reference range, is often used as a marker for malnutrition.[8] It is proposed that malnutrition increases an individual's susceptibility to postoperative infection in two ways. Firstly, malnutrition impairs wound healing by diminishing fibroblast proliferation and collagen synthesis.[6] Secondly, albumin deficiency is linked to lymphocytopenia and immune dysfunction.[6] It is therefore unsurprising that much of the global literature has reported preoperative hypoalbuminemia to be associated with an increased risk of SSI.[9-11] Our recent study in South African surgical patients also identified preoperative hypoalbuminemia as a risk factor for SSI.[12] With reference to SSI prediction in South African patients undergoing open abdominal surgery, the objective of the current study was to compare the overall predictive accuracy for preoperative hypoalbuminemia with that obtained for the SENIC and NNIS methods. As this has not been previously investigated in the South African context, this study also sought to address an important gap in the literature.

5.1.4 Methods

5.1.4.1 Ethical approval

This study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, South Africa (Protocol number: BCA208/18).

5.1.4.2 Study design

This was a sub-analysis of patient data from our prior study of SSI risk factors.[12]

5.1.4.3 Study setting

The study setting was the Inkosi Albert Luthuli Central Hospital (IALCH) located in Durban, South Africa. IALCH is a public sector facility which provides quaternary-level healthcare services to the populace of the KwaZulu-Natal Province on the east coast of South Africa.

5.1.4.4 Study sample

We included all 439 patients from our prior study in the current sub-analysis. All patients were adults and had undergone laparotomy procedures at IALCH between 1 January 2006 and 31 December 2010. The minimum sample size required for this study was 100 patients, prioritizing sensitivity at 80%, SSI incidence of 15-20%, statistical power = 80%). Thus, the final sample size of 439 patients was deemed appropriate.

5.1.4.5 Data and definitions

Data for our prior study were collected via a retrospective chart review. We had collected the following variables for each patient: demographic information, comorbidities, medication use, preoperative laboratory test results (including serum albumin measurements), surgery-related variables, and all parameters of the SENIC/NNIS risk scores. Cumulative SENIC/NNIS scores were computed for each patient. SENIC and NNIS were complete for all patients in this study. The study outcome was SSI up to 30 days postoperatively. This outcome was based on the widely used definition proposed by the Centers for Disease Control (CDC).[13]This definition incorporates clinical signs and symptoms of infection and is not solely based on microbiological evidence of infection. Preoperative hypoalbuminemia was defined as a preoperative serum albumin measurement <30 g/L. This threshold for preoperative hypoalbuminemia has been proposed in recent perioperative nutrition guidelines.[14]All preoperative serum albumin measurements were taken at least one month prior to surgery, which is in keeping with the current preoperative work-up practices at IALCH. All serum albumin measurements were performed by a South African National Accreditation System (SANAS)-accredited chemical pathology laboratory.

5.1.4.6 Statistical analysis

Descriptive statistics were used to summarise the characteristics of the study sample. Descriptive results for categorical variables are presented as frequencies (%). We analysed all the continuous variables in the study for normality using the Kolmogorov-Smirnov (KS) test. All KS test results were found to be statistically significant ($p<0.05$), indicating that the data for all continuous variables did not demonstrate a normal distribution. Therefore, summary data for the continuous variables in this study are presented as medians with interquartile range (IQR). The overall predictive accuracy of hypoalbuminemia, the SENIC risk score, and the NNIS risk score were assessed using receiver-operator-characteristic (ROC) curves. The resulting C-statistic was used to classify overall predictive accuracy as follows: <0.500 = not any better than chance, -0.600-0.699 = fair, >0.700 = good. Standard 2x2 epidemiological tables and equations were used to determine the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for each risk stratification method. For this aspect of the analysis, conventional SENIC/NNIS thresholds for high-risk individuals were adopted from the published literature.[4, 5] In addition, 95% Confidence intervals (95%CIs) are provided for all estimates of predictive accuracy. When comparing the three risk stratification methods, estimates of predictive accuracy with discreet confidence intervals were considered to be statistically different (i.e. $p<0.05$).

5.1.5 Results

The characteristics of the study sample are presented in Table I. The median age of the study sample was 42.0 (IQR: 30.0-56.0) years. One-third of the study population were males. The most common indication for surgery was cancer (183 patients, 41.7%). ASA preoperative classification was high for 207 patients (47.2%). A total of 62 patients (14.1%) reported preoperative non-steroidal anti-inflammatory drug use. Statins were used preoperatively in 25 patients (5.7%). The most common comorbidity was obesity (152 patients, 34.6%). Median preoperative leukocyte, platelet, serum creatinine, haemoglobin, and serum sodium were within the laboratory reference ranges. A total of 159 patients (36.2%) were classified as having hypoalbuminemia. Just over one-third of the study population had emergency surgery (150 patients, 34.2%). Contaminated-dirty procedures were reported for 88 patients (20.0%). Surgery was of extended duration (>2 hours long) in 153 patients (34.9%). Surgical incisions were closed with Bogota bags in 70 patients (15.9%). The vast majority of patients (366 patients, 83.4%) received antibiotics. A total of 157 patients (35.8%) received perioperative blood transfusions. Very few patients used patient-controlled analgesia pumps after their surgery (33 patients, 7.5%). Regarding discharge diagnoses, 136 patients (31.0%) had ≥3 discharge diagnoses listed under the surgical admission in their medical records. Seventy-three patients (16.6%) had a SSI within 30 days following their surgery. SENIC scores were high in 285 patients (64.9%). Only 88 patients (20.0%) had high NNIS scores.

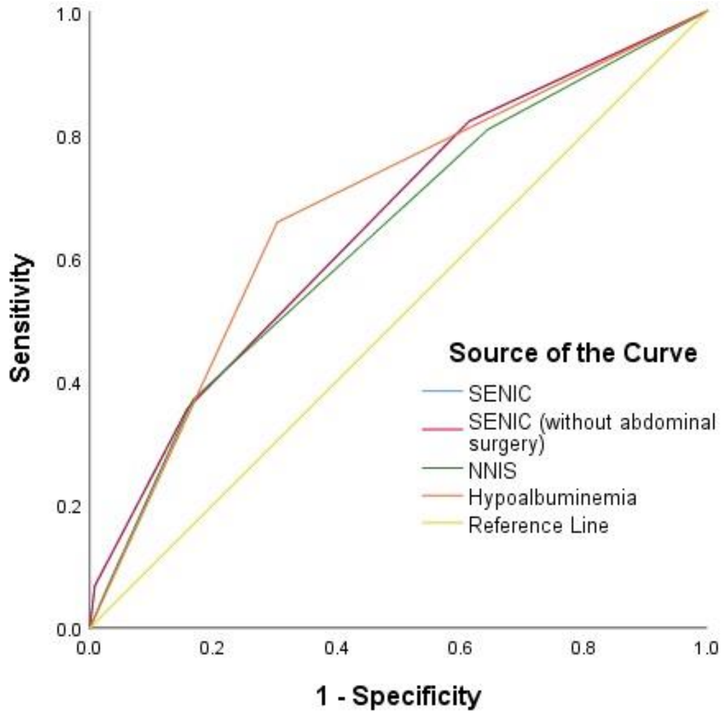
Table I. Description of the study sample

Characteristic	**Summary statistic**
Median age, years (IQR)	42.0 (30.0-56.0)
Male gender, n (% of N=439)	145 (33.0)
Indication for surgery - Bleed, n (% of N=439)	12 (2.7)
Indication for surgery - Cancer, n (% of N=439)	183 (41.7)
Indication for surgery - Infection, n (% of N=439)	36 (8.2)
Indication for surgery - Other, n (% of N=439)	151 (34.4)
Indication for surgery - Trauma, n (% of N=439)	57 (13.0)
ASA preoperative classification ≥3, n (% of N=439)	207 (47.2)
Preoperative non-steroidal anti-inflammatory use, n (% of N=439)	62 (14.1)
Preoperative statin use, n (% of N=439)	25 (5.7)
Obesity, n (% of N=439)	152 (34.6)
Hypertension, n (% of N=439)	140 (31.9)
Diabetes, n (% of N=439)	57 (13.0)
Cardiovascular disease, n (% of N=439)	50 (11.4)
HIV, n (% of N=439)	30 (6.8)
Metastatic cancer, n (% of N=439)	86 (19.6)
Obstructive airway disease, n (% of N=439)	25 (5.7)
Gastric ulcers, n (% of N=439)	17 (3.9)
Current smoker, n (% of N=439)	44 (10.0)
Preoperative leukocyte count x10^9 cells/L, median (IQR)	8.0 (5.9-10.6)
Preoperative platelets count x10^9/L, median (IQR)	263.0 (187.0-351.0)
Preoperative serum creatinine µmol/L, median (IQR)	75.0 (65.0-108.0)
Preoperative haemoglobin g/dL, median (IQR)	10.9 (9.2-12.4)
Preoperative serum sodium mEq/L, median (IQR)	139.0 (137.0-142.0)
Preoperative serum albumin g/L, median (IQR)	35.0 (22.0-42.0)
Preoperative hypoalbuminemia, n (% of N=439)	159 (36.2)
Abdominal procedure, n (% of N=439)	439 (100.0)
Emergency procedure, n (% of N=439)	150 (34.2)
Contaminated-dirty procedure, n (% of N=439)	88 (20.0)
Surgery duration > T-time (2 hours), n (% of N=439)	153 (34.9)
Bogota bag, n (% of N=439)	70 (15.9)
Antibiotic prophylaxis, n (% of N=439)	366 (83.4)
Perioperative blood transfusion, n (% of N=439)	157 (35.8)
Patient-controlled analgesia postoperatively, n (% of N=439)	33 (7.5)
≥3 discharge diagnoses, n (% of N=439)	136 (31.0)
SSI within 30 days postoperatively, n (% of N=439)	73 (16.6)
SENIC score ≥2, n (% of N=439)	285 (64.9)
NNIS score ≥2, n (% of N=439)	88 (20.0)

IQR: Interquartile range, SSI: Surgical site infection, SENIC: Study on the Efficacy of Nosocomial Infection Control, NNIS: National Nosocomial Infections Surveillance.

Figure 1 shows the results of the ROC curve analysis. The performance of each risk stratification method is presented as a separate line (four lines). In keeping with the general format of ROC curve analyses, a reference line (fifth line) indicating the threshold for a test/risk method performing better than pure chance is also included (C-statistic for reference line = 0.500).

Figure 1. Results of the ROC curve analysis



We had some concerns related to overestimation of SSI when applying SENIC to our study sample, which was comprised solely of abdominal surgery patients (abdominal surgery is a component of the original SENIC score). We tested an adapted SENIC score (with abdominal surgery omitted) against the original score and did not find any difference in the predictive accuracy between the two variations of the SENIC score (C-statistic, 95%CI for both = 0.652, 0.582-0.721). This explains why the two lines overlap with each other on the ROC curve graph. A decision was made to continue with the use of the original SENIC score for the subsequent aspects of the statistical analysis. The C-statistic obtained for the NNIS score was 0.634 (95%CI: 0.563-0.705). The C-statistic obtained for preoperative hypoalbuminemia was 0.677 (95%CI: 0.609-0.746). Based on the observed C-statistics, all methods were found to demonstrate “fair” predictive accuracy for SSI. The 95%CIs for all estimates were found to overlap, suggesting no statistically significant difference ($p>0.05$) in the overall predictive accuracy between all three risk stratification methods.

The sensitivity, specificity, PPV, and NPV for all three risk stratification methods is presented in Table II. Comparison of the 95%CIs for sensitivity and specificity between the three methods revealed several statistically significant ($p<0.05$) differences. Preoperative hypoalbuminemia and the SENIC score were found to have a higher sensitivity for SSI than the NNIS score. Based on the overlapping 95%CIs for the sensitivity estimates obtained for hypoalbuminemia and SENIC, there was no difference in overall sensitivity between the two tests. The NNIS score had a higher specificity when compared with preoperative hypoalbuminemia and SENIC. Preoperative hypoalbuminemia had a higher specificity when compared with SENIC. Comparison of the 95%CIs obtained for PPV/NPV estimates did not reveal any statistically significant differences between the three risk stratification methods for these parameters.

Table II. Sensitivity, specificity, PPV, and NPV for each risk stratification method

Method	**Sensitivity, % (95%CI)**	**Specificity, % (95%CI)**	**PPV, % (95%CI)**	**NPV, % (95%CI)**
Hypoalbuminemia	65.8 (53.7-76.5)	69.7 (64.7-74.3)	30.2 (23.2-38.0)	91.1 (87.1-94.1)
SENIC risk score	82.2 (71.5-90.2)	38.5 (33.5-43.7)	21.1 (16.5-26.3)	91.6 (86.0-95.4)
NNIS risk score	37.0 (26.0-49.1)	83.3 (79.1-87.0)	30.7 (21.3-41.4)	86.9 (82.9-90.2)

CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, SENIC: Study on the Efficacy of Nosocomial Infection Control, NNIS: National Nosocomial Infections Surveillance.

5.1.6 Discussion

Preoperative hypoalbuminemia, the SENIC score, and the NNIS score displayed similar overall predictive accuracy for SSI. A more in-depth comparison of predictive parameters (sensitivity, specificity, PPV, NPV) between the three risk stratification methods revealed that the similar performance was due to either high sensitivity being offset by low specificity (preoperative hypoalbuminemia and the SENIC score) or high specificity being offset by low sensitivity (the NNIS score).

Notwithstanding the similar predictive performance for SSI, preoperative hypoalbuminemia has several practical advantages over the SENIC and NNIS risk scores. Serum albumin measurements are a particularly important assessment in patients with abdominal pathologies, such as our study sample of laparotomy patients, where it is often used as a measure of liver function.[15] Serum albumin measurements are included as part of the preoperative work-up in patients undergoing surgery for abdominal pathologies. Therefore, an assessment of SSI risk can be made for almost all patients awaiting abdominal surgery procedures. The serum albumin test is also widely available and can be performed by a laboratory or as a point-of-care assay.[16, 17] Serum albumin measurements are also cost-effective, with current costs per test invoiced at approximately US$3 in our setting. This cost is negligible when compared to the excessive costs required to treat SSI.[3] The process of risk score computation, such as that in the SENIC and NNIS methods,[4, 5] might be viewed as a tedious process by the often-inundated surgeon in the South African public healthcare sector. In comparison, identifying high-risk patients through evaluation of preoperative serum albumin measurements is a simpler process. While the SENIC/NNIS were complete for each patient in this study, there also exists a potential drawback in the SENIC/NNIS risk scores when a component of the score is missing or inaccurately recorded for a patient. For example, the ASA preoperative classification is a component of the NNIS risk score,[5] but evidence from a South African setting suggests that this score is inconsistently recorded or missing from the preoperative assessments completed by anaesthetists.[18] In such situations, it becomes impossible to compute a cumulative risk score, and subsequently estimate SSI risk in a patient using the NNIS score. Awareness of the various risk stratification methods might also be an issue, and thus clinical decision-making tools which seek to improve postoperative outcomes (such as the various SSI risk stratification methods) also need to be promoted amongst surgeons.

In addition, the most crucial difference between evaluating preoperative serum albumin measurements and the SENIC/NNIS methods for SSI prediction is that the SENIC/NNIS methods require certain information which is only available intraoperatively or postoperatively. This information includes the surgical incision wound classification, the duration of surgery, and the number of discharge diagnoses.[4, 5] The World Health Organisation (WHO) has proposed multiple preventative interventions for SSI, some of which can be considered for implementation in high-risk patients during the preoperative period.[19] It would be more resource-efficient to target high-risk patients for these interventions, rather than all patients. Therefore, the added advantage of using preoperative hypoalbuminemia to predict SSI is that it would allow for a full range of SSI preventative measures (pre-, intra-, and postoperatively) to be implemented in high-risk patients, whereas the SENIC/NNIS risk scores would only allow for postoperative interventions (ie. once the cumulative SENIC/NNIS score is computed) to be implemented.

Along with the SSI preventative interventions proposed by the WHO, possible consideration must be given to optimising preoperative serum albumin as a risk reduction strategy for SSI in our setting. Optimisation of preoperative serum albumin can be achieved through the provision of comprehensive preoperative nutrition to patients awaiting surgery.[20, 21] The appropriate time-point in the preoperative period when it would be best to initiate such a strategy in our patient population is unknown, but it is inevitable that the duration of the nutritional intervention would have a direct impact on expenditure within health departments. The costs incurred by health departments in ensuring appropriate perioperative nutrition in patients awaiting surgery will likely be far lower than the costs which would be incurred if these patients were to develop SSI. Therefore, new research studies should be conducted in our setting to evaluate the impact of preoperative serum albumin optimisation on SSI risk.

There were limitations to this research, some of which have been declared in our previous manuscript involving the same laparotomy patient registry.[12] Amongst these previously declared limitations was a possible lack of generalisability in our findings as the patient registry was compiled at a single, quaternary-level institution which might not necessarily reflect the patient population in other South African settings. Another previously declared study limitation was that there might have been some patients who had developed SSI outside of the 30-day period proposed by the CDC definition.[13] There is also the possibility that some patients with minor forms of SSI might have self-managed their condition or presented for treatment at lower-level healthcare facilities. These patients would have been considered as not having SSI in our statistical analysis. A limitation unique to our current sub-analysis is that we did not investigate other predictive biomarkers for SSI proposed in the literature, such as C-reactive protein,[22] due to the inconsistency in which the tests were ordered preoperatively at our institution. Another limitation unique to our current study is that we did not stratify our results by age and gender. We believe that a more in-depth investigation of this nature would require a larger sample size far beyond the scope of our pre-existing laparotomy patient registry. Any sub-analyses (such as stratification by gender or age) would require a substantially higher overall sample size, as the analysis performed in smaller subgroups will need to be adequately powered.

5.1.7 Conclusion

Preoperative hypoalbuminemia and the SENIC/NNIS scores demonstrated a similar predictive accuracy for SSI. There are, however, several practical advantages to using preoperative hypoalbuminemia over the SENIC/NNIS risk scores for SSI prediction. The most important of these advantages is that evaluating serum albumin levels allows for the preoperative calculation of SSI risk and the implementation of SSI preventative strategies in high-risk patients when compared with those which can only be implemented postoperatively following calculation of SENIC/NNIS scores. Further research in our setting, namely large prospective studies which seek to investigate the impact of preoperative serum albumin optimisation on SSI risk, is required.

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5.2.1 Manuscript 5

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5.2.2 Manuscript abstract

Background: We previously reported a statistical trend toward a harmful association between lower preoperative serum sodium levels and surgical site infection (SSI) in South African laparotomy patients. Serum sodium tests are widely available and could serve as a cost-effective method for preoperatively identifying patients at risk for SSI who might benefit from additional preventative strategies. We sought to investigate the possible association between lower serum sodium levels and SSI further, in a larger sample of South African patients undergoing various surgical procedures.

Objective: To determine if preoperative serum sodium levels are associated with SSI in South African surgical patients.

Method: This was a propensity matched case-control study involving data from 729 surgical patients who attended a South African quaternary hospital between 01 January 2012 and 31 July 2016. Cases were defined as patients who developed SSI. Controls were defined as patients who did not develop SSI. Multivariate logistic regression was used to investigate the association between preoperative serum sodium levels (in mmol/L) and SSI.

Results: Lower preoperative serum sodium levels were associated with a higher risk of SSI (Odds ratio per 1.0 mmol/L decrease in serum sodium: 1.051, 95% Confidence interval: 1.007-1.097; p=0.026).

Conclusion: Although we report a statistically significant association between lower preoperative serum sodium levels and a higher risk of SSI, the magnitude of this effect size (odds ratio) is minimal and clinically insignificant. Preoperative serum sodium levels are unlikely to be useful for SSI risk stratification in our setting.

5.2.3 Introduction

Surgical site infection (SSI) is an important postoperative complication in African settings, where it is associated with increased morbidity, mortality, and healthcare resource utilisation.[1, 2] Preoperative identification of high-risk patients in these settings would allow for a full range of preventative strategies to be implemented throughout the perioperative period.[3] We recently demonstrated the pitfalls of using conventional SSI risk stratification methods, namely the National Nosocomial Infections Surveillance (NNIS) score and the Study of the Efficacy of Nosocomial Infection Control (SENIC) score, in South African patients undergoing abdominal surgery.[4] A major limitation is that intraoperative variables are required to compute these scores. Accordingly, these scoring systems cannot be used preoperatively to estimate postoperative SSI risk.[4]

On the other hand, our previous research also suggests that routinely measured analytes, such as serum albumin, can be used during the preoperative period to provide postoperative estimates of SSI risk that are comparable to the those provided by the NNIS and SENIC scores.[4] In another of our prior studies, involving 439 South African laparotomy patients, we found a statistical trend toward a harmful association between lower preoperative serum sodium (hyponatremia) and SSI.[5] Serum sodium measurements are widely available, cost-effective tests that are usually ordered as part of the urea and electrolyte panel.[6] The panel is used to screen for renal impairment during the preoperative and postoperative period.[7]

We sought to investigate the possible association between serum sodium levels and SSI further, in a larger sample of patients undergoing various surgical procedures.

5.2.4 Methods

5.2.4.1 Ethical approval

This research was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (Protocol number: BE595/16).

5.2.4.2 Study design

This was a propensity matched case-control study.

5.2.4.3 Study setting

The study setting was the Inkosi Albert Luthuli Central Hospital (IALCH) in Durban, South Africa. This public-sector, quaternary level hospital provides surgical and medical services to residents of the eastern seaboard of South Africa.

5.2.4.4 Study sample

The study sample consisted of adult patients (aged ≥18 years old) who underwent surgical procedures at IALCH between 01 January 2012 and 31 July 2016. Additional eligibility criteria used to derive the study sample are provided in Table I. Our decision to include only patients who had orthopaedic, vascular, general, or gynaecologic surgeries in this study was based on the findings of our prior research involving procedure rates and SSI at IALCH.[2]

Table I. Additional eligibility criteria for this study

Inclusion criteria	Exclusion criteria
Patients who underwent orthopaedic, vascular, general, or gynaecologic surgery.	Patients with missing data required for matching or missing preoperative sodium measurement.
	Patients with complete datasets but who could not be matched.

The minimum sample size for this study was 378 patients (at case:control ratio of 1:2, 80% power, and alpha risk of 5% = 126 cases and 252 controls). However, to maximize the statistical power of our analysis we included as many cases and matched controls as possible.

5.2.4.5 Data sources and definitions

The hospital electronic admissions system was used to identify surgical patients, establish the surgical specialty involved, determine patient age and gender, determine the nature of the surgery and its indication, as well as calculate the duration of surgery in minutes. This information, along with the patient hospital number, was directly extracted from the electronic admissions system and saved as a Microsoft Excel spreadsheet. The duration of surgery was calculated as the time in minutes between skin incision and closure of the surgical wound. Surgical wounds were classified as clean, clean/contaminated, contaminated, or dirty/infected.[8] Serum sodium measurements and microbiological culture tests were performed by a National Health Laboratory Service (NHLS) facility located on IALCH premises. We received approval from the NHLS to access preoperative serum sodium test results and microbiological culture results during the study period. We used the patient hospital number to link patients in the Microsoft Excel spreadsheet with preoperative serum sodium and postoperative microbiology results on the NHLS system. The closest preoperative serum sodium measurement was used. Although the preoperative sodium is usually measured by surgeons and anaesthetists within 4 weeks prior to surgery, measurements outside this period are acceptable for patients who are clinically stable (i.e. those patients without significant comorbidity or those considered very low risk for perioperative complications) in our setting.

It is common practice at IALCH for surgeons to collect pus swabs for microbiological culture from surgical wounds which appear infected on clinical examination. For the purpose of this research, all pus swabs were treated as SSIs (irrespective of the final culture result). This is in keeping with the definition of SSI proposed by the Centers for Disease Control, which does not necessarily require a positive microbiological culture result when establishing the presence of a SSI.[9] We extended our review of microbiological culture orders for each patient up to 30 days postoperatively. Cases were defined as patients who experienced SSI within 30 days postoperatively. Controls were defined as patients who did not experience SSI within 30 days postoperatively. The Microsoft Excel spreadsheet was imported into R version 3.6.2 (R Foundation, Vienna, Austria) for the matching process and the subsequent statistical analysis.

5.2.4.6 Matching

Patients were matched on surgical specialty, surgical wound class, and duration of surgery using “nearest neighbour” propensity matching.[10] This approach involves deriving a propensity score based on an initial binary logistic regression model in which all the matching variables are entered. Cases are then matched with controls that share similar propensity score values. A case:control ratio of 1:2 was used as this ratio has been demonstrated to add optimal statistical power to a case-control study.[11] The matching process was qualitatively evaluated using a jitter plot.

5.2.4.7 Statistical analysis

Descriptive statistics were used to summarise the characteristics of the entire study sample. This involved calculating means with standard deviations (SD) for continuous variables, and frequency distributions with percentages for categorical variables. We compared characteristics between case and control groups using univariate binary logistic regression.

We then tested for a possible relationship between preoperative serum sodium levels and SSI using a conditional multivariate binary logistic regression model which was adjusted for patient age, gender, and time in weeks between the sodium measurement and surgery. For conditional regression models, only those variables which did not form part of the matching process are entered into the regression equation. Results of the univariate and multivariate binary logistic regression analyses are presented as odds ratios (OR) with 95% confidence intervals (95%CI). Statistical significance was set at p<0.05.

5.2.5 Results

Figure 1 shows how the final study sample was derived. The final study sample consisted of 729 patients (243 cases matched with 486 controls).

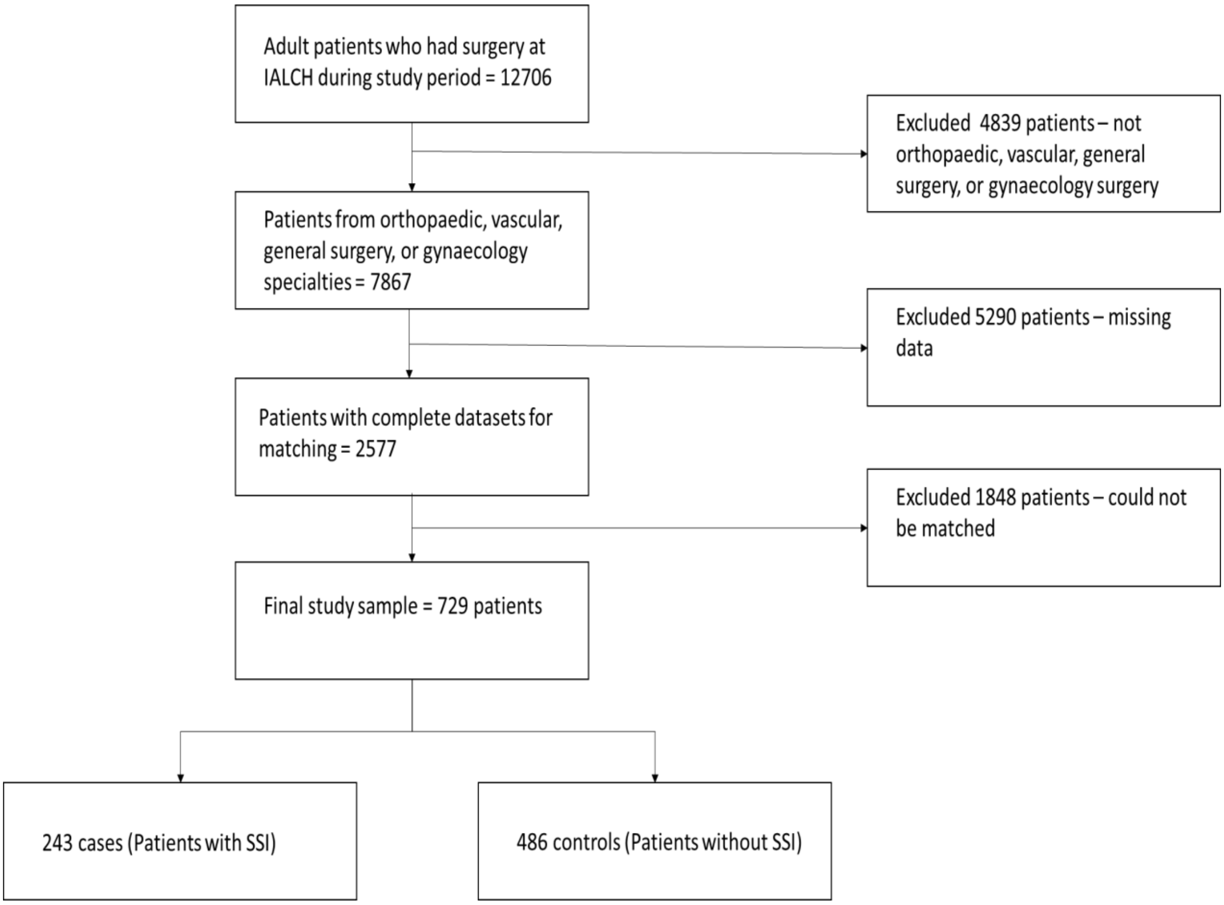

Figure 1. Derivation of the study sample

For major surgeries all patients are required to have the Urea and Electrolytes test (which includes the serum sodium measurements) done preoperatively. The patients excluded from the matching pool because they had missing data, were in fact patients who had minor surgical procedures (including those under regional and local anaesthesia) and thus did not have the Urea and Electrolytes test done. Furthermore, many of the patients who had minor operative procedures did not have incisional surgery (i.e. endoscopic examination, etc) and thus would not be at risk of surgical site infection. The jitter plot shows a fairly similar distribution of propensity scores in matched case and control groups (Figure 2), indicating that the matching process was satisfactory.

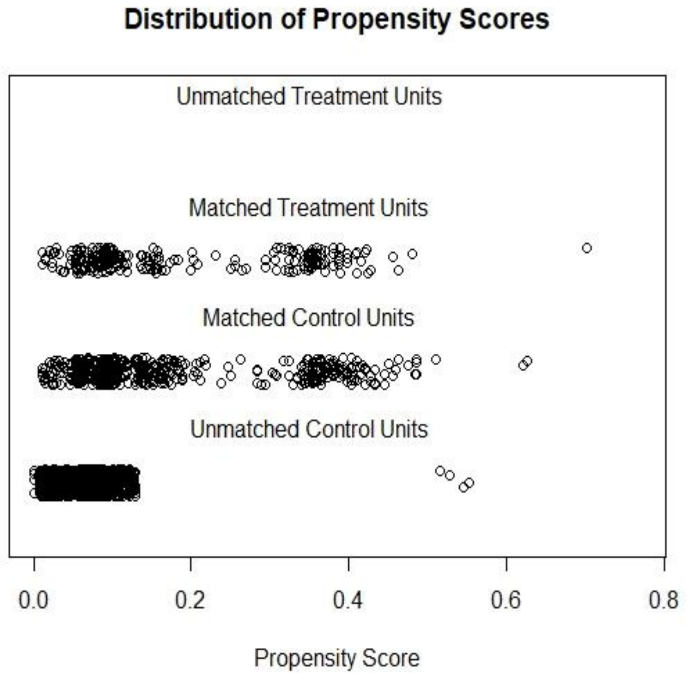

Figure 2. Jitter plot showing distribution of propensity scores in matched cases and controls.

The characteristics of the study sample are described in Table II. The mean age of the study sample was 54.4 (SD: 16.0) years old, and the median age was 58.0 (interquartile range: 43.0-66.0) years old. Just over half of the study population were male. The most common procedures were vascular surgery procedures, which comprised 52.9% of the study sample

(386 patients). While most patients' surgical wounds were categorised as clean wounds (420 patients, 57.6%), there was still a substantial proportion of surgical wounds which were categorised as dirty/infected wounds (207 patients, 28.4%). The mean duration of the surgical procedure was 102.7 (SD: 79.3) minutes. The mean preoperative sodium level in the study sample was 138.7 (SD: 3.6) mmol/L.

Table II. Description of the study sample

Characteristic	**Summary statistic**
Mean age, years (SD)	54.4 (16.0)
Female gender, n (% of N=729)	352 (48.3)
Male gender, n (% of N=729)	377 (51.7)
Orthopaedic surgery, n (% of N=729)	202 (27.7)
Vascular surgery, n (% of N=729)	386 (52.9)
General surgery, n (% of N=729)	120 (16.5)
Gynaecologic surgery, n (% of N=729)	21 (2.9)
Clean wound, n (% of N=729)	420 (57.6)
Clean-contaminated wound, n (% of N=729)	86 (11.8)
Contaminated wound, n (% of N=729)	16 (2.2)
Dirty/infected wound, n (% of N=729)	207 (28.4)
Mean duration of surgery, minutes (SD)	102.7 (79.3)
Mean time between sodium test and surgery, weeks (SD)	3.5 (10.2)
Mean preoperative serum sodium, mmol/L (SD)	138.7 (3.6)

SD: Standard deviation.

The distribution of characteristics between case-control groups and the results of the univariate statistical analysis is shown in Table III. As expected, the matching process produced no statistical differences in surgical specialty, wound class, or duration of surgery between case and control groups. For the unmatched variables, there was no statistically significant difference observed for age, gender, or number of weeks between sodium measurement and surgery. However, there was a statistically significant difference in preoperative serum sodium levels between case and control groups.

Table III. Results of the univariate statistical analysis

Characteristic	**Cases (N=243)**	**Controls (N=486)**	**OR (95%CI)***	**p**
Mean age, years (SD)	54.8 (15.1)	54.2 (16.4)	1.002 (0.993-1.102)	0.656
Female gender, n (% of N)	125 (51.4)	226 (46.7)	Reference category	-
Male gender, n (% of N)	118 (48.6)	259 (53.3)	0.827 (0.608-1.126)	0.228
Orthopaedic surgery, n (% of N)	78 (32.1)	124 (25.5)	Reference category	-
Vascular surgery, n (% of N)	118 (48.6)	268 (55.1)	0.700 (0.490-1.000)	0.050
General surgery, n (% of N)	39 (16.0)	81 (16.7)	0.765 (0.476-1.232)	0.271
Gynaecologic surgery, n (% of N)	8 (3.3)	13 (2.7)	0.978 (0.388-2.468)	0.963
Clean wound, n (% of N)	126 (51.9)	294 (60.5)	Reference category	-
Clean-contaminated wound, n (% of N)	31 (12.8)	55 (11.3)	1.315 (0.808-2.141)	0.270
Contaminated wound, n (% of N)	8 (3.3)	8 (1.7)	2.333 (0.857-6.355)	0.097
Dirty/infected wound, n (% of N)	78 (32.0)	129 (26.5)	1.411 (0.994-2.002)	0.054
Mean duration of surgery, minutes (SD)	95.7 (77.9)	106.2 (79.9)	0.998 (0.996-1.000)	0.094
Mean time between sodium test and surgery, weeks (SD)	4.0 (14.5)	2.6 (8.2)	1.011 (0.997-1.026)	0.119
Mean preoperative serum sodium, mmol/L (SD)	138.3 (4.0)	138.9 (3.4)	1.051 (1.007-1.097)	0.022

*Risk estimate for age and surgery duration based on per unit increase. Risk estimate for mean preoperative serum sodium based on per unit decrease. Reference category for male gender = "Female". Statistical significance was set at $p<0.05$. CI: Confidence interval, SD: Standard deviation.

The results of the conditional binary logistic regression analyses are shown in Table IV. When the analysis was adjusted for age, gender, and time between the sodium measurement and surgery, lower preoperative serum sodium levels (per 1.0 mmol/L decrease) were found to be associated with a higher likelihood of developing SSI (OR: 1.051, 95%CI: 1.007-1.097; p=0.026).

Table IV. Results of the multivariate statistical analyses

Characteristic	**OR (95%CI)***	**p**
Age in years, per unit increase	0.999 (0.989-1.009)	0.840
Male gender	0.820 (0.599-1.122)	0.215
Time between sodium test and surgery, per week increase	1.011 (0.996-1.026)	0.147
Preoperative serum sodium in mmol/L, per unit decrease	1.051 (1.007-1.097)	0.026

*Reference category for male gender = "Female". Statistical significance was set at $p<0.05$. OR: Odds ratio, CI: Confidence interval.

The overall relationship between serum sodium and SSI risk observed in this study is summarized in the graph below (Figure 3).

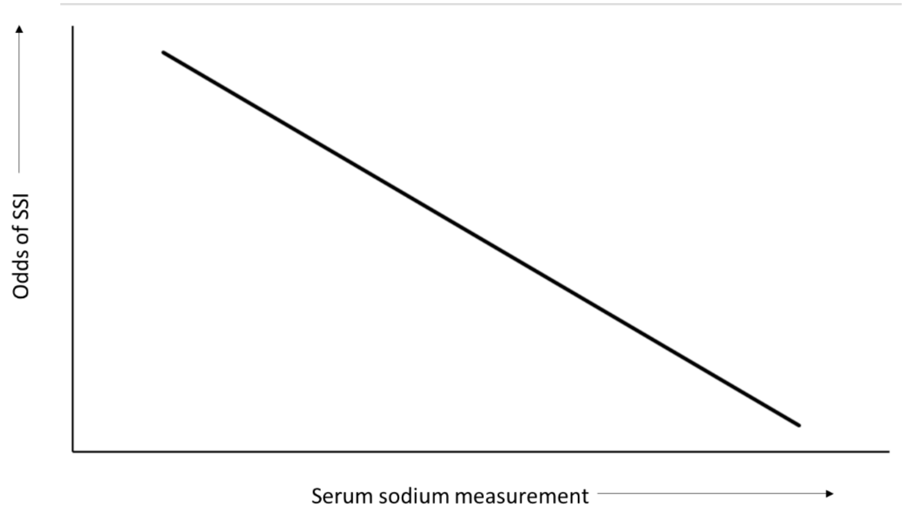

Figure 3. Graph simplifying the relationship between serum sodium and risk of surgical site infection

5.2.6 Discussion

We found a statistically significant association between lower preoperative serum sodium levels and a higher risk of SSI. This finding is in general agreement with a study of a large American surgical registry by Leung et al., which also reported a higher rate of SSI amongst patients with lower preoperative serum levels.[12] There are two potential pathophysiological mechanisms which might explain our observation of a statistically significant association between lower preoperative serum sodium levels and SSI. The first mechanism relates to the role played by sodium during wound healing. Sodium is an important component of the exudate fluid. This fluid keeps wound surfaces moist and promotes wound healing.[13] Reduced sodium levels could impair wound healing by reducing the effectiveness of the exudate fluid, thereby making the surgical wound more susceptible to bacterial colonisation.

The second mechanism relates to the role played by sodium during the immune response to infection. Phagocytes, particularly neutrophils, are involved during the initial immune response to bacteria that breach the upper epithelial layers of the skin.[14] Neutrophils eliminate bacteria via the combined processes of phagocytosis and reactive oxygen/nitrogen species production.[14] Although low sodium levels have little effect on the production of antimicrobial reactive oxygen/nitrogen species, low sodium levels can almost completely inhibit phagocytic activity in neutrophils.[15] The reduced killing activity of neutrophils can allow bacteria to survive and proliferate in the surgical wound.[15]

Although the observed association between lower preoperative serum sodium levels and a higher risk of SSI was statistically significant, this result is clinically insignificant. An odds ratio of 1.05 per unit decrease in serum sodium levels is indeed a small effect size. Such a trivial association might not be sufficient to impact surgeons' clinical decision-making and prompt them to institute additional interventions during the perioperative period in order to reduce SSI risk. Therefore, preoperative serum sodium levels are unlikely to have substantial clinical utility as a risk stratification tool for SSI in our setting. We do not believe that the findings of the current study should be seen as a barrier to investigating the potential association between levels of other analytes routinely that are measured during the preoperative period and SSI in our setting. Our prior work involving preoperative albumin levels is testament to this, and we strongly recommend that associations between other analytes and SSI be investigated in future studies.

There were limitations to our study. Our study involved data from a single, quaternary level hospital. This has implications for the generalisability of our findings to other hospitals which may have different case-mixes, procedure rates, or SSI rates. Multicentre studies are recommended to address the limitation regarding the generalisability of our study findings.[16] The American Society of Anesthesiologists (ASA) score is noted as an important predictor of SSI,[17] but was not collected as part of the hospital administrative database. Patient age was used as a proxy for ASA score in this study, as both variables show a strong correlation.[18] A large number of patients were excluded from the case and control pools. However, these excluded patients were in fact patients who had minor surgical procedures (including those under regional and local anaesthesia) and thus did not have the Urea and Electrolytes test done. Furthermore, many of the patients who had minor operative procedures did not have incisional surgery (i.e. endoscopic examination, etc) and thus would not be at risk of SSI. This was a retrospective analysis, and we did not have any information on pre-analytical variables such as patient preparation prior to the blood specimen being taken, whether the specimen was correctly taken (i.e. in the correct blood tube for the required test), and whether the specimen was correctly handled and processed on receipt at the laboratory. Therefore, we could not adjust our analysis for these variables. We adjusted our analysis, through matching and multivariate methods, for as many confounders as possible with the dataset that was available to us. This includes known risk factors for surgical site infection that are components of the NNIS score. However, we were limited by the number of variables and patient characteristics that are routinely collected as part of the hospital electronic admissions system from which the patient and surgery data was obtained. Owing to this, we could not investigate adjust our analysis for other, lesser-known risk factors associated with surgical site infection which were not captured by the hospital electronic admissions system. Future research investigating the association between various routine preoperative laboratory tests and SSI should seek to address these limitations.

5.2.7 Conclusion

Although we report a statistically significant association between lower preoperative serum sodium levels and a higher risk of SSI, this association lacks clinical significance. Preoperative serum sodium levels are unlikely to have value as a risk stratification tool for SSI in our setting. Nevertheless, the findings of the current study should not be seen as a barrier to investigating the association between other routinely performed preoperative laboratory tests and SSI in our setting for future risk stratification purposes.

5.2.8 References

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Chapter 6

Synthesis and concluding remarks

6.1 Incidence of surgical site infection and associated risk factors in patients undergoing high-risk surgery at a South African quaternary hospital

6.1.1 Incidence of surgical site infection

The most important finding from Manuscript 1 (Chapter 3) was that one in every six patients (16.6%) undergoing major intra-abdominal surgery developed postoperative SSI.[1] The high rate of SSI in the specific population of intra-abdominal surgery is unsurprising, and is congruent with well-established views on the incidence of SSI associated with these procedures.[2] It is likely that the high rate of SSI following intra-abdominal surgery at our quaternary-level hospital is explained by a combination of patient- and procedure-related factors.

Many patients attending a quaternary hospital would already have significant preoperative comorbidity,[3] which predisposes them to SSI. Open intra-abdominal surgery, such as laparotomy, is considered a major surgical procedure and might go on for longer than other types of surgical procedures, which can increase the duration of exposure during which bacteria can be transferred to surgical incisions.[4] The longer surgical duration might be further exacerbated by the complex disease pathologies of patients attending quaternary hospitals.[3] Open intra-abdominal procedures also involve long surgical incisions,[5] and this provides an additional opportunity for bacteria to colonise the surgical wound. In the case of organ-space infection, penetrating injuries to the abdomen or bowel perforation during a surgical procedure might introduce bacteria into the usually sterile peritoneal space.[6]

The incidence of SSI reported for our quaternary hospital is similar to the overall rate reported for middle-income countries participating in the GlobalSurg-2 Study (14.0% in patients undergoing gastrointestinal surgery).[7] Given that quaternary hospitals in South

Africa are well-resourced, it is evident that there is still room for improvement in reducing SSI at our hospital. This calls for the strengthening of existing SSI prevention methods and establishing the feasibility of new approaches for SSI prevention in our setting. The GlobalSurg-2 Study also reported a difference in SSI incidence based on resource availability between countries (high-income countries = 9.4%, middle-income countries = 14.0%, and low-income countries = 23.2%; p<0.001).[7] We posit that the SSI incidence in our well-resourced quaternary-level hospital is likely to be lower than that in more resource-constrained South African regional and district hospitals. Thus, the findings of this research indirectly highlight the potential magnitude of SSI burden at South African regional and district hospitals. This hypothesis requires further investigation.

6.1.2 Surgical site infection risk factors

Manuscript 1 also confirms the multifactorial nature of SSI in our South African setting. Five characteristics were found to be risk factors for SSI in patients undergoing laparotomy: infectious indication for surgery, preoperative non-steroidal anti-inflammatory use, preoperative hypoalbuminemia, Bogota bag use, and perioperative blood transfusion.

Most of the SSI risk factors identified in the international literature were not applicable in our setting. Studies from the same South African quaternary hospital investigating other perioperative outcomes, such as myocardial infarction and inpatient mortality, have also shown a discordance in risk factors for these outcomes between our setting and what is reported in the international literature.[8, 9] This also appears to be true for SSI and advocates for cautious clinical decision-making when stratifying SSI risk in South African settings, particularly if a set of risk factors that were established in other countries is used. If a set of SSI risk factors are to be used for risk stratification in a South African hospital, it would be best if appropriate consideration is given to whether these risk factors are in fact applicable in this setting. The tiered structure of the South African public healthcare system and potential differences in SSI risk factors between facility levels necessitates that a multifactorial risk stratification model also be tested and/or adapted for use at regional and district level hospitals. This requires multicentre research studies, with large sample sizes to facilitate the derivation and validation of these risk stratification models. Lastly, at least three of the five SSI risk factors identified in this research (preoperative non-steroidal anti-inflammatory use, preoperative hypoalbuminemia, and perioperative blood transfusion) are potentially modifiable. This presents an opportunity for surgeons to reduce the risk of SSI in their patients by appropriately managing these specific risk factors during the perioperative period.

6.2 The impact of surgical site infection on healthcare utilisation and healthcare expenditure at a South African quaternary hospital

Manuscripts 2 and 3 (Chapter 4) provide a new insight on how SSI impacts healthcare utilisation and expenditure in the context of a public-sector South African quaternary hospital. Manuscript 2 highlights the need for additional preventative measures to reduce post-discharge SSI rates in our setting.[10] Although inpatient preventative measures are often cited as being crucial in SSI reduction, the extension of preventative measures well beyond discharge from hospital also appears to be of equal relevance. This is even more important as the analysis undertaken in Manuscript 2, which involved a mixed surgical population of South African patients undergoing minor and major procedures, also suggests that 1) Inpatient and post-discharge SSI rates might be similar; and 2) Mortality might be similar for inpatient and post-discharge SSI cases. Interventions for reducing post-discharge SSI, such as wound care educational materials for patients and mobile phone-based SSI surveillance, have been proposed and should be explored for acceptability among South African surgical patients. Another novel finding was that post-discharge SSI was spatially concentrated around urban areas. Although the geospatial analysis was not adjusted for other factors which might have influenced the distribution of post-discharge SSI, it generates a new hypothesis of a potential urban-rural disparity for post-discharge SSI in our setting. Manuscript 3 provides a report of healthcare resource utilisation at a South African quaternary hospital attributed to inpatient SSI following major intra-abdominal surgery.[11] More specifically, we found that inpatient SSI following laparotomy contributes to additional length of stay, which translates to additional healthcare costs. The South African public healthcare sector is already considered a resource-constrained environment.[12] Thus, our research shows that inpatient and outpatient SSI, which are both preventable postoperative complications, can unnecessarily consume much needed resources in our resource-constrained setting.

6.3 Prognostic relevance of routinely performed laboratory tests for surgical site infection in a South African setting

The prognostic relevance of routine preoperative serum albumin and serum sodium tests for SSI in our South African setting is outlined in Manuscripts 4 and 5 (Chapter 5). There is great potential for the expanded use of preoperative serum albumin measurements as a risk stratification tool for SSI at resource-constrained South African public hospitals. Preoperative hypoalbuminemia demonstrated fair predictive accuracy for SSI in South African patients undergoing laparotomy (Manuscript 4), which was similar to that of the well-established NNIS and SENIC risk stratification models.[13] There are several practical reasons supporting the use of preoperative serum albumin measurements as a risk stratification tool for SSI: 1) Preoperative serum albumin measurements are routinely performed, cost-effective, and widely available in the South African public healthcare sector; 2) The dichotomisation of preoperative serum albumin measurements using a threshold of <30 g/L represents a simple method that South African surgeons can use for SSI risk stratification; 3) In most patients, risk stratification for SSI using preoperative serum albumin can be done in the absence of NNIS and SENIC risk model components; and 4) Unlike the NNIS and SENIC risk models, SSI risk stratification using preoperative serum albumin allows for patient risk profiles to be determined prior to surgery and provides an opportunity to initiate additional preoperative preventative measures in high-risk patients.

The findings for preoperative serum sodium measurements were less encouraging (Manuscript 5).[14] Although a statistically significant relationship suggesting a 5% higher odds of SSI per 1.0 mmol/L decrease in serum sodium was observed, it lacks clinical significance as the minimally increased odds of SSI would be insufficient to influence surgeons' decision-making around additional, resource-intensive SSI preventative measures in patients with low serum sodium. Despite the contrasting findings for the two preoperative analytes investigated in this research (serum albumin and serum sodium), there is still sufficient impetus to investigate the utility of other laboratory tests which are routinely performed as part of the preoperative work-up as SSI risk stratification tools.

6.4 Concluding remarks

This PhD research has limitations which must be declared, of which the three most important were selection bias, reporting bias, and missing data. The data used in all of the analyses was from a single hospital, and predominantly involved patients undergoing major surgery. This may have introduced some selection bias into the analyses. Given that the study outcome of SSI required that the attending physician detect the clinical presence of infection, there might have been some infections which were mild and missed. Therefore, potential reporting bias should also be considered when interpreting the findings of this research. Lastly, most of the data used in this research was obtained retrospectively, and there were instances in which relevant variables were not consistently recorded in the patient medical record. These missing variables were excluded from our analyses. Future research should consider these limitations and possible ways to overcome them. Prospective multicenter cohorts will ensure that a more representative study sample is acquired. Routine monitoring for SSI and the use of a standardized definition for this outcome will minimize reporting bias. Research that is prospectively conducted will also minimize missing variables and missing data for the subsequent analyses.

Nevertheless, this PhD research has yielded the following key findings regarding the epidemiology, impact, and prediction of SSI in patients attending a South African quaternary hospital –

a) One in every six patients having high-risk intra-abdominal surgery will develop SSI.
b) SSI is multifactorial.
c) Inpatient and post-discharge SSIs contribute to unnecessary healthcare utilisation and expenditure in this resource-constrained setting.
d) It is possible to use certain routine preoperative laboratory tests as simple, cost-effective risk stratification tools for SSI.

In closing, this PhD research contributes toward improving our sparse knowledge of SSI in the South African context and has the potential to enhance patient management and healthcare resource utilisation/expenditure in this setting. Furthermore, new hypotheses have been generated which could serve as the basis for future research on this topic.

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Appendix I

Published manuscripts

Incidence And Risk Factors For Surgical Site Infection Following Laparotomy At A South African Quaternary Hospital

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Abstract

Background**:** A published report of surgical site infection (SSI) incidence and risk factors following laparotomy in a South African (SA) setting is lacking. This information would have important implications for SSI clinical prediction rules in SA patients undergoing this common surgical procedure. This study sought to determine the incidence and associated risk factors for SSI following laparotomy in a SA setting.

Methods: This was a retrospective chart review study of 439 patients who underwent laparotomy at a SA quaternary hospital over a 5-year period. Demographic information, comorbidities, medication use, and surgery-related variables were collected for each patient. The Centers for Disease Control definition of SSI was used in this study. The incidence of SSI was determined using conventional epidemiological methods. Logistic regression was used to identify risk factors for SSI.

Results: The incidence of SSI was 16.6% (CI: 13.4-20.4%). Risk factors for SSI included infectious indication for surgery (Odds Ratio, OR: 3.32, CI: 1.16-9.47; p=0.003), preoperative non-steroidal anti-inflammatory use (OR: 2.82, CI: 1.33-5.95; p=0.007), preoperative hypoalbuminemia (OR: 2.47, CI: 1.12-5.42; p=0.025), Bogota bag use (OR: 2.23, CI: 1.05-4.74; p=0.036), and perioperative blood transfusion (OR: 2.51, CI: 1.33-4.75; p=0.004).

Conclusion: The incidence of SSI in SA patients undergoing laparotomy is higher than that reported for mixed surgical populations. Several risk factors for SSI were identified. The prognostic relevance of these risk factors, and the reduction in SSI risk when these factors are addressed requires further investigation.

Keywords: Surgical site infection, Risk factors, Laparotomy, South Africa

Introduction

Over 234 million people undergo surgery around the world each year [1]. A proportion of these patients will suffer postoperative complications, with surgical site infection (SSI) being amongst the most commonly encountered [2]. Findings from the International Surgical Outcomes Study (ISOS) suggest that the global incidence of SSI is between 0.8% for organ space SSI and 2.9% for superficial SSI [2]. ISOS also reported that mortality in patients with SSI was between 1.3% for patients with superficial SSI and 7.0% for patients with organ space SSI [2]. The African Surgical Outcomes Study (ASOS) reported a higher incidence of SSI in African settings, ranging from 1.1% for organ space SSI to 7.2% for superficial SSI [3]. Mortality in patients with SSI was also higher in ASOS when compared with ISOS, and ranged between 5.2% for superficial SSI to 22.4% for organ space SSI [3]. Information for healthcare expenditure related to SSIs in African settings is not readily available. However, it is likely that there is an association between SSIs and increased healthcare expenditure in African settings, as is the case in other countries around the world [4, 5].

The morbidity, mortality, and potentially increased healthcare expenditure associated with SSIs in African settings highlights the importance of identifying individual patients who might be at risk for this complication in these settings. These patients can then be targeted for additional preventative interventions for SSI which are over and above those interventions that are instituted as standard of care, in order to mitigate some of this risk. Targeting individual high-risk patients for additional SSI prevention interventions rather than all surgical patients would also ensure that this process would not be too resource intensive. This point is relevant in African settings, where public healthcare systems are often under-resourced. Clinical prediction rules are one possible method which can be used to identify high-risk patients for SSI [6, 7]. This method involves the identification of high-risk patients based on the number of risk factors for a specific complication. Every risk factor carries a point score, and a total point score is computed for each patient [8]. A total point score threshold is determined which is then used to classify patients as high-risk or low-risk for the complication [8]. Studies for other postoperative outcomes suggest that some clinical prediction rules might not perform equally well in African surgical settings and in overseas surgical settings where these methods were originally developed [9]. This can be attributed to the difference in the general health profiles between surgical populations in these different settings, which might then impact the relative importance of a risk factor between these different settings [9]. Risk factors for SSI following common major surgical procedures, such as laparotomy, in a South African (SA) setting have not yet been identified. This information would have great importance with regard to the development of a setting-specific clinical prediction rule for SSI. Therefore, the objective of this study was to determine the incidence and associated risk factors for SSI following laparotomy at a SA quaternary hospital.

Patients and methods

Study design and setting:

This retrospective chart review study was conducted at a quaternary hospital located in Durban, SA. The 850-bed quaternary hospital is a public-sector facility and provides various healthcare services to the residents of KwaZulu-Natal province, which is on the east coast of SA. Admission to the hospital is strictly by referral from lower level healthcare facilities. The population served by the hospital is predominantly of black African ethnicity.

Study sample:

The study sample consisted of 439 adult patients undergoing laparotomy. These patients were retrospectively identified from the hospital theater lists. All 439 patients had their surgical procedures performed between 1 January 2006 and 31 December 2010.

Data collection:

Demographic information, comorbidities, medication use, and surgery-related variables were collected for each patient. Demographic information was collected from the patients' admission note. A comorbidity was considered present if there was a physicians' diagnosis attesting to this in the patients' admission notes or progress notes. The indication for surgery was classified as bleed, cancer, infection, trauma, or other. Indication for surgery was established from the operative notes. Medication use was ascertained from the patients' admission notes or from the list of medications administered to the patient while he or she was admitted to hospital. Information for surgery-related variables were obtained from the operative notes and anesthetic record of each patient. The study outcome was SSI following laparotomy. The Centers for Disease Control (CDC) definition of SSI requires the evidence of clinical signs and symptoms of infection and is not solely based on microbiological evidence of infection [10]. Clinical signs and symptoms of infection can include the following: swelling and redness, pain at the site of surgical incision, presence of pus, fever, surgical wound dehiscence, or histopathological or radiological evidence of infection. The CDC further categorizes SSI according to the extent of the infection (Superficial incisional, deep incisional, and organ space infection) [10]. The CDC definition of SSI was used in this study, however there was no additional categorization according to the extent of the infection as all SSIs in this study were deemed to be of importance, irrespective of the extent of the infection. The SSI outcome was measured up to 30 days postoperatively.

Statistical analysis:

Descriptive statistical methods were used to determine the distribution of various characteristics in the study sample. Results for the descriptive statistical analysis are presented as frequencies and percentages. The incidence of SSI in the study sample was calculated using conventional epidemiological equations. Results for this aspect of the statistical analysis are presented as a percentage along with a 95% confidence interval (CI). Potential statistical associations between the various characteristics and SSI were initially tested using bivariate statistical analysis (χ^2 test or Fishers Exact test). Results for the bivariate statistical analysis are presented as frequencies and percentages, along with a corresponding p-value. Characteristics with $p<0.100$ from the bivariate statistical analysis were then selected for inclusion as independent variables in a logistic regression analysis, with SSI being the dependent variable. This "purposeful" selection of characteristics for inclusion in the logistic regression analysis was performed to ensure that the subsequent regression model was parsimonious [11]. The fit of the regression model was evaluated using the Hosmer-Lemeshow test, with $p>0.050$ indicative of appropriate model fit. Results for the regression analysis are presented as odds ratios (OR) with CI, and a corresponding p-value. Characteristics with an OR >1.00 and $p<0.050$ were classified as risk factors for SSI. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp, USA).

Ethical approval:

This study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, and the KwaZulu-Natal Provincial Department of Health (Protocol number: BCA208/18).

Results

The characteristics of the study sample, as well as the results of the bivariate statistical analysis are presented in Table 1. Out of the 439 patients undergoing laparotomy in the study sample, 73 patients were identified as having SSI following their procedure. This equated to an estimated SSI incidence of 16.6% (CI: 13.4-20.4%) in the study sample. Variables with $p<0.050$ which were subsequently included in the logistic regression analysis included: indication for surgery, American Society of Anesthesiologists Score, preoperative non-steroidal anti-inflammatory use, metastatic cancer, preoperative renal impairment, preoperative anemia, preoperative hyponatremia, preoperative hypoalbuminemia, emergency procedure, contaminated procedure, Bogota bag use, antibiotic prophylaxis, and preoperative blood transfusion.

The results of the logistic regression analysis are shown in Table 2. The Hosmer-Lemeshow test indicated appropriate model fit ($p=0.381$). Statistically significant results were noted for infectious indication for surgery (OR: 3.32, CI: 1.16-9.47; $p=0.025$), preoperative non-steroidal anti-inflammatory use (OR: 2.82, CI: 1.33-5.95; $p=0.007$), preoperative hypoalbuminemia (OR: 2.47, CI: 1.12-5.42; p=0.025), Bogota bag use (OR: 2.23, CI: 1.05-4.74; p=0.036), and perioperative blood transfusion (OR: 2.51, CI: 1.33-4.75; p=0.004).

Table 1. Characteristics of the study sample and results of bivariate statistical analysis

Characteristic	**Category**	**All (N=439), n (% N)**	**SSI (N=73), n (% N)**	**No SSI (N=366), n (% N)**	**p**
Age>60	>60 years	82 (18.7)	11 (15.1)	71 (19.4)	0.386
	≤60 years	357 (81.3)	62 (84.9)	295 (80.6)	
Gender	Male	145 (33.0)	26 (35.6)	119 (32.5)	0.607
	Female	294 (67.0)	47 (64.4)	247 (67.5)	
Obesity	Yes	152 (34.6)	31 (42.5)	121 (33.1)	0.302
	No	105 (23.9)	15 (20.5)	90 (24.6)	
	Missing	182 (41.5)	27 (37.0)	155 (42.3)	
Indication for surgery	Bleed	12 (2.7)	2 (2.8)	10 (2.7)	<0.001
	Cancer	183 (41.7)	19 (26.0)	164 (44.8)	
	Infection	36 (8.2)	19 (26.0)	17 (4.6)	
	Other	151 (34.4)	19 (26.0)	132 (36.1)	
	Trauma	57 (13.0)	14 (19.2)	43 (11.8)	
American Society of Anesthesiologists Score	>2	207 (47.2)	44 (60.3)	163 (44.5)	0.014
	≤2	232 (52.8)	29 (39.7)	203 (55.5)	
Preoperative non-steroidal anti-inflammatory	Yes	62 (14.1)	17 (23.3)	45 (12.3)	0.014
	No	377 (85.9)	56 (76.7)	321 (87.7)	
Preoperative statin	Yes	25 (5.7)	6 (8.2)	19 (5.2)	0.280
	No	414 (94.3)	67 (91.8)	347 (94.8)	
Hypertension	Yes	140 (31.9)	26 (35.6)	114 (31.1)	0.454
	No	299 (68.1)	47 (64.4)	252 (68.9)	
Diabetes	Yes	57 (13.0)	13 (17.8)	44 (12.0)	0.179
	No	382 (87.0)	60 (82.2)	322 (88.0)	
Cardiovascular disease	Yes	50 (11.4)	5 (6.8)	45 (12.3)	0.181
	No	389 (88.6)	68 (93.2)	321 (87.7)	
HIV	Yes	30 (6.8)	2 (2.7)	28 (7.7)	0.200
	No	409 (93.2)	71 (97.3)	338 (92.3)	
Metastatic cancer	Yes	86 (19.6)	9 (12.3)	77 (21.0)	0.087
	No	353 (80.4)	64 (87.7)	289 (79.0)	
Obstructive airway disease	Yes	25 (5.7)	6 (8.2)	19 (5.2)	0.280
	No	414 (94.3)	67 (91.8)	347 (94.8)	
Gastric ulcers	Yes	17 (3.9)	4 (5.5)	13 (3.6)	0.502
	No	422 (96.1)	69 (94.5)	353 (96.4)	
Current smoker	Yes	44 (10.0)	7 (9.6)	37 (10.1)	0.892
	No	395 (90.0)	66 (90.4)	329 (89.9)	
Preoperative leukopenia	Yes	35 (8.0)	6 (8.2)	29 (7.9)	0.932
	No	404 (92.0)	67 (91.8)	337 (92.1)	
Preoperative thrombocytosis	Yes	47 (10.7)	7 (9.6)	40 (10.9)	0.735
	No	392 (89.3)	66 (90.4)	326 (89.1)	
Preoperative renal impairment	Yes	67 (15.3)	18 (24.7)	49 (13.4)	0.014
	No	372 (84.7)	55 (75.3)	317 (86.6)	
Preoperative anemia	Yes	314 (71.5)	62 (84.9)	252 (68.9)	0.005
	No	125 (28.5)	11 (15.1)	114 (31.1)	
Preoperative hyponatremia	Yes	54 (12.3)	14 (19.2)	40 (10.9)	0.050
	No	385 (87.7)	59 (80.8)	326 (89.1)	
Preoperative hypoalbuminemia	Yes	159 (36.2)	48 (65.8)	111 (30.3)	<0.001
	No	280 (63.8)	25 (34.2)	255 (69.7)	
Emergency procedure	Yes	150 (34.2)	36 (49.3)	114 (31.1)	0.003
	No	289 (65.8)	37 (50.7)	252 (68.9)	
Contaminated procedure	Yes	88 (20.0)	31 (42.5)	57 (15.6)	<0.001
	No	351 (80.0)	42 (57.5)	309 (84.4)	
Surgery duration >2 hours	Yes	153 (34.9)	20 (27.4)	133 (36.3)	0.143
	No	286 (65.1)	53 (72.6)	233 (63.7)	
Bogota bag	Yes	70 (15.9)	47 (64.4)	322 (88.0)	<0.001
	No	369 (84.1)	26 (35.6)	44 (12.0)	
Antibiotic prophylaxis	Yes	366 (83.4)	55 (75.3)	311 (85.0)	0.044
	No	73(16.6)	18 (24.7)	55 (15.0)	
Perioperative blood transfusion	Yes	157 (35.8)	46 (63.0)	111 (30.3)	<0.001
	No	282 (64.2)	27 (37.0)	255 (69.7)	

Patient-controlled analgesia postoperatively	Yes	33 (7.5)	3 (4.1)	30 (8.2)	0.227
	No	406 (92.5)	70 (95.9)	336 (91.8)	

Table 2. Results of the logistic regression analysis

Characteristic	**Category**	**OR (CI)**	**p**
Indication for surgery	Bleed	0.44 (0.08-2.57)	0.361
	Cancer	1.03 (0.34-3.10)	0.961
	Infection	3.32 (1.16-9.47)	0.025
	Other	0.78 (0.31-1.94)	0.588
	Trauma/injury	1.00 (Reference group)	-
American Society of Anesthesiologists Score	>2	1.36 (0.75-2.48)	0.313
	≤2	1.00 (Reference group)	-
Preoperative non-steroidal anti-inflammatory	Yes	2.82 (1.33-5.95)	0.007
	No	1.00 (Reference group)	-
Metastatic cancer	Yes	0.46 (0.20-1.10)	0.080
	No	1.00 (Reference group)	-
Preoperative renal impairment	Yes	0.99 (0.45-2.17)	0.970
	No	1.00 (Reference group)	-
Preoperative anemia	Yes	1.25 (0.57-2.75)	0.582
	No	1.00 (Reference group)	-
Preoperative hyponatremia	Yes	1.35 (0.61-3.00)	0.458
	No	1.00 (Reference group)	-
Preoperative hypoalbuminemia	Yes	2.47 (1.12-5.42)	0.025
	No	1.00 (Reference group)	-
Emergency procedure	Yes	0.59 (0.26-1.31)	0.194
	No	1.00 (Reference group)	-
Contaminated procedure	Yes	1.22 (0.58-2.55)	0.599
	No	1.00 (Reference group)	-
Bogota bag	Yes	2.23 (1.05-4.74)	0.036
	No	1.00 (Reference group)	-
Antibiotic prophylaxis	Yes	0.66 (0.32-1.34)	0.247
	No	1.00 (Reference group)	-
Perioperative blood transfusion	Yes	2.51 (1.33-4.75)	0.004
	No	1.00 (Reference group)	-

Discussion

The incidence of SSI in this study was far higher than that reported for ISOS and ASOS [2, 3]. It is possible that this finding is due to one crucial difference between the current study and ISOS/ASOS, which is that the current study was performed solely in a high-risk major surgery group while ISOS and ASOS were performed in surgical populations which were a mix of major and minor surgical procedures [2, 3]. Open intra-abdominal surgery itself is associated with an increased risk of developing SSI [12]. It is likely that the SSI incidence in ISOS and ASOS was "diluted" by the inclusion of lower risk surgical procedures in these two studies.

Several risk factors for SSI were identified in this study, which confirms the established view of SSI as being multifactorial [13]. These risk factors were infectious indication for surgery, preoperative non-steroidal anti-inflammatory use, preoperative hypoalbuminemia, Bogota bag use, and perioperative blood transfusion. These characteristics were associated with an approximately two- to three-fold increase in risk for SSI. The immune response provides protection against infection. Therefore, when there is a perturbation in the immune response an individual might be more susceptible to infection. The finding for infectious indication for surgery being associated with a higher risk of SSI is probably reflective of underlying immune dysfunction in patients with pre-existing infection. Nonsteroidal anti-inflammatory medications are often prescribed for pain control during the perioperative period [14]. These are also often given when patient is discharged from hospital for pain control, and can be administered orally or as a suppository. As the name implies, these medications control pain by reducing inflammation [15]. This might contribute to an impaired immune response in surgical patients, resulting in a predisposition to SSI. The link between hypoalbuminemia and a higher risk of SSI is well established [16, 17]. Hypoalbuminemia is often considered a sign of malnutrition [18]. Besides impairment of the immune response, malnutrition might also cause impaired wound healing [19]. The intact integument acts as a physical barrier against infection and surgical incisions, which represent disruptions in the integumentary system [20], would remain open for far longer in malnourished individuals. During this time period the disrupted integument at the site of the surgical incision might be susceptible to bacterial colonization [20]. Similarly, the use of a Bogota bag would also leave the disrupted integument susceptible to bacterial colonization [21]. Some blood loss is inevitable during open intra-abdominal surgery [22, 23]. Perioperative transfusion might be proposed to address perioperative blood loss. However, transfusion itself has been found to be associated with an increased risk of several postoperative complications, including SSI [24]. In agreement with the pathophysiology of other risk factors identified in this study, it has been postulated that perioperative transfusion might impair the immune response. This appears to be supported by the findings of a recent study involving patients undergoing gastrointestinal surgery, wherein there was an immunosuppressive gene expression profile exhibited by patients who had received a perioperative blood transfusion [25]. The study had specifically found that that this gene expression profile could have a profoundly negative impact on cells of innate immune response [25], which would therefore make patients who received blood transfusions at higher risk for postoperative infectious complications.

We recommended that additional cohort studies be conducted in order to investigate the prognostic performance of these risk factors as components of a SSI clinical prediction rule. This would assist with the preoperative identification of patients who are at high-risk for SSI following their procedures. It might also be worth considering the potential benefits of trying to address some of the SSI risk factors identified in this study. This could mitigate a portion of the risk for SSI in high-risk patients. For instance, pain in surgical patients could be managed using other analgesics. Malnourished patients should be offered adequate nutritional support [26]. Optimizing surgical technique and the use of anti-fibrinolytic agents are strategies which can be used to prevent excess perioperative blood loss [27]. This could reduce the need for a perioperative blood transfusion. Where there is no option for patients other than blood transfusion, then these patients should have their surgical incisions reviewed more often during the postoperative period for SSI. One cannot mitigate the risk of SSI associated with the indication for surgery. Furthermore, one cannot completely mitigate for the risk of SSI associated with the use of a Bogota bag. These risk factors can be used to identify high-risk patients for more stringent postoperative monitoring.

There were limitations to this research. This study was conducted at a single, quaternary level hospital. The patient profile at this hospital is that of very complex cases which cannot be managed at lower level healthcare facilities. Therefore, the findings of this research might not necessarily be generalizable to other hospitals or other surgical populations. Information regarding the use of over-the-counter and herbal medications, which might have an immune boosting effect in surgical patients, was not collected as part of this study as it was difficult to retrospectively establish the use of these medications from the patients' medical chart. There were also some variables which were not consistently recorded on the patients' notes, for example the composition of suture material used to close the surgical incision. These variables could not be reliably investigated in this study and were excluded from the statistical analysis. The study outcome was only measured until 30 days postoperatively, which is in keeping with the CDC definition for SSI. However, there might possibly have been some patients with delayed SSI, in that they presented with SSI at a time point which fell outside the 30 day postoperative period. These patients would have been considered as SSI-negative in the statistical analysis. Prospective research studies are required to address all the aforementioned limitations.

In conclusion, the incidence of SSI observed in the study sample of SA patients undergoing laparotomy was much higher than that reported in larger studies involving mixed surgical populations. This study also identified several risk factors for SSI following laparotomy in a SA setting. The prognostic relevance of these risk factors, and the reduction in SSI risk when these factors are addressed requires further investigation.

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Admissions for post-discharge surgical site infection at a quaternary South African public sector hospital

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Background: Reports of post-discharge admissions for surgical site infection (SSI) in African settings are lacking. This information could assist with allocating resources within hospitals, as well as developing targeted interventions aimed at reducing post-discharge SSI. The primary objective of this study was to determine trends in admissions for post-discharge SSI at a South African quaternary/teaching hospital. The secondary objective was to determine trends in mortality rates for these admissions.
Methods: This was a retrospective review of adult admissions for post-discharge SSI at a quaternary/teaching South African hospital between 2006 and 2015. Admissions for post-discharge SSI were identified using the hospital administrative database and appropriate International Classification of Disease, 10th Revision codes. Mortality was determined from the discharge disposition for each admission. Data were analysed with simple regression and trend line statistics. The geospatial distribution of post-discharge SSI, based on the residential postal codes recorded on the hospital administrative database for each admission, was determined using the Power Map® software program.
Results: There was no change in admissions for post-discharge SSI over the study period ($p = 0.17$). Mortality in elderly admissions declined during the study period ($p = 0.03$). Most admissions for post-discharge SSIs originated from urban areas.
Conclusion: Despite the implementation of universal SSI prevention methods, admissions for post-discharge SSI remained consistent during the study period. Urban areas appeared to be more severely affected by post-discharge SSI than rural areas. Additional prevention methods for post-discharge SSI are required.
Keywords: surgical site infection, post-discharge, admissions, mortality, South Africa

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Introduction

Surgical site infection (SSI) is an important postoperative complication,[1,2] and contributes towards increased healthcare expenditure and resource utilisation at healthcare facilities.[3] Postoperative surgical site infection can occur as an in-hospital event or a post-discharge event.[4,5] The incidence of inpatient and post-discharge SSI differs according to surgical procedure.[4]

Inpatient data from the African Surgical Outcomes Study (ASOS) has highlighted the importance of SSI in African settings.[6] However, loss to follow up once the patient is discharged from hospital is a challenge,[7] and most studies from African settings are usually investigations of inpatient outcomes only. Even ASOS did not extend investigations of most postoperative complications beyond hospital discharge.[6] There is a gap in the literature regarding post-discharge SSI in an African setting. Addressing this deficiency could be important for three reasons. Firstly, it could assist public health specialists and surgeons in deciding how resources should be allocated within healthcare facilities for SSI-related admissions. Secondly, it could assist with the development of interventions aimed at reducing post-discharge SSI. Lastly, the demand for surgical procedures is increasing on the African continent,[8] and some of these surgical cases are at risk for SSI.[6]

The primary objective of this study was to determine trends in admissions for post-discharge SSI at a South African quaternary/teaching hospital. The secondary objective of this study was to determine trends in mortality for these admissions.

Methods

Study design and setting

This study was a retrospective review of data obtained from the admissions database of the Inkosi Albert Luthuli Central

Hospital (IALCH), located in Durban, South Africa. This quaternary/teaching hospital has 850 beds and offers various specialised medical and surgical services to the populace of the KwaZulu-Natal province. A description of surgical procedure rates at IALCH is provided in Table 1. Cardiac surgery procedures were defined as procedures performed on the heart by cardiac surgeons. Noncardiac surgery procedures were defined as procedures which did not meet the definition of cardiac surgery, and are stratified by surgical sub-specialty (Table 1).

Study sample

The study sample was comprised of all adult admissions at IALCH between 01 January 2006 and 31 December 2015, with a primary International Classification of Disease 10th Revision (ICD-10) diagnosis indicative of SSI. The ICD-10 diagnosis codes used to identify admissions with post-discharge SSI are shown in Table 2. In addition, ICD-10 codes were broadly classified as SSIs not involving grafts/prostheses (ICD-10 code T81.4) and SSIs involving grafts/prostheses (all remaining ICD-10 codes listed in Table 2).

Data source and data description

The data for this study were extracted directly from the hospital admissions database and stored as a Microsoft Excel® file in preparation for statistical analysis. Beside the ICD-10 primary diagnosis code for SSI, variables contained in the database included: date of admission, admission age and gender, discharge disposition, and residential postal code. Mortality was determined by reviewing the discharge disposition recorded for each admission in the hospital admissions database.

Data analysis

Characteristics of the entire study sample were analysed using descriptive statistical methods and are presented as frequencies and percentages, or rates with confidence intervals (CI). Simple regression and trend line analysis was used to investigate trends in post-discharge SSI admissions and mortality in these admissions. Trends analyses were stratified according to age, gender, the nature of SSI ICD-10 code, and broad surgical category (i.e. noncardiac surgery versus cardiac surgery). The direction of a trend was determined from the slope of the trend line, with a negative slope indicating a declining trend while a positive slope would be indicative of an increasing trend. The R^2 value from the simple regression analysis was used to interpret the strength of a trend. Trends with an R^2 value of < 0.5000 were considered "weak", trends with an R^2 value of 0.5000–0.7000 were considered "moderate", and trends with an R^2 value of > 0.7000 were considered "strong". The descriptive statistics and simple regression/trend line analyses were performed using Microsoft Excel®. For the trends analysis, a p-value < 0.05 was considered a statistically significant result.

The geospatial distribution of post-discharge SSI admissions was semi-quantitatively determined using the Power Map® add-on software for Microsoft Excel®. Briefly, the Power Map® add-on software uses postal codes

Table 1. Procedure rates at IALCH*

Specialty	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Cardiac	93.1 (87.2-99.0)	89.2 (83.6-94.8)	86.6 (81.2-92.0)	78.4 (73.3-83.5)	73.9 (68.8-78.9)	82.7 (78.0-87.5)	72.5 (68.1-76.8)	70.7 (66.5-74.9)	76.2 (71.9-80.5)	74.0 (69.5-78.5)
Noncardiac	906.9 (912.6-900.8)	910.8 (905.0-916.2)	913.4 (907.9-918.0)	921.6 (916.3-926.6)	926.1 (920.9-930.9)	917.3 (912.4-921.9)	927.5 (923.0-931.8)	929.3 (925.0-933.4)	923.8 (919.3-928.0)	926.0 (921.4-930.4)
ENT	58.7 (53.9-63.5)	57.8 (53.2-62.4)	68.1 (63.3-72.9)	83.7 (78.4-89.0)	70.1 (65.3-75.0)	67.2 (62.9-71.5)	70.4 (66.1-74.7)	72.8 (68.5-77.0)	79.5 (75.1-83.9)	69.1 (64.8-73.5)
Gynaecology	54.4 (49.8-59.0)	50.2 (45.9-54.5)	35.4 (31.9-38.9)	49.1 (45.0-53.2)	56.7 (52.3-61.1)	61.9 (57.7-66.0)	58.3 (54.3-62.2)	61.1 (57.2-65.0)	51.8 (48.2-55.4)	55.0 (51.1-59.0)
Neurosurgery	229.6 (221.1-238.1)	252.6 (244.0-261.1)	258.1 (249.7-266.5)	222.7 (214.8-230.6)	240.0 (231.9-248.2)	227.8 (220.6-235.0)	216.2 (209.3-223.2)	218.8 (212.1-225.5)	215.1 (208.5-221.8)	211.7 (204.6-218.7)
Obstetric	1.7 (0.9-2.6)	3.2 (2.1-4.3)	38.5 (34.9-42.2)	34.5 (31.0-38.0)	36.0 (32.4-39.5)	42.9 (39.4-46.4)	45.3 (41.8-48.8)	44.9 (41.5-48.2)	46.3 (42.9-49.7)	37.7 (34.4-41.0)
Ophthalmology	83.8 (78.2-89.5)	73.5 (68.4-78.6)	77.8 (72.6-82.9)	83.2 (78.0-88.5)	83.0 (77.7-88.3)	87.7 (82.8-92.6)	98.0 (93.0-103.0)	104.4 (99.5-109.4)	102.3 (97.4-107.2)	103.4 (98.1-108.6)
Orthopaedics	59.2 (54.4-64.0)	63.4 (58.6-68.2)	55.8 (51.4-60.2)	60.1 (55.6-64.7)	71.4 (66.5-76.3)	84.4 (79.6-89.2)	98.1 (93.1-103.2)	96.4 (91.6-101.2)	100.8 (95.9-105.7)	118.7 (113.1-124.3)
Plastic surgery	100.2 (94.1-106.3)	96.3 (90.5-102.1)	98.0 (92.3-103.7)	93.7 (88.2-99.3)	79.1 (74.0-84.3)	83.5 (78.7-88.3)	86.0 (81.3-90.8)	86.6 (82.1-91.2)	88.5 (83.9-93.1)	79.2 (74.5-83.8)
Specialised surgery	49.3 (44.9-53.7)	48.4 (44.2-52.6)	40.0 (36.2-43.7)	36.6 (33.0-44.2)	40.0 (36.3-43.6)	48.7 (45.0-54.2)	45.3 (41.8-48.8)	52.8 (49.1-56.4)	55.3 (51.6-59.0)	52.7 (48.9-56.6)
Thoracics	106.6 (100.4-112.9)	96.2 (90.4-102.0)	90.6 (85.1-96.1)	102.9 (97.1-108.7)	106.8 (100.9-112.6)	81.7 (77.0-86.5)	75.4 (71.0-79.9)	66.2 (62.2-70.3)	60.9 (57.0-64.8)	67.6 (63.3-71.9)
Urology	70.3 (65.1-75.5)	65.1 (60.3-69.9)	65.5 (60.8-70.3)	70.3 (65.4-75.1)	68.6 (63.8-73.4)	61.3 (57.2-65.5)	68.0 (63.7-72.2)	66.3 (62.3-70.3)	71.7 (67.5-75.9)	64.2 (60.0-68.4)
Vascular	93.0 (87.1-98.9)	104.0 (98.0-110.0)	85.7 (80.3-91.1)	84.7 (79.4-90.0)	74.4 (69.4-79.4)	70.1 (65.7-74.5)	66.5 (62.3-70.7)	59.1 (55.3-62.9)	51.5 (47.9-55.1)	66.7 (62.4-71.0)

* Expressed as rate per 1 000 procedures (Confidence interval - CI).
Main categories are indicated by italic text.

Table 2. ICD-10 diagnosis codes used to identify admissions with a post-discharge SSI

Code	Description
T81.4	Infection following a procedure, not elsewhere classified
T85.7	Infection and inflammatory reaction due to other internal prosthetic devices, implants and grafts
T82.6	Infection and inflammatory reaction due to cardiac valve prosthesis
T82.7	Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts
T83.5	Infection and inflammatory reaction due to prosthetic device, implant and graft in urinary system
T83.6	Infection and inflammatory reaction due to implanted penile prosthesis
T84.5	Infection and inflammatory reaction due to internal joint prosthesis
T84.6	Infection and inflammatory reaction due to internal fixation device
T84.7	Infection and inflammatory reaction due to other internal orthopaedic prosthetic devices, implants and grafts

in the Microsoft Excel® database and blank maps available through Microsoft Bing® to create new maps which display the geospatial distribution of a given characteristic, which in this instance would be admissions for post-discharge SSI. The display options for the map can be set such that areas with a high density of admissions for post-discharge SSI appear as red "hot spots", while areas with a low density of admissions for post-discharge SSI would appear green. Areas with an intermediate density of admissions for post-discharge SSI would appear yellow.

Results

The study sample consisted of 1 240 post-discharge SSI admissions which were recorded during the 10-year study period. The mean age of the study sample was 46.9 years with 15.3% (190 admissions) of the study sample aged > 65 years. Six hundred and sixty eight (53.8%) admissions in the study sample were male. A total of 808 (67.1%) admissions did not involve SSI of grafts/prostheses. Mortality across the study period was 9.5% (118 admissions).

The results of the trends analysis are shown in Figures 1 and 2. A weak, but statistically significant trend toward a reduction in mortality amongst elderly admissions with post-discharge SSI ($R^2 = 0.4847$, $p = 0.03$) was observed (Figure 2). There were no other statistically significant trends for the admission and mortality outcomes investigated in this study.

The geospatial distribution of SSI admissions in this study is shown in Figure 3. A high-density area of post-discharge SSI admissions was noted around Durban, as well as several peri-urban areas surrounding Durban. Post-discharge admissions for SSI from rural areas in the north and south, as well as the midlands of KwaZulu-Natal province were less common.

Discussion

Along with the inpatient findings reported in ASOS,[6] this study contributes toward a better overall understanding of SSI on the African continent. Most admissions in the study sample were of younger age. There is evidence to suggest that the risk of SSI increases up to the age of 65 years of age, following which there is a decrease in risk.[9] In addition, most post-discharge SSIs were in admissions that did not have recent

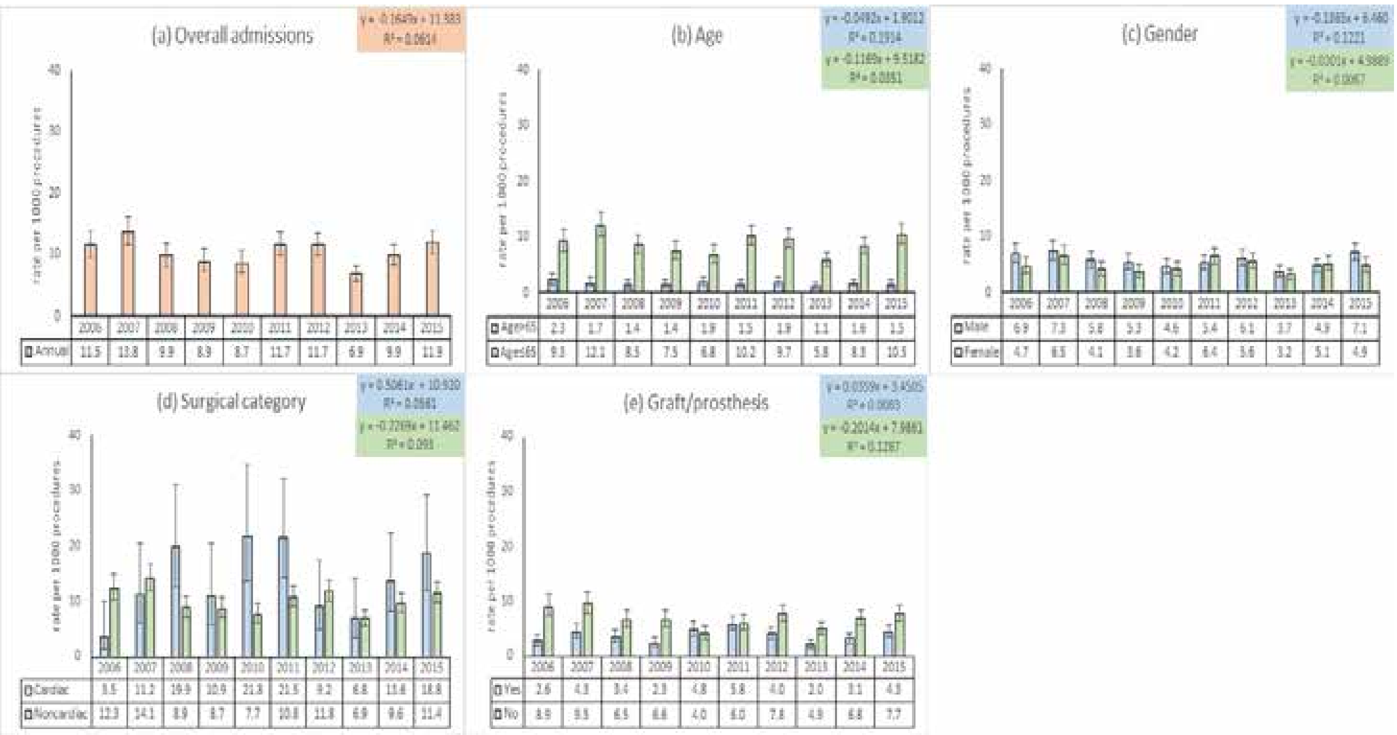

*Figure 1. Overall and stratified trends in admissions for post-discharge SSI**

* Colour-coded boxes contain trend line equations and R^2 values for corresponding colour-coded variables and sub-categories.
Error bars on graph indicate confidence intervals for estimates.

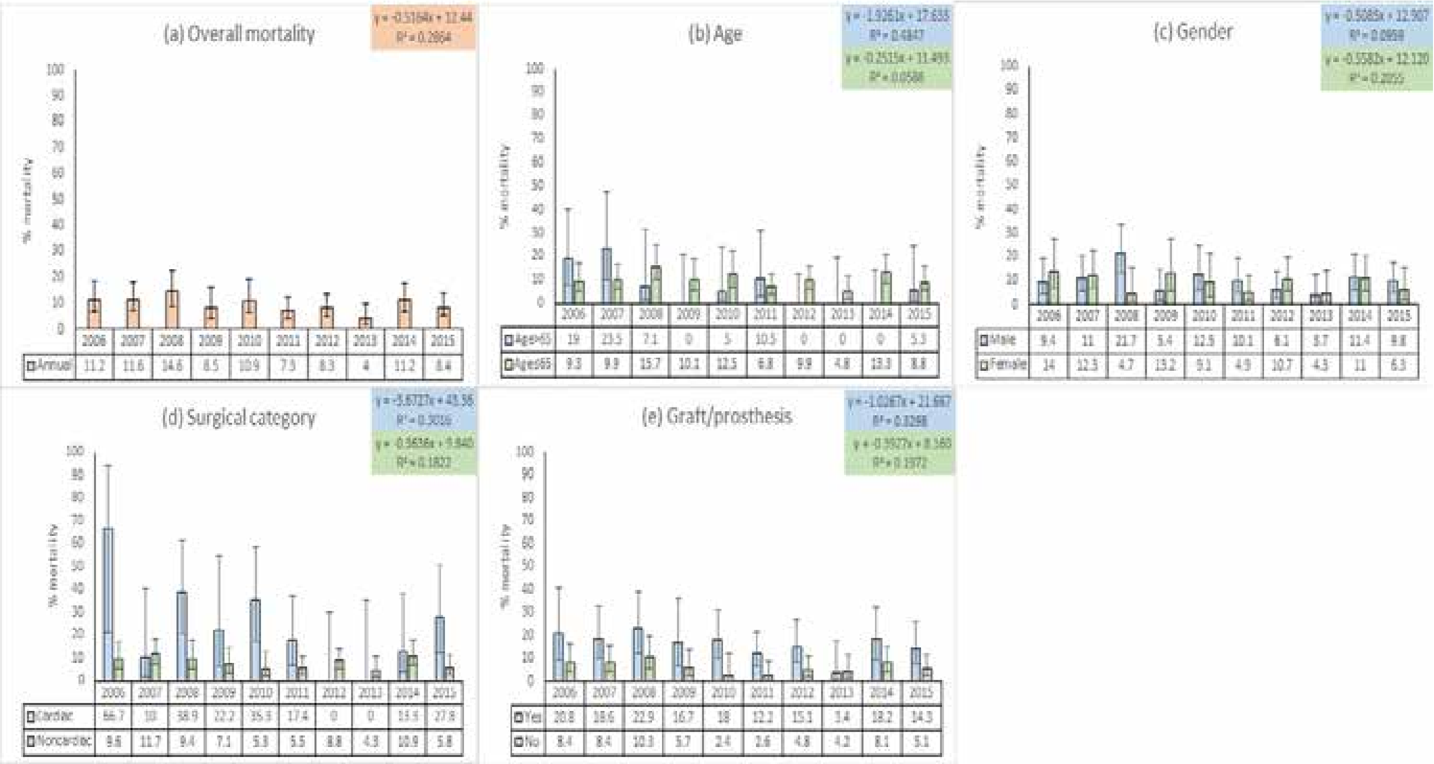

Figure 2. Overall and stratified trends for mortality in admissions with post-discharge SSI

* Colour-coded boxes contain trend line equations and R^2 values for corresponding colour-coded variables and sub-categories.
Error bars on graph indicate confidence intervals for estimates.

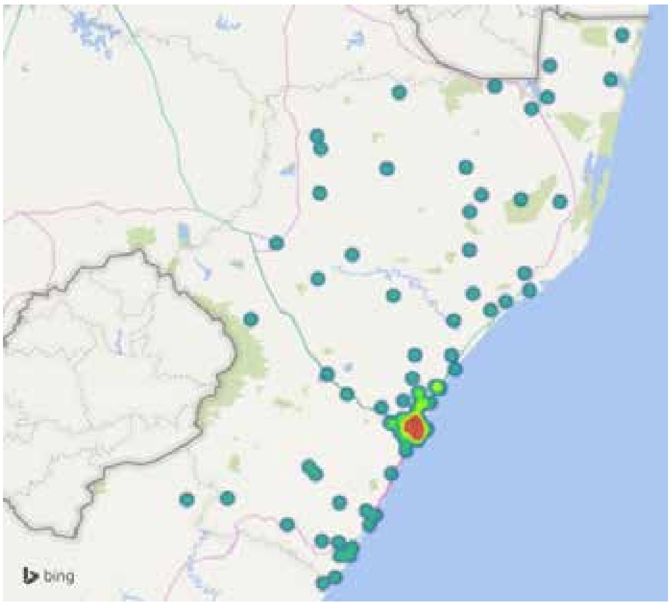

*Figure 3. Geospatial distribution of post-discharge admissions for SSI in this study**

* Across entire study period (2006-2015). With reference to the density of post-discharge admissions for SSI: Green – area with low density, yellow – area with intermediate density, and red – area with high density.

graft/prosthesis procedures. Surgical procedures involving grafts or prostheses are more likely in older patients rather than younger patients, which might explain this finding. For example, while there has been an increase in knee arthroplasty amongst persons younger than 60 years of age, the majority of arthroplasties continue to be performed in persons older than 60 years.[10]

The findings of the trends analysis suggest admissions for post-discharge SSI at IALCH, irrespective of stratification level, have remained consistent during the 10-year study period. Ideally, there should have been a declining trend in post-discharge SSI during the study period. The hospital follows the World Health Organization (WHO) recommendations for the prevention of SSI,[11] and no new policies were specifically implemented during the study period. This demonstrates that although WHO recommendations for SSI prevention have been adopted at IALCH, further efforts are required to significantly reduce admissions for post-discharge SSI. Surgical site infection is multifactorial. Although the WHO recommendations seek to prevent SSI by addressing risk factors at the facility and healthcare worker levels, addressing risk factors at the patient level is also important. A potential method of reducing post-discharge SSI is patient empowerment through health promotion and educational initiatives. These health promotion activities and educational materials should be related to risk factor avoidance and proper wound care following discharge from hospital.[12] Health promotion materials would need to be culturally relevant to African settings to be effective. Early detection and treatment of post-discharge SSI might reduce the chances of the SSI advancing to the point where it requires patient hospitalisation for treatment. Mobile phone technology has been used in the surveillance of post-discharge SSI in some settings.[13,14] This intervention has the potential to identify post-discharge SSI at an early stage. Patients can then receive timeous treatment. As access to mobile phones in African settings is increasing,[15] post-discharge SSI surveillance through a mobile phone-based intervention in these settings should be considered.

One in ten admissions for post-discharge SSI in this study died in hospital. Overall mortality in patients with SSI in ASOS was 9.0%, but ranged between 5.2% and 22.4% depending on the extent of the SSI.[6] However, ASOS was a study of inpatient outcomes and did not investigate post-discharge complications.[6] As the mortality findings reported for this study of post-discharge SSI admissions are similar to those reported for inpatient SSI in ASOS,[6] it would appear that inpatient and post-discharge SSIs have a similar importance with regard to mortality in African settings. This once again highlights the importance of prevention of pre- and post-discharge SSI, as well as the timely diagnosis and treatment of SSI in African settings. Another finding of this study was a trend toward a reduction in mortality amongst elderly admissions with post-discharge SSI. However, we do believe that this finding is artefactual, and is likely explained by factors which lie beyond the scope of the dataset used in this study.

Rural patient groups have been reported as having worse postoperative outcomes (including SSI) when compared with their urban counterparts.[16] While our semi-quantitative geospatial analysis revealed high density clusters of post-discharge admissions in Durban, this finding should be interpreted with caution as it may have been influenced by our dichotomous definition of population density (whether clusters of admissions were located around a major urban centre or not), as well as the inability of the semi-quantitative analysis to account for socioeconomics, demographic group, or other potential confounders.

Strengths of this study include the large sample size and the ten-year study duration, which allowed for an appropriate trends analysis to be conducted. Another strength of this study was that the geospatial distribution of post-discharge admissions for SSI was mapped in KwaZulu-Natal. This study also had several limitations. The data used in this study were from a single, quaternary-level South African hospital. Therefore, the findings might not necessarily be generalisable to other healthcare facilities in South Africa or other African settings. There is also a possibility that some patients, such as those patients from rural areas, may have been admitted or managed for post-discharge SSI at another healthcare facility much closer to their place of residence. These would represent "missed" post-discharge SSIs. There might have also been some admissions which were incorrectly coded on the hospital administrative database as having SSI. Conversely, there might have been some admissions with a primary diagnosis of SSI which were missed. The medical informatics system at IALCH has been changed several times between 2006 and 2015, during which some of the finer details related to procedures performed at the hospital were lost. Therefore, surgical procedures have been broadly classified in this study as cardiac or noncardiac (with sub-specialties) procedures. Data related to other comorbidities and medication use were not recorded on the hospital administrative database, and therefore could not be investigated in this study. The specific cause of death could not be established for those patients who died in hospital. Lastly, there was no sub-classification of SSI according to extent (superficial, deep incisional, or organ space) in this study.

Conclusion

Despite implementation of universal SSI prevention methods, the number of admissions for post-discharge SSI at IALCH remained consistent during the study period. Additional efforts are required to reduce the number of post-discharge SSI admissions at IALCH. Such efforts would need to consider the multifactorial aetiology of SSI. A prevention package which simultaneously addresses risk factors at various levels would be best suited for reducing SSI in this setting. Patients from urban areas appear to be more affected by post-discharge SSI than patients from rural areas. Further research, which accounts for socioeconomic and demographic characteristics, is required to confirm this finding. While this study had strengths, it also had limitations which should be addressed in future studies on the topic.

Ethics approval

This study was a component of a larger healthcare utilisation project which was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, the KwaZulu-Natal Provincial Department of Health (Protocol number: BE595/16), and the Medical Manager of IALCH.

Conflicts of interest/Commercial interests

None.

Orchid

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Impact of surgical site infection on postoperative length of stay and hospitalization costs at a quaternary South African hospital

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Abstract

Background: Surgical site infection (SSI) is reported to increase postoperative length of stay (LoS) and hospitalization costs in non-African settings. The impact of SSI on postoperative LoS and hospitalization costs in an African country such as South Africa (SA) is unknown. The aim of this research was to address this gap in the knowledge.

Patients and Methods: This was a sub-analysis of data from a pre-existing laparotomy patient registry, collected at a quaternary SA hospital over a 5-year period. Demographic information, comorbidity, surgery-related variables, SSI, and other inpatient complications were collected for each patient during a retrospective chart review. Postoperative LoS was the primary study outcome. Quantile regression was used to investigate the impact of SSI across percentiles of postoperative LoS. Crude estimates of hospitalization costs attributed to SSI were also determined.

Results: SSI was associated with an additional 1.06 days of hospitalization at the 25th percentile of postoperative LoS. The additional cost attributed to SSI at this percentile of postoperative LoS was ZAR8900/ $1180. SSI had no significant impact at other percentiles of postoperative LoS.

Conclusion: SSI had implications for healthcare resource utilization and hospitalization costs in our setting, but only in patients who had shorter postoperative stays in hospital.

Keywords: Surgical wound infection, Length of stay, Health expenditures, South Africa.

Introduction

Surgical site infection (SSI) rates range between 0.8% and 2.9% [1]. Although SSI is associated with morbidity and mortality, attention must also be given to the consequences of this complication on healthcare resource utilization and healthcare expenditure. A systematic review by Broex et al.,[2] found that SSI contributed to a 176% mean increase and a 173% median increase in hospital length of stay (LoS). The same systematic review also found a 115% mean increase and a 110% median increase in costs [2]. Studies included in this review were predominantly from high-income, non-African settings [2]. An overall increase in healthcare resource utilization and healthcare expenditure in cases with SSI was confirmed in a subsequent systematic review of the European literature conducted by Badia and colleagues [3].

Both systematic reviews pointed out that the biggest driver of healthcare-associated costs in patients with SSI was additional LoS [2, 3]. It is unknown whether the findings for the LoS and subsequent healthcare costs associated with SSI obtained from predominantly high-income, non-African countries are applicable to a middle-income African country such as South Africa (SA). Should SSI place a significant burden on healthcare resource utilization and healthcare expenditure in a SA setting, then there would be an additional incentive for reducing SSI in this setting. The current study sought to address this gap in the knowledge.

The primary objective of this study was to determine the impact of SSI on postoperative LoS in a sample of SA surgical patients. The secondary objective was to determine the additional costs associated with SSI in a sample of SA surgical patients.

Patients and methods

Study design

This was a sub-analysis of data from a pre-existing registry of surgical patients.

Study setting

The pre-existing registry was compiled at a quaternary-level hospital located in the urban setting of Durban, SA. The hospital is a public-sector facility which offers free specialist services to residents of the KwaZulu-Natal Province on the east coast of SA. As the only quaternary-level hospital in this region, this facility represents a scarce healthcare resource and admission to the facility is strictly referral-based.

Study sample

The pre-existing surgical registry was comprised of adult patients who underwent laparotomy at the hospital. All patients in the registry were retrospectively identified from the hospital operating room lists for the period 1 January 2006 to 31 December 2010. Laparotomy patients were considered the most appropriate population for this study as open abdominal procedures are traditionally considered to be high-risk for the development of SSI [4].

Data collection

The registry data were collected through a retrospective chart review. Demographic information, summarized comorbidity (American Society of Anesthesiologists Score – ASA Score), surgery-related variables, SSI, and other inpatient complications were collected for each patient. The source documents screened for the presence or absence of these variables included admission notes, progress notes, operation notes, anesthetic records, laboratory reports, and hospital discharge summaries.

SSI was based on documented clinical signs and symptoms of infection which may or may not have been accompanied by a positive microbiological culture result, during the period of hospitalization following the surgery. This definition of SSI is similar to that proposed by the Centers for Disease Control [5]. All other postoperative complications were based on a physician's diagnosis which was recorded in the relevant source documents. Postoperative LoS was determined as the number of days between the date of surgery and the date of hospital discharge as listed on the patient's hospital discharge summary. The registry data were maintained on a password-protected electronic spreadsheet, with quality control processes being implemented at regular time points during the data collection process.

Statistics

Characteristics of the study sample were summarized using the relevant descriptive statistical methods for categorical and continuous variables. The relationship between SSI and postoperative LoS was investigated using quantile regression. This method allowed for the effects of SSI to be tested across various quantiles (also known as percentiles) of postoperative LoS, while controlling for potentially important covariates [6]. The statistical analysis in this study was stratified by three percentile values – the 25th, 50th, and 75th percentiles. SSI was the main independent variable under investigation. The analysis was controlled for patient demographics, summarized comorbidity, surgery related variables, and other complications. Results for the quantile regression are presented as regression coefficients (corresponding to a duration of postoperative LoS in days) with 95% confidence intervals (CIs). Where applicable, a p-value <0.050 was considered statistically significant.

For the descriptive cost analysis, the unit cost per day stay at the hospital was standardized using costs reported for 2010 (8396 SA Rands – ZAR or $ 1114 per day). This unit cost per day stay at the hospital was obtained from an annual report document and is inclusive of the facility fee and healthcare professional fee. Crude hospitalization costs specifically attributed to SSI, if any, were extrapolated from statistically significant quantile regression results for this outcome by multiplying the regression coefficients and CIs obtained for SSI by the unit cost per day stay. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., USA).

Study ethical approval: This research was approved as a sub-study of the pre-existing patient registry by the Biomedical Research Ethics Committee at the University of KwaZulu-Natal, SA (Protocol number: BCA208/18).

Results

Derivation and description of the study sample:

The original laparotomy patient registry consisted of 439 adult patients. It was subsequently noted that there were four patients for which the hospital discharge date could not be cross validated with other source documents in the patient medical charts. These four patients were excluded from the final analysis, as a reliable estimate of postoperative LoS could not be obtained for them. Therefore, 435 patients were included in the final analysis. A description of important characteristics in the study sample is presented in Table 1. Briefly, one-third of the study sample was male. The median age of the study sample was 42.0 years. Almost half of the study sample had moderate-to-severe systemic diseases (ASA score >2). Approximately one-third of surgeries were emergency procedures. The most common complications in the study sample were death and SSI. The median postoperative LoS was 7.0 days.

Table 1. Description of the study sample

Characteristic	n (% of N=435)
Male gender	143 (32.9)
Median age in years (IQR)	42.0 (30.0 to 56.0)
ASA score >2	205 (47.1)
Non-communicable disease indication for surgery	398 (91.5)
Emergency procedure	150 (34.5)
Perioperative blood transfusion	156 (35.9)
Reoperation	82 (18.9)
SSI	65 (14.9)
Cardiovascular complications	24 (5.5)
Respiratory complications	32 (7.4)
Renal complications	28 (6.4)
Other infection	63 (14.5)
Death	80 (18.4)
Median postoperative LoS in days (IQR)	7.0 (4.0 to 14.0)

IQR: Interquartile range, ASA: American Society of Anesthesiologists, SSI: Surgical site infection.

Impact of SSI on postoperative LoS:

The impact of SSI on postoperative LoS is shown in Table 2. When adjustments for important covariates were made, the impact of SSI was observed to be most profound at the 25th percentile of postoperative LoS. SSI did not have a significant impact on postoperative LoS at the 50th and 75th percentiles.

Table 2. Results of the quantile regression analysis

CI: Confidence interval, SSI: Surgical site infection, ASA: American Society of Anesthesiologists. Regression coefficient represents difference (either positive or negative based on sign preceding the coefficient value) in postoperative LoS days.*Statistically significant result (p<0.050).

Characteristic	Regression coefficient: 25th percentile (CI)	Regression coefficient: 50th percentile (CI)	Regression coefficient: 75th percentile (CI)
Main variable			
SSI	1.06 (0.06 to2.07)*	1.37 (-0.41 to 3.15)	3.12 (-1.52 to 7.76)
Other covariates			
Male gender	0.75 (0.01 to 1.48)*	2.71 (1.40 to 4.02)*	4.47 (1.06 to 7.88)*
Per year increase in age	0.02 (-0.01 to 0.04)	0.40 (0.01 to 0.08)*	0.01 (-0.08 to 0.11)
ASA score >2	-3.10 (-0.97 to 0.35)	0.19 (-0.97 to 1.36)	-0.58 (-3.62 to 2.46)
Noncommunicable disease indication for surgery	-0.06 (-1.30 to 1.18)	-0.92 (-3.12 to 1.28)	0.60 (-5.66 to 5.79)
Emergency procedure	1.71 (0.89 to 2.54)*	1.36 (-0.09 to 2.82)	3.81 (0.01 to 7.60)*
Perioperative blood transfusion	0.68 (-0.08 to 1.43)	1.64 (0.30 to 2.97)*	2.40 (-1.08 to 5.88)
Reoperation	2.47 (1.55 to 3.39)*	6.04 (4.41 to 7.67)*	
Cardiovascular complications	-0.20 (-1.76 to 1.37)	3.02 (0.25 to 5.80)*	2.89 (-4.35 to 10.13)
Respiratory complications	0.23 (-1.10 to 1.56)	1.55 (-0.81 to 3.91)	-0.21 (-6.36 to 5.95)
Renal complications	5.32 (3.87 to 6.77)*	6.44 (3.87 to 9.02)*	3.19 (-3.52 to 9.91)
Other infection	2.39 (1.28 to 3.50)*	3.02 (1.04 to 4.99)*	7.01 (1.86 to 12.16)*
Death	-4.44 (-5.47 to -3.42)*	-5.93 (-7.74 to -4.11)*	-5.71 (-10.44 to -0.98)*

Impact of SSI on additional hospitalization costs:

As a crude estimate, additional hospitalization costs associated with SSI amounted to an extra ZAR 8900 (CI: ZAR 504 to ZAR 17340) in the 25th percentile of postoperative LoS. This was equivalent to $ 1180 (CI: $ 67 to $ 2300). Costs for the 50th and 75th percentiles were not calculated as SSI did not significantly impact postoperative LoS in these percentile groups (p>0.050 in the quantile regression analysis).

Discussion

SSI was associated with a minimal increase in postoperative LoS, which was most evident in the group of patients who did not stay very long in hospital (i.e. the 25th percentile group). The minimal increase in postoperative LoS of 1.06 days caused by SSI in the 25th percentile group incurred an additional healthcare expenditure of ZAR 8900 ($ 1180).

The findings of this study partially confirm those from non-African studies which reported longer postoperative LoS in surgical patients with SSI [2, 3]. However, the extra days of hospitalization attributed to SSI in this study was not as excessive as that in the non-African studies [2, 3]. Furthermore, the additional days of hospitalization attributed to SSI in this study was not generalized across all quantiles of postoperative LoS. This confirms our notion that findings related to SSI and postoperative LoS derived from non-African populations might not be entirely applicable in the SA context. Although the additional days of hospitalization associated with SSI in the 25th percentile group was minimal, this could have important consequences for patient turnover in surgical wards at the hospital. Additional LoS associated with preventable conditions such as SSI can cause unnecessary delays in patient turnover. This would be further complicated by the high demand for quaternary-level healthcare services in the province of KwaZulu-Natal, SA. A high incidence of SSI would entail a considerable total number of extra days during which the afflicted patients would be kept in hospital. As such, SSI rates should be carefully monitored, with preventative strategies recommended for high-risk surgical populations. The crude estimate for additional costs attributed to SSI in the 25th percentile of postoperative LoS suggests that SSI also has an economic impact in our setting. Depending on the overall incidence of SSI, treatment of this preventable condition has the potential to divert healthcare finances away from other aspects of postoperative care where such finances are most needed. Therefore, there also seems to be a financial incentive for preventing SSI at the hospital.

The association between SSI and postoperative LoS at the 25th percentile was not observed at the 50th and 75th percentiles of postoperative LoS. Patients who have a much shorter postoperative stay are often those who do not experience any serious complications during the immediate postoperative period. Patients who have severe complications other than SSI are unlikely to be discharged early and are given more stringent monitoring and care due to their postoperative condition. As a consequence of the more stringent monitoring, more SSIs might be detected at an early stage in development. These SSIs can then be timeously treated and will not contribute to any significant additional LoS in these patients. The potential benefits of increased postoperative monitoring in reducing postoperative complications is the basis for an ongoing randomized controlled trial on the African continent [7]. In situations where the management of perioperative complications that are unrelated to SSI involves administration of prophylactic or therapeutic antibiotics, then this might simultaneously address an existing SSI.

There were both strengths and limitations to this research. The first strength of this study is the appropriate sample size of 435 patients which allowed for an adjusted statistical analysis to be performed. The second strength is our selection of a high-risk intra-abdominal (laparotomy) population for investigation in this study. The third strength is that this study is amongst the very few from African settings which delve into the impact of SSI on postoperative LoS and healthcare expenditure. The fourth and final strength of this study is that quantile regression was used to investigate the impact of SSI across various percentiles, rather than ordinary least squares regression which focuses on a mean value only [6]. The first limitation of this study is that it involved data from a single, urban, quaternary-level hospital. There is a possibility that the findings of this study might not be applicable to other facilities in rural areas or lower-level facilities. The second limitation is that this study did not consider the impact of post-discharge SSI. Lastly, the crudely estimated cost data does not include treatment costs for SSI. However, we anticipate that this would have contributed to additional overall costs in those afflicted with the condition based on existing published economic reports of SSI.

In conclusion, SSI had healthcare resource and economic consequences in the group of patients who had shorter hospital stays following their surgery. The estimates of cost in this group of patients would be directly proportional to SSI rates. Therefore, the findings of this research serve as an added impetus for reducing SSI rates at the hospital. We recommend that additional research be conducted to confirm the findings of this study.

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ORIGINAL RESEARCH

A comparison of preoperative hypoalbuminaemia with the NNIS and SENIC risk scores for the prediction of surgical site infection in a South African setting

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Introduction: Preoperative hypoalbuminaemia is a risk factor for surgical site infection (SSI) in the South African (SA) setting. However, the predictive accuracy of preoperative hypoalbuminaemia has not been tested against established SSI risk stratification models in our setting, which could have important implications for SSI prevention strategies. With reference to SSI in SA settings, the study objective was to compare the overall predictive accuracy of preoperative hypoalbuminaemia with that obtained for the SENIC/NNIS risk scores.

Method: This was a sub-analysis of a pre-existing laparotomy patient registry ($N = 439$). Variables collected as part of the registry included preoperative serum albumin measurements and all parameters of the SENIC/NNIS risk scores. Preoperative hypoalbuminaemia was defined as preoperative serum albumin of < 30 g/L. The study outcome was SSI up to 30 days postoperatively. Overall predictive accuracy was determined through a receiver-operator-characteristic (ROC) curve analysis, with results presented as C-statistics (95% confidence intervals [CI]).

Results: The C-statistics obtained for preoperative hypoalbuminaemia, the SENIC risk score, and the NNIS risk score were 0.677 (CI: 0.609–0.746), 0.652 (CI: 0.582–0.721), and 0.634 (CI: 0.563–0.705).

Conclusion: All three methods display similar predictive accuracy for SSI. However, preoperative hypoalbuminaemia has several practical advantages over the SENIC/NNIS scores which must be considered.

Keywords: hypoalbuminaemia, surgical site infection, predictive accuracy, SENIC, NNIS, South Africa

Introduction

Surgical site infection (SSI) is recognised as an important cause of morbidity, mortality, and increased healthcare resource utilisation amongst surgical populations across the world.[1-3] The identification of surgical patients at high-risk of developing SSI and implementation of preventative strategies in these patients therefore remains an important consideration for surgeons.[4,5] There are two commonly used risk stratification models for SSI: The Study on the Efficacy of Nosocomial Infection Control (SENIC) risk score and the National Nosocomial Infections Surveillance (NNIS) risk score.[4,5]

The SENIC risk score was developed by Hayley et al. using data collected during the 1970s for almost 59 000 American surgical patients.[4] It is a multivariate risk model consisting of four variables, including: abdominal operation, operation > 2 hours in duration, contaminated-dirty wound, and having ≥ 3 discharge diagnoses. Each variable in the model, if present, is allocated a point score of "1". Cumulative scores, which could theoretically range between 0 and 4 points, are then determined for each patient. Hayley et al. reported that the incidence of SSI in individuals with a cumulative score of ≥ 2 points ranged between 10% and 30%.[4] Accordingly, the cumulative score of ≥ 2 points for the SENIC method was used as a threshold to define the "high-risk" group for SSI. From their study sample of almost 59 000 surgical patients, these authors determined that the high-risk group accounted for approximately 90% of all SSIs.[4]

The NNIS risk score was proposed during the early 1990s as an improvement on the SENIC risk stratification for SSI.[5] Using a cohort of almost 85 000 surgical patients, Culver and colleagues were able to develop a multivariate risk model consisting of three factors: surgical wound class, operation longer than T-time (where "T" is the usual duration of a surgical procedure), and American Society of Anesthesiologists (ASA) preoperative physical status classification of ≥ 3. The inclusion of the ASA classification in the NNIS risk score was thought to have improved the predictive accuracy of the model by accounting for intrinsic risk. Similar to the SENIC risk score, all components in the NNIS risk score are allocated a single point. Cumulative scores for the NNIS risk score can range between 0 and 3 points. Culver et al. found that the incidence of SSI was much higher in patients with cumulative NNIS scores ≥ 2 points (6.8–13.0%) when compared with patients who had cumulative NNIS scores < 2 (1.5–2.9%).[5]

Although the SENIC and NNIS risk stratification methods represent an important move forward in the prediction of SSI, the ability of these models to discriminate between patients with and without SSI has been questioned in recent years. Some experts have suggested that future methods aimed at SSI prediction should be based on biomarkers, as this approach might demonstrate an improved ability to discriminate between patients with and without SSI.[6] Albumin is one biomarker which has been proposed for the prediction of SSI. This small, globular protein is produced in the liver and accounts for 50% of the total serum protein content in healthy individuals.[7] Hypoalbuminaemia, or a serum albumin measurement below the lower limit of the normal reference range, is often used as a marker for malnutrition.[8] It is proposed that malnutrition increases an individual's susceptibility to postoperative infection in two ways. Firstly, malnutrition impairs wound healing by diminishing fibroblast proliferation and collagen synthesis.[6] Secondly, albumin deficiency is linked to lymphocytopaenia and immune dysfunction.[6] It is not surprising that much of the global literature has reported preoperative hypoalbuminaemia to be associated with an increased risk of SSI.[9-11] Our recent study in South African (SA) surgical patients also identified preoperative hypoalbuminaemia as a risk factor for SSI.[12]

With reference to SSI prediction in SA patients undergoing open abdominal surgery, the objective of the current study was to compare the overall predictive accuracy for preoperative hypoalbuminaemia with that obtained for the SENIC and NNIS methods. As this has not been previously investigated in the SA setting, the current study also sought to address an important gap in the literature.

Materials and methods

Study design and setting

This was a sub-analysis of patient data from our prior study of SSI risk factors in a SA setting.[12] The study setting was the Inkosi Albert Luthuli Central Hospital (IALCH) located in Durban, SA. IALCH is a public sector facility which provides quaternary-level healthcare services to the populace of the KwaZulu-Natal Province, located on the east coast of SA.

Study sample

We included all 439 patients from our prior study[12] in the current sub-analysis. All patients were adults, and had undergone laparotomy procedures at IALCH between 01 January 2006 and 31 December 2010.

Data collection

Data for our prior study were collected via a retrospective chart review. We had collected the following variables for each patient: demographic information, comorbidities, medication use, preoperative laboratory test results (including serum albumin measurements), surgery-related variables, and all parameters of the SENIC/NNIS risk scores. Cumulative SENIC/NNIS scores were computed for each patient. SENIC and NNIS scores were complete for all patients in this study. The study outcome was SSI up to 30 days postoperatively. This outcome was based on the widely used definition proposed by the Centers for Disease Control (CDC).[13] This definition incorporates clinical signs and symptoms of infection and is not solely based on microbiological evidence of infection. Preoperative hypoalbuminaemia was defined as a preoperative serum albumin measurement < 30 g/L. This threshold for preoperative hypoalbuminaemia has been proposed in recent perioperative nutrition guidelines.[14] All preoperative serum albumin measurements were taken at least one month prior to surgery, which is in keeping with the current preoperative work-up practices at IALCH. All serum albumin measurements were performed by a SANAS-accredited chemical pathology laboratory located on the hospital premises.

Data analysis

Descriptive statistics were used to summarise the characteristics of the study sample. Descriptive results for categorical variables are presented as frequencies (%). We analysed all the continuous variables in the study for normality using the Kolmogorov-Smirnov (KS) test. All KS test results were found to be statistically significant ($p < 0.05$), indicating that the data for all continuous variables did not demonstrate a normal distribution. Therefore, summary data for the continuous variables in this study are presented as medians with interquartile range (IQR). The overall predictive accuracy of hypoalbuminaemia, the SENIC risk score, and the NNIS risk score were assessed using receiver-operator-characteristic (ROC) curves. The resulting C-statistic was used to classify overall predictive accuracy as follows: < 0.500 = not any better than chance, 0.600–0.699 = fair, > 0.700 = good. Standard 2 x 2 epidemiological tables and equations were used to determine the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for each risk stratification method. For this aspect of the analysis, conventional SENIC/NNIS thresholds for high-risk individuals were adopted from the published literature.[4,5] In addition, 95% confidence intervals (CIs) are provided for all estimates of predictive accuracy. When comparing the three risk stratification methods, estimates of predictive accuracy with discreet confidence intervals were considered to be statistically different (i.e. $p < 0.05$).

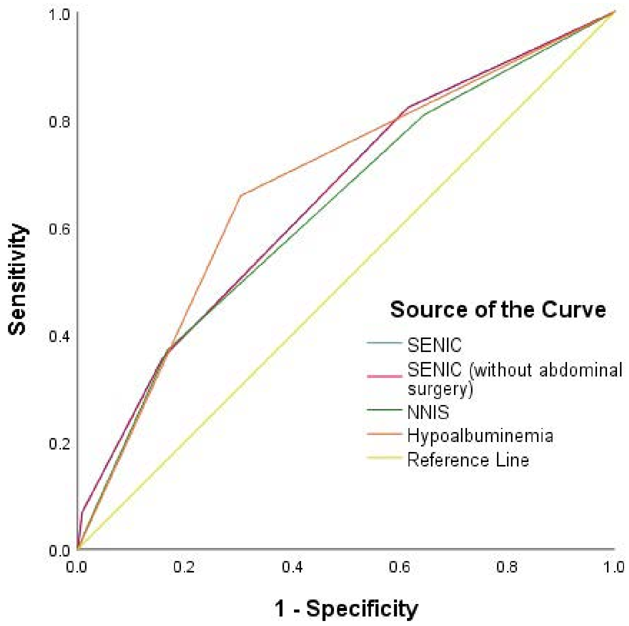

Figure 1: Results of the ROC curve analysis

Results

The characteristics of the study sample are presented in Table I.

Figure 1 shows the results of the ROC curve analysis. The performance of each risk stratification method is presented as a separate line (four lines). In keeping with the general format of ROC curve analyses, a reference line (fifth line) indicating the threshold for a test/risk method performing better than pure chance is also included (C-statistic for reference line = 0.500). We had some concerns related to overestimation of SSI when applying SENIC to our study sample, which was comprised solely of abdominal surgery patients (abdominal surgery is a component of the original SENIC score). We tested an adapted SENIC score (with abdominal surgery omitted) against the original score and did not find any difference in the predictive accuracy between the two variations of the SENIC score (C-statistic, CI for both = 0.652, 0.582–0.721). This explains why the two lines overlap with each other on the ROC curve graph. A decision was made to continue with the use of the original SENIC score for the subsequent aspects of the statistical analysis. The C-statistic obtained for the NNIS score was 0.634 (CI: 0.563–0.705). The C-statistic obtained for preoperative hypoalbuminaemia was 0.677 (CI: 0.609–0.746). Based on the observed C-statistics, all methods were found to demonstrate "fair" predictive accuracy for SSI. The CIs for all estimates were found to overlap, suggesting no statistically significant difference ($p > 0.05$) in the overall predictive accuracy between all three risk stratification methods.

Table I: Description of the study sample (*N* = 439)

Characteristic	**Median (IQR) or *n* (% *N*)**
Age in years	42.0 (30.0–56.0)
Male gender	145 (33.0)
Obesity	152 (34.6)
Indication for surgery	
Bleed	12 (2.7)
Cancer	183 (41.7)
Infection	36 (8.2)
Other	151 (34.4)
Trauma	57 (13.0)
ASA preoperative classification ≥ 3	207 (47.2)
Preoperative nonsteroidal anti-inflammatory use	62 (14.1)
Preoperative statin use	25 (5.7)
Hypertension	140 (31.9)
Diabetes	57 (13.0)
Cardiovascular disease	50 (11.4)
HIV	30 (6.8)
Metastatic cancer	86 (19.6)
Obstructive airway disease	25 (5.7)
Gastric ulcers	17 (3.9)
Current smoker	44 (10.0)
Preoperative leukocyte count, x10^9 cells/L	8.0 (5.9–10.6)
Preoperative platelets count, x10^9/L	263.0 (187.0–351.0)
Preoperative serum creatinine, µmol/L	75.0 (65.0–108.0)
Preoperative haemoglobin, g/dL	10.9 (9.2–12.4)
Preoperative sodium, mEq/L	139.0 (137.0–142.0)
Preoperative serum albumin, g/L	35.0 (22.0–42.0)
Preoperative hypoalbuminaemia	159 (36.2)
Abdominal procedure	439 (100.0)
Emergency procedure	150 (34.2)
Contaminated-dirty procedure	88 (20.0)
Surgery duration > T-time (2 hours)	153 (34.9)
Bogota bag	70 (15.9)
Antibiotic prophylaxis	366 (83.4)
Perioperative blood transfusion	157 (35.8)
Patient-controlled analgesia postoperatively	33 (7.5)
≥ 3 discharge diagnoses	136 (31.0)
SSI within 30 days postoperatively	73 (16.6)
SENIC score ≥ 2	285 (64.9)
NNIS score ≥ 2	88 (20.0)

The sensitivity, specificity, PPV, and NPV for all three risk stratification methods are presented in Table II. Comparison of the CIs for sensitivity and specificity between the three methods revealed several statistically significant ($p < 0.05$) differences. Preoperative hypoalbuminaemia and the SENIC score were found to have a higher sensitivity for SSI than the NNIS score. Based on the overlapping CIs for the sensitivity estimates obtained for hypoalbuminaemia and SENIC, there was no difference in overall sensitivity between the two tests. The NNIS score had a higher specificity when compared with preoperative hypoalbuminaemia and SENIC. Preoperative hypoalbuminaemia had a higher specificity when compared with SENIC. Comparison of the CIs obtained for PPV/NPV estimates did not reveal any statistically significant differences between the three risk stratification methods for these parameters.

Discussion

Preoperative hypoalbuminaemia, the SENIC score, and the NNIS score displayed similar overall predictive accuracy for SSI. A more in-depth comparison of predictive parameters (sensitivity, specificity, PPV, NPV) between the three risk stratification methods revealed that the similar performance was due to either high sensitivity being offset by low specificity (preoperative hypoalbuminaemia and the SENIC score) or high specificity being offset by low sensitivity (the NNIS score).

Notwithstanding the similar predictive performance for SSI, preoperative hypoalbuminaemia has several practical advantages over the SENIC and NNIS risk scores. Serum albumin measurements are a particularly important assessment in

Table II: Sensitivity, specificity, PPV, and NPV for each risk stratification method

Method	**Sensitivity % (CI)**	**Specificity % (CI)**	**PPV % (CI)**	**NPV % (CI)**
Hypoalbuminaemia	65.8 (53.7–76.5)	69.7 (64.7–74.3)	30.2 (23.2–38.0)	91.1 (87.1–94.1)
SENIC risk score	82.2 (71.5–90.2)	38.5 (33.5–43.7)	21.1 (16.5–26.3)	91.6 (86.0–95.4)
NNIS risk score	37.0 (26.0–49.1)	83.3 (79.1–87.0)	30.7 (21.3–41.4)	86.9 (82.9–90.2)

patients with abdominal pathologies, such as our study sample of laparotomy patients, where it is often used as a measure of liver function.[15] Serum albumin measurements are included as part of the preoperative work-up in patients undergoing surgery for abdominal pathologies. Therefore, an assessment of SSI risk can be made for almost all patients awaiting abdominal surgery procedures. The serum albumin test is also widely available, and can be performed by a laboratory or as a point-of-care assay.[16,17] Serum albumin measurements are also cost-effective, with current costs per test invoiced at approximately US$ 3 in our setting. This cost is negligible when compared to the excessive costs required to treat SSI.[3] The process of risk score computation, such as that in the SENIC and NNIS methods,[4,5] might be viewed as a tedious process by the often inundated surgeon in the SA public healthcare sector. In comparison, identifying high-risk patients through evaluation of preoperative serum albumin measurements is a simpler process. While the SENIC/NNIS were complete for each patient in this study, there also exists a potential drawback in the SENIC/NNIS risk scores when a component of the score is missing or inaccurately recorded for a patient. For example, the ASA preoperative classification is a component of the NNIS risk score,[5] but evidence from a SA setting suggests that this score is inconsistently recorded or missing from the preoperative assessments completed by anaesthetists.[18] In such situations, it becomes impossible to compute a cumulative risk score, and subsequently estimate SSI risk in a patient using the NNIS score.

In addition, the most crucial difference between evaluating preoperative serum albumin measurements and the SENIC/NNIS methods for SSI prediction is that the SENIC/NNIS methods require certain information which is only available intraoperatively or postoperatively. This information includes the surgical incision wound classification, the duration of surgery, and the number of discharge diagnoses.[4,5] The World Health Organization (WHO) has proposed multiple preventative interventions for SSI, some of which can be considered for implementation in high-risk patients during the preoperative period.[19] It would be more resource-efficient to target high-risk patients for these interventions, rather than targeting all patients. Therefore, the added advantage of using preoperative hypoalbuminaemia to predict SSI is that it would allow for a full range of SSI preventative measures (pre-, intra-, and postoperatively) to be implemented in high-risk patients, whereas the SENIC/NNIS risk scores would only allow for postoperative interventions (i.e. once the cumulative SENIC/NNIS score is computed) to be implemented.

Along with the SSI preventative interventions proposed by the WHO, possible consideration must be given to optimising preoperative serum albumin as a risk reduction strategy for SSI in our setting. Optimisation of preoperative serum albumin can be achieved through the provision of comprehensive preoperative nutrition to patients awaiting surgery.[20,21] The appropriate time-point in the preoperative period when it would be best to initiate such a strategy in our patient population is unknown, but it is inevitable that the duration of the nutritional intervention would have a direct impact on expenditure within health departments. The costs incurred by health departments in ensuring appropriate perioperative nutrition in patients awaiting surgery will likely be far lower than the costs which would be incurred if these patients were to develop SSI. Therefore, new research studies should be conducted in our setting to evaluate the impact of preoperative serum albumin optimisation on SSI risk.

There were limitations to this research, some of which have been declared in our previous manuscript involving the same laparotomy patient registry.[12] Amongst these previously declared limitations was a possible lack of generalisability in our findings as the patient registry was compiled at a single, quaternary-level institution which might not necessarily reflect the patient population in other SA settings. Another previously declared study limitation was that there might have been some patients who had developed SSI outside of the 30 day period proposed by the CDC definition.[13] There is also the possibility that some patients with minor forms of SSI might have self-managed their condition or presented for treatment at lower level healthcare facilities. These patients would have been considered as not having SSI in our statistical analysis. A limitation unique to our current sub-analysis is that we did not investigate other predictive biomarkers for SSI proposed in the literature, such as C-reactive protein,[22] due to the inconsistency in which the tests were ordered preoperatively at our institution. Another limitation unique to our current study is that we did not stratify our results by age and gender. We believe that a more in-depth investigation of this nature would require a larger sample size far beyond the scope of our pre-existing laparotomy patient registry.

Conclusion

In conclusion, preoperative hypoalbuminaemia and the SENIC/NNIS scores demonstrated a similar predictive accuracy for SSI. There are however, several practical advantages to using preoperative hypoalbuminaemia over the SENIC/NNIS risk scores for SSI prediction. The most important of these advantages is that evaluating serum albumin levels allows for the preoperative calculation of SSI risk and the implementation of SSI preventative strategies in high-risk patients when compared with those which can be only be implemented postoperatively following calculation of SENIC/NNIS scores. Further research in our setting is recommended which seeks to investigate the impact of preoperative serum albumin optimisation on SSI risk.

Conflicts of interest/Commercial interests

The authors declare no conflict of interest.

Funding source

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Ethical approval

This study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, South Africa (Protocol number: BCA208/18).

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ORIGINAL RESEARCH

Are lower preoperative serum sodium levels associated with postoperative surgical site infection? Results from a propensity matched case-control study

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Background: We previously reported a statistical trend toward a harmful association between lower preoperative serum sodium levels and surgical site infection (SSI) in South African (SA) laparotomy patients. Serum sodium tests are widely available and could serve as a cost-effective method for preoperatively identifying patients at risk for SSI who might benefit from additional preventative strategies. We sought to investigate the possible association between lower serum sodium levels and SSI further, in a larger sample of SA patients undergoing various surgical procedures.

Objective: To determine if lower preoperative serum sodium levels are associated with SSI in SA surgical patients.

Method: This was a propensity matched case-control study involving data from 729 surgical patients who attended a quaternary SA hospital between 01 January 2012 and 31 July 2016. Cases were defined as patients who developed SSI. Controls were defined as patients who did not develop SSI. Multivariate logistic regression was used to investigate the association between preoperative serum sodium levels (in mmol/L) and SSI.

Results: Lower preoperative serum sodium levels were associated with a higher risk of SSI (odds ratio per 1.0 mmol/L decrease in serum sodium: 1.051, 95% confidence interval: 1.007–1.097; $p = 0.026$).

Conclusion: Although we report a statistically significant association between lower preoperative serum sodium levels and a higher risk of SSI, the magnitude of this effect size (odds ratio) is minimal and clinically insignificant. Preoperative serum sodium levels are unlikely to be useful for SSI risk stratification in our setting.

Keywords: preoperative period, sodium, surgical wound infection, surgical site infection

Introduction

Surgical site infection (SSI) is an important postoperative complication in African settings, where it is associated with increased morbidity, mortality, and healthcare resource utilisation.[1,2] Preoperative identification of high-risk patients in these settings would allow for a full range of preventative strategies to be implemented throughout the perioperative period.[3] We recently demonstrated the pitfalls of using conventional SSI risk stratification methods, namely the National Nosocomial Infections Surveillance (NNIS) score and the Study of the Efficacy of Nosocomial Infection Control (SENIC) score, in South African (SA) patients undergoing abdominal surgery.[4] A major limitation is that intraoperative variables are required to compute these scores. Accordingly, these scoring systems cannot be used preoperatively to estimate postoperative SSI risk.[4] On the other hand, our previous research also suggests that routinely measured analytes, such as serum albumin, can be used during the preoperative period to provide postoperative estimates of SSI risk that are comparable to those provided by the NNIS and SENIC scores.[4] In another of our prior studies, involving 439 SA laparotomy patients, we found a statistical trend toward a harmful association between lower preoperative serum sodium and SSI.[5] Serum sodium measurements are widely available, cost-effective tests that are usually ordered as part of the urea and electrolyte panel.[6] The panel is used to screen for renal impairment during the preoperative and postoperative period.[7] We sought to investigate the possible association between lower serum sodium levels and SSI further, in a larger sample of patients undergoing various surgical procedures.

Materials and methods

Study design

This was a propensity matched case-control study.

Study setting

The study setting was the Inkosi Albert Luthuli Central Hospital (IALCH) in Durban, South Africa. This public-sector, quaternary level hospital provides surgical and medical services to residents of the eastern seaboard of South Africa.

Study sample

The study sample consisted of adult patients (aged ≥ 18 years old) who underwent surgical procedures at IALCH between 01 January 2012 and 31 July 2016. Additional eligibility criteria used to derive the study sample are provided in Table I. Our decision to include only patients who had orthopaedic, vascular, general, or gynaecology surgeries in this study was based on the findings of our prior research involving procedure rates and SSI at IALCH.[2]

Table I: Additional eligibility criteria for this study

Inclusion criteria	Exclusion criteria
Patients who underwent orthopaedic, vascular, general, or gynaecology surgery	Patients with missing data required for matching or missing preoperative sodium measurement Patients with complete datasets but who could not be matched

Data sources and definitions

The hospital electronic admissions system was used to identify surgical patients, establish the surgical speciality involved, determine patient age and gender, determine the nature of the surgery and its indication, as well as calculate the duration of surgery in minutes. This information, along with the patient hospital number, was directly extracted from the electronic admissions system and saved as a Microsoft Excel spreadsheet. The duration of surgery was calculated as the time in minutes between skin incision and closure of the surgical wound. Surgical wounds were classified as clean, clean/contaminated, contaminated, or dirty/infected.[8] Serum sodium measurements and microbiological culture tests were performed by a National Health Laboratory Service (NHLS) facility located on IALCH premises. We received approval from the NHLS to access preoperative serum sodium test results and microbiological culture results during the study period. We used the patient hospital number to link patients in the Microsoft Excel spreadsheet with preoperative serum sodium and postoperative microbiology results on the NHLS system. The closest preoperative serum sodium measurement was used. Although the preoperative sodium is usually measured by surgeons and anaesthetists within four weeks prior to surgery, measurements outside this period are acceptable for patients who are clinically stable (i.e. those patients without significant comorbidity or those considered very low risk for perioperative complications) in our setting. It is common practice at IALCH for surgeons to collect pus swabs for microbiological culture from surgical wounds which appear infected on clinical examination. For the purpose of this research, all pus swabs were treated as SSIs (irrespective of the final culture result). This is in keeping with the definition of SSI proposed by the Centers for Disease Control, which does not necessarily require a positive microbiological culture result when establishing the presence of a SSI.[9] We extended our review of microbiological culture orders for each patient up to 30 days postoperatively. Cases were defined as patients who experienced SSI within 30 days postoperatively. Controls were defined as patients who did not experience SSI within 30 days postoperatively. The Microsoft Excel spreadsheet was imported into R version 3.6.2 (R Foundation, Vienna, Austria) for the matching process and the subsequent statistical analysis.

Matching

Patients were matched on surgical speciality, surgical wound class, and duration of surgery using "nearest neighbour" propensity matching.[10] This approach involves deriving a propensity score based on an initial binary logistic regression model in which all the matching variables are entered. Cases are then matched with controls that share similar propensity score values. A case:control ratio of 1:2 was used as this ratio has been demonstrated to add optimal statistical power to a case-control study.[11] The matching process was qualitatively evaluated using a jitter plot.

Statistical analysis

Descriptive statistics were used to summarise the characteristics of the entire study sample. This involved calculating means with standard deviations (SD) for continuous variables, and frequency distributions with percentages for categorical variables. We compared characteristics between case and control groups using univariate binary logistic regression. We then tested for a possible relationship between preoperative serum sodium levels and SSI using a conditional multivariate binary logistic regression model which was adjusted for patient age, gender, and time in weeks between the sodium measurement and surgery. For conditional regression models, only those variables which did not form part of the matching process are entered into the regression equation. Results of the univariate and multivariate binary logistic regression analyses are presented as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was set at $p < 0.050$.

Results

Figure 1 shows how the final study sample was derived. The final study sample consisted of 729 patients (243 cases matched with 486 controls). The jitter plot shows a fairly similar distribution of propensity scores in matched case and control groups (Figure 2), indicating that the matching process was satisfactory.

The characteristics of the study sample are described in Table II. The mean age of the study sample was 54.4 years old, and just over half of the study population were male. The most common procedures were vascular surgery procedures, which comprised 52.9% of the study sample. While most surgical wounds were categorised as clean wounds (57.6%), there was still a substantial proportion of surgical wounds which were categorised as dirty/infected wounds (28.4%). The mean duration of the surgical procedure was 102.7 minutes. The mean preoperative sodium level in the study sample was 138.7 mmol/L.

A distribution of characteristics between case-control groups and the results of the univariate statistical analysis is shown in Table III. As expected, the matching process produced no statistical differences in surgical speciality, wound class, or duration of surgery between case and control groups. For the unmatched variables, there was no statistically significant difference observed for age, gender, or number of weeks between sodium measurement and surgery. However, there was a

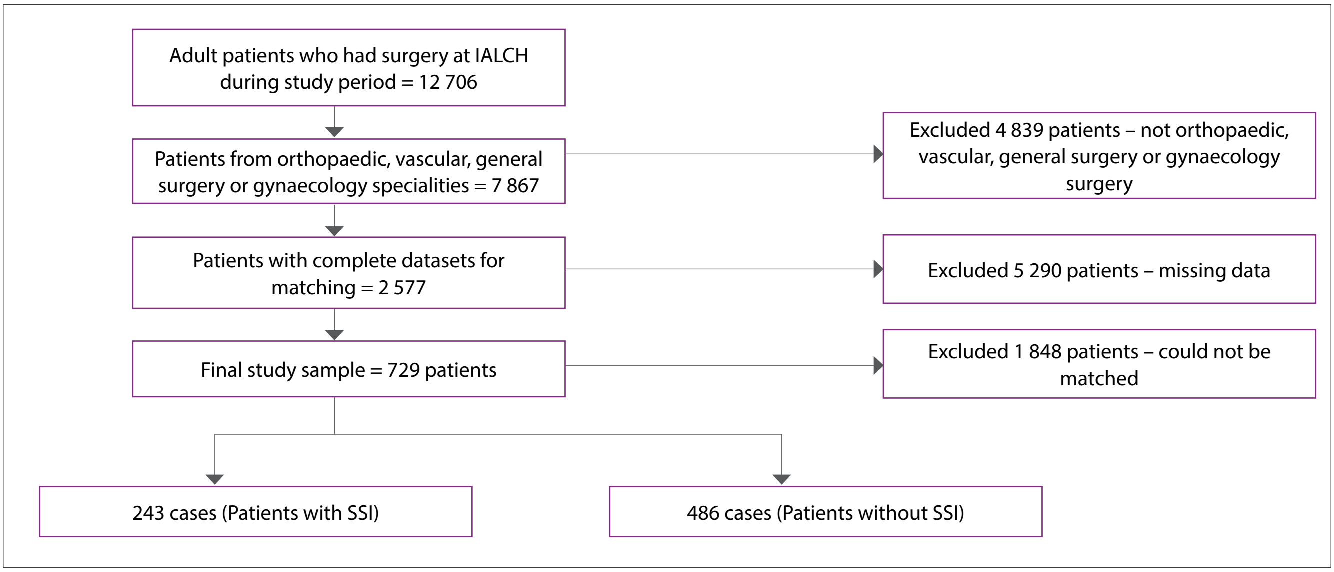

Figure 1: Derivation of the study sample

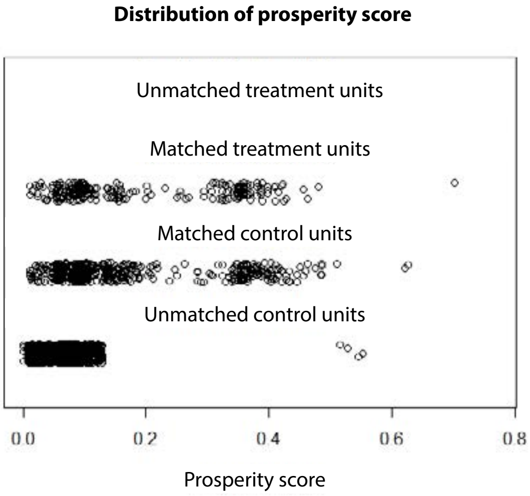

Figure 2: Jitter plot showing distribution of propensity scores in matched cases (treatment units) and controls.

Table II: Description of the study sample

Characteristic	Summary statistic
Mean age, years (SD)	54.4 (16.0)
Female gender, *n* (% of *n* = 729)	352 (48.3)
Male gender, *n* (% of *n* = 729)	377 (51.7)
Orthopaedic surgery, *n* (% of *n* = 729)	202 (27.7)
Vascular surgery, *n* (% of *n* = 729)	386 (52.9)
General surgery, *n* (% of *n* = 729)	120 (16.5)
Gynaecology surgery, *n* (% of *n* = 729)	21 (2.9)
Clean wound, *n* (% of *n* = 729)	420 (57.6)
Clean-contaminated wound, *n* (% of *n* = 729)	86 (11.8)
Contaminated wound, *n* (% of *n* = 729)	16 (2.2)
Dirty/infected wound, *n* (% of *n* = 729)	207 (28.4)
Mean duration of surgery, minutes (SD)	102.7 (79.3)
Mean time between sodium test and surgery, weeks (SD)	3.5 (10.2)
Mean preoperative serum sodium, mmol/L (SD)	138.7 (3.6)

Table III: Results of the univariate statistical analysis

Characteristic	Cases (*n* = 243)	Controls (*n* = 486)	OR (CI)*	*p*
Mean age, years (SD)	54.8 (15.1)	54.2 (16.4)	1.002 (0.993–1.102)	0.656
Female gender, n (% of *n*)	125 (51.4)	226 (46.7)	Reference category	–
Male gender, n (% of *n*)	118 (48.6)	259 (53.3)	0.827 (0.608–1.126)	0.228
Orthopaedic surgery, n (% of *n*)	78 (32.1)	124 (25.5)	Reference category	–
Vascular surgery, n (% of *n*)	118 (48.6)	268 (55.1)	0.700 (0.490–1.000)	0.050
General surgery, n (% of *n*)	39 (16.0)	81 (16.7)	0.765 (0.476–1.232)	0.271
Gynaecology surgery, n (% of *n*)	8 (3.3)	13 (2.7)	0.978 (0.388–2.468)	0.963
Clean wound, n (% of *n*)	126 (51.9)	294 (60.5)	Reference category	–
Clean-contaminated wound, n (% of *n*)	31 (12.8)	55 (11.3)	1.315 (0.808–2.141)	0.270
Contaminated wound, n (% of *n*)	8 (3.3)	8 (1.7)	2.333 (0.857–6.355)	0.097
Dirty/infected wound, n (% of *n*)	78 (32.0)	129 (26.5)	1.411 (0.994–2.002)	0.054
Mean duration of surgery, minutes (SD)	95.7 (77.9)	106.2 (79.9)	0.998 (0.996–1.000)	0.094
Mean time between sodium test and surgery, weeks (SD)	4.0 (14.5)	2.6 (8.2)	1.011 (0.997–1.026)	0.119
Mean preoperative serum sodium, mmol/L (SD)	138.3 (4.0)	138.9 (3.4)	1.051 (1.007–1.097)	0.022

*Risk estimate for age and surgery duration based on per unit increase. Risk estimate for mean preoperative serum sodium based on per unit decrease. Reference category for male gender = "Female".

Table IV: Results of the multivariate statistical analyses

Characteristic	OR (CI)*	*p*
Age in years, per unit increase	0.999 (0.989–1.009)	0.840
Male gender	0.820 (0.599–1.122)	0.215
Time between sodium test and surgery, per week increase	1.011 (0.996–1.026)	0.147
Preoperative serum sodium in mmol/L, per unit decrease	1.051 (1.007–1.097)	0.026

*Reference category for male gender = "Female".

statistically significant difference in preoperative serum sodium levels between case and control groups.

The results of the conditional binary logistic regression analyses are shown in Table IV. When the analysis was adjusted for age, gender, and time between the sodium measurement and surgery, lower preoperative serum sodium levels (per 1.0 mmol/L decrease) were found to be associated with a higher likelihood of developing SSI (OR: 1.051, CI: 1.007–1.097; $p = 0.026$).

Discussion

We found a statistically significant association between lower preoperative serum sodium levels and a higher risk of SSI. This finding is in general agreement with a study of a large American surgical registry by Leung et al., which also reported a higher rate of SSI amongst patients with lower preoperative serum levels.[12] There are two potential pathophysiological mechanisms which might explain our observation of a statistically significant association between lower preoperative serum sodium levels and SSI. The first mechanism relates to the role played by sodium during wound healing. Sodium is an important component of the exudate fluid. This fluid keeps wound surfaces moist and promotes wound healing.[13] Reduced sodium levels could impair wound healing by reducing the effectiveness of the exudate fluid, thereby making the surgical wound more susceptible to bacterial colonisation. The second mechanism relates to the role played by sodium during the immune response to infection. Phagocytes, particularly neutrophils, are involved during the initial immune response to bacteria that breach the upper epithelial layers of the skin.[14] Neutrophils eliminate bacteria via the combined processes of phagocytosis and reactive oxygen/nitrogen species production.[14] Although low sodium levels have little effect on the production of antimicrobial reactive oxygen/nitrogen species, low sodium levels can almost completely inhibit phagocytic activity in neutrophils.[15] The reduced killing activity of neutrophils can allow bacteria to survive and proliferate in the surgical wound.[15]

Although the observed association between lower preoperative serum sodium levels and a higher risk of SSI was statistically significant, this result is clinically insignificant. An odds ratio of 1.05 per unit decrease in serum sodium levels is indeed a small effect size. Such a trivial association might not be sufficient to impact surgeons' clinical decision-making and prompt them to institute additional interventions during the perioperative period in order to reduce SSI risk. Therefore, preoperative serum sodium levels are unlikely to have substantial clinical utility as a risk stratification tool for SSI in our setting. We do not believe that the findings of the current study should be seen as a barrier to investigating the potential association between levels of other analytes routinely that are measured during the preoperative period and SSI in our setting. Our prior work involving preoperative albumin levels is testament to this, and we strongly recommend that associations between other analytes and SSI be investigated in future studies.

There were limitations to our study. Our study involved data from a single, quaternary level hospital. This has implications for the generalisability of our findings to other hospitals which may have different case-mixes, procedure rates, or SSI rates. Multicentre studies are recommended to address the limitation regarding the generalisability of our study findings.[16] The American Society of Anesthesiologists (ASA) score is noted as an important predictor of SSI,[17] but was not collected as part of the hospital administrative database. Patient age was used as a proxy for ASA score in this study, as both variables show a strong correlation.[18] This was a retrospective analysis and we did not have any information on pre-analytical variables such as patient preparation prior to the blood specimen being taken, whether the specimen was correctly taken (i.e. in the correct blood tube for the required test), and whether the specimen was correctly handled and processed on receipt at the laboratory. Therefore, we could not adjust our analysis for these variables. We adjusted our analysis, through matching and multivariate methods, for as many confounders as possible with the dataset that was available to us. This includes known risk factors for surgical site infection that are components of the NNIS score. However, we were limited by the number of variables and patient characteristics that are routinely collected as part of the hospital electronic admissions system from which the patient and surgery data was obtained. Owing to this, we could not adjust our analysis for other, lesser known risk factors associated with surgical site infection which were not captured by the hospital electronic admissions system. Future research investigating the association between various routine preoperative laboratory tests and SSI should seek to address these limitations.

Conclusion

Although we report a statistically significant association between lower preoperative serum sodium levels and a higher risk of SSI, this association lacks clinical significance. Preoperative serum sodium levels are unlikely to have value as a risk stratification tool for SSI in our setting. Nevertheless, the findings of the current study should not be seen as a barrier to investigating the association between other routinely performed preoperative laboratory tests and SSI in our setting for future risk stratification purposes.

Conflict of interest

The authors declare no conflict of interest.

Funding source

None.

Ethical approval

This research was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (Protocol number: BE595/16).

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Appendix II

Regulatory documents

UNIVERSITY OF
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16 July 2018

Student no: 204500477

Dr N Naidoo
Department of Surgery
School of Clinical Medicine
College of Health Science

Dear Dr Naidoo

Degree: Doctor of Philosophy (Medicine)
Title: "Surgical site infections at a tertiary South African hospital: Epidemiology and impact on healthcare resources."

Supervisor: Dr Y Moodley
Co-Supervisor: Professor TE Madiba

I have pleasure in advising you that you have been accepted as a candidate for the above degree.

Programme Details:
Year of Acceptance: 2018, 2nd Semester
Offering Type: Full-Time

Attached please find the 2018 College Hand Book for your perusal.

I trust that your research will be both stimulating and productive, and wish you success in this venture.

Yours sincerely

Veronica Jantjies

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7 September 2018

Dr Y Moodley
Discipline of Anaesthisiology and Critical Care
School of Clinical Medicine
College of Health Science

Dear Dr Moodley

Degree: Doctor of Philosophy (Medicine)

Title: "Surgical site infections at a tertiary South African hospital: Epidemiology and impact on healthcare resources."
Student: Dr N Naidoo, student number: 204500477, (*Department of Surgery*)

I am pleased to inform you that the abovementioned study has been approved.

Please note:

- The Academic Leader: Research must review any changes made to this study

May I take this opportunity to wish the student every success with the study.

Yours sincerely

Veronica Jantjies

for Dr JM Van Wyk
Academic Leader Research
School of Clinical Medicine

C: Dr N Naidoo
Prof TE Madiba

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14 August 2018

Dr Y Moodley
Discipline of Anaesthisiology and Critical Care
School of Clinical Medicine
Pietermaritzburg
moodleyyo@ukzn.ac.za

Dear Dr Moodley

Protocol: Patient quality of care and healthcare resource utilization at a tertiary South African hospital. Degree: Non-degree
BREC reference number: BE595/16

We wish to advise you that your application for Amendments dated 27 July 2018 to **include Dr Natasha Naidoo and Prof TE Madiba** in the above study has been **noted and approved** by a subcommittee of the Biomedical Research Ethics Committee.

The committee will be advised of the above at its next meeting to be held on 11 September 2018.

Yours sincerely

[redacted]

pp Professor V Rambiritch
Chair: Biomedical Research Ethics Committee

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14 August 2018

Dr Y Moodley
School of Clinical Medicine
College of Health Sciences
moodleyyo@ukzn.ac.za

Dear Dr Moodley

Protocol: Exploratory laparotomy registry
Degree: Non-Degree
BREC Ref No: BCA208/18

We wish to advise you that your application for Amendments received on 28 July 2018 to **add Dr N Naidoo and Prof TE Madiba** to the above study has been **noted and approved** by a subcommittee of the Biomedical Research Ethics Committee.

The committee will be notified about the above approval at its next meeting to be held on 11 September 2018.

Yours sincerely

[redacted]

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

cc postgraduate administrator: SCMpgrad@ukzn.ac.za