Clinical Prediction Models for Risk-adjusted Outcomes in South African Surgical Patients

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Declaration

I, Hyla-Louise Kluyts, declare that the thesis, which I hereby submit for the degree Doctor of Medicine (DMed) in Anaesthesiology at the University of Pretoria, is my own work, and has not previously been submitted by me for a degree at this or any other tertiary institution.

This thesis is the result of a study entitled ‘Development of a model to predict outcome after elective non-cardiac surgery using a preoperative self-assessment questionnaire in a South African private hospital population’. The study report is contained in Chapter Three of the thesis.

Chapter Two of the thesis contains a report on the development of a clinical prediction model using data from the South African cohort of the African Surgical Outcomes Study. The data was collected by investigators participating under the guidance of the principal investigator, Prof BM Biccard. I was the national lead investigator for South Africa in this study. Permission to use the data to develop a clinical prediction model was given by Prof BM Biccard. The analysis, reporting of results and the discussion in Chapter Two is my own work.

Ethics statement

I, Hyla-Louise Kluyts, have obtained, for the research described in this work, the applicable research ethics approval. The ethics approval letter for the study protocol entitled ‘Development of a model to predict outcome after elective non-cardiac surgery using a preoperative self-assessment questionnaire in a South African private hospital population’ is attached as Appendix B. The ethics approval letters for the African Surgical Outcomes Study are attached as Appendix C, from the University of KwaZulu-Natal Biomedical Research Ethics Committee; and as Appendix D, from the Research Ethics Committee, Faculty of Health Sciences, University of Pretoria. I declare that I have observed the ethical standards required in terms of the University of Pretoria’s Code of Ethics for Research and the Policy and Procedures for Responsible Research.

Summary

Background

National clinical data on perioperative care in South Africa are scarce. There is both an urgent need, and the imminent opportunity, to increase the body of evidence necessary to inform on initiatives to improve safety, affordability and access to surgical- and anaesthesia care in this country.

Clinical prediction models are a useful way to present factors that predict a specific endpoint, and the relationships of these factors in influencing the endpoint. Such summarised information is important for perioperative clinicians and teams to understand how their circumstances and their practice influence a patient's outcome after surgery, and how this influence, and the outcome, compare to teams in different circumstances or institutions.

Developing clinical prediction models is an exercise in defining and identifying predictors and endpoints that should form part of a core set of measures for research on perioperative care. It is crucial to validate clinical prediction models in settings other than where it was developed before it is implemented. Prediction models may require updating before it can be generalisable.

The aim of this thesis is to report on clinical prediction model development in two surgically heterogeneous South African cohorts: i) a public sector cohort; the South African dataset from the African Surgical Outcomes Study (ASOS); and ii) a private sector cohort, from data gathered for the purpose of model development, in patients presenting for elective non-cardiac surgery in a single private hospital.

Methods

Data from two cohorts of patients that differ with regards to the sample population, and the healthcare sector, were used to develop two separate clinical prediction models.

A clinical prediction model with in-hospital mortality as endpoint was developed in the public sector cohort. A prediction model with healthcare resource use as endpoint was developed from a self-assessment questionnaire in the private sector cohort.

Using clinical judgement, predictors for the prediction models were identified from univariate regression analysis and subsequent forward stepwise regression techniques. The prediction models were assessed for performance regarding calibration, discrimination and clinical usefulness, and were internally validated by fitting to a bootstrap sample.

The prediction model that was developed from the ASOS South Africa cohort was validated in the cohort of patients participating in the South African Surgical Outcomes Study, which is a temporally separate dataset containing data collected in 2014. The possibility of validating the Surgical Outcomes Risk Tool, an established prediction tool, in the ASOS South Africa cohort, was investigated.

There is currently no data available for external validation of the prediction model developed in the private sector cohort.

Results

During prediction model development, important variables (predictors and endpoints) were identified that should form part of a core dataset. The ASOS

South Africa prediction model was developed with postoperative in-hospital mortality, censored at thirty days, as the endpoint. The predictors included in the prediction model were largely related to the risk inherent to the urgency, severity and type of surgical procedure. The private sector prediction model was developed with the cost of hospital admission, excluding fees, as endpoint. The predictors included were the type of surgery and predictors defined from patient-reported information.

Although both prediction models performed fairly well with regard to calibration, discrimination and clinical usefulness, the prediction models will require validation in cohorts of patients representing a different South African population. It is expected that the prediction models will require adjustment or updating after external validation. The definitions of predictors will also have to be reconsidered when validating these prediction models in cohorts from other settings.

Conclusion

During the development of the clinical prediction models, predictor definitions were investigated. Variables (predictors and endpoints) should be defined in such a way as to align with international classification systems, since these are used to ‘code’ variables in electronic health information systems to enable aggregation of data.

The advantages of external validation of clinical prediction models, and the subsequent prediction model updating, would be: the opportunity to further refine the definitions of candidate predictors to enable international comparisons; the potential to include health economic measures to inform on

the cost-effectiveness of surgery; and the chance to define and include patient-reported measures in the core data set. The result may well be that evidence gathered in this way would assist in developing strategies for optimal delivery of perioperative care to the entire South African population.

Doctors, and their patients, will have to voluntarily participate in national multicentre research projects to gather evidence on perioperative care in South Africa. One has to consider the additional burden the collection of perioperative data would entail, and how such ‘citizen scientists’ would be motivated to participate.

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Dedication

This work is dedicated to

My father, *Thomas McDonald Kluyts*, for instilling in me a PASSION for healthcare

My mother, *Hester Francina Hendrina Kluyts*, for teaching me how to WORK

My husband, *Henry Pieter Pennells*, whose equanimity and LOGIC in dealing with challenges has made life easier for me

My daughters, *Hyla-Louise* and *Siena Elizabeth*, who personify HOPE

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List of abbreviations

ACS NSQIP	American College of Surgeons National Quality Improvement Programme
ADLs	Activities of daily living
AGS	American Geriatric Society
AHA/ACC	American College of Cardiologists/American Heart Association
AIDS	Acquired Immune Deficiency Syndrome
APACHE II	Acute Physiology and Chronic Health Evaluation II
ASA PS	American Society of Anaesthesiologists' Physical Status
ASA	American Society of Anaesthesiologists
ASOS	African Surgical Outcomes Study
AUDIT-C	Alcohol Use Disorders Identification Test-Consumption
AUROC	Area under the Receiver Operating Characteristic
BFI	Brief fatigue inventory
BMI	Body mass index
BUPA	British United Provident Association
CCSA	Complete CPT for South Africa
CCVS	Canadian Cardiovascular Society
CEPOD	Confidential Enquiry into Perioperative Deaths

CHF	Congestive heart failure
COMPAC	Core Outcomes Measures in Perioperative and Anaesthetic Care
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardiopulmonary exercise testing
CPT	Current Procedural Terminology
DALY	Disability-adjusted life years
DASI	Duke Activity Status Index
DHIS	District Health Information System
DS3	Decision Support for Safer Surgery
ERAS	Enhanced Recovery After Surgery
ESC/ESA	European Society of Cardiology/European Society of Anaesthesiology
ESPEN	European Society for Parenteral and Enteral Nutrition
FoSAS	Federation of South African Surgeons
GDS	Geriatric depression scale
GERD	Gastro-oesophageal reflux disease
GOLD	Global Initiative for Obstructive Lung Disease
HIV	Human Immunodeficiency Virus
HPCSA	Health Professions Council of SA

ICD	International Classification of Diseases
ICU	Intensive care unit
IQR	Interquartile range
ISWT	Incremental shuttle walk test
LAPAQ	LASA Physical Activity Questionnaire
LASA	Longitudinal Aging Study Amsterdam
LOS	Length of stay
LOWESS	Locally weighted scatterplot smoothing
MDGs	Millennium Development Goals
METs	Metabolic equivalents
MINS	Myocardial injury after noncardiac surgery
MMSE	Mini mental status exam
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NDoH	National Department of Health
NPC	Non-profit company
NRS	Nutrition Risk Score
NSI NHC	Nutritional Screening Initiative Nutritional Health Checklist
NSOAPs	National Surgery, Obstetrics and Anaesthesia Plans
NYHA	New York Heart Association

OPCS4	Office of Population Censuses and Surveys version 4
OSA	Obstructive sleep apnoea
POMR	Perioperative mortality rate
PONV	Postoperative nausea and vomiting
POPI	Protection of Personal Information
POSSUM	Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity
PQIP	Perioperative Quality Improvement Programme
PROMIS	Patient Reported Outcomes Measurement Information System
PROMs	Patient-reported outcome measures
PTCA	Percutaneous Transluminal Coronary Angioplasty
RAI	Risk Analysis Index
RCRI	Revised Cardiac Risk Index
RVU	Relative value unit
SA	South Africa (n)
SAMA	SA Medical Association
SAPORG	SA Perioperative Research Group
SAS	Specific Activity Scale
SASA	South African Society of Anaesthesiologists

SASOS	South African Surgical Outcome Study
SDI	Socio-demographic index
SORT	Surgical Outcomes Risk Tool
SPOR	Swedish Perioperative Registry
SSSA	Safe Surgery South Africa
StEP	Standardising Endpoints in Perioperative Care
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis
TUGT	Timed Up and Go Test
UK	United Kingdom
USA	United States of America
VISION	Vascular events In noncardiac Surgery patIents cOhort evaluatioN
WHO	World Health Organisation
YLDs	Years lived with disability
YLLs	Years of life lost

Chapter One: Introduction

1 Problem statement

There is a paucity of evidence on the perioperative care delivered to the diverse South African population to inform clinicians on opportunities to enhance healthcare delivery.

The proposed solution to the problem is to use what evidence exists to develop clinical prediction models that summarize the effect of predictors on surgical outcome. Developing such tools will a) improve understanding of the factors influencing outcome after surgery in South Africa and b) generate further evidence if the tools are validated in other populations more representative of the broader South African population.

2 Overview of proposal

Perioperative care includes surgery and anaesthesia and all the support and services required to care for a patient that requires treatment for disease that can be managed with surgical intervention.

Planning perioperative care on an individual patient level as well as on a population level requires information about the health status of the patient and the population, the resources available to effect treatment of surgical disease, the success, effectiveness and risk of the intervention, and the expected outcome of the intervention.

Clinical prediction models provide a summary of the combined influence of these factors (predictors) on outcome after surgery. Clinical prediction models can be used in clinical practice to support surgical decision-making for

individual patients. It can also be used to study differences in outcome while adjusting for differences in patient- and procedure characteristics.

Both the outcome (dependent variable) and the predictors (independent variables) used in a clinical prediction model must be well defined for a prediction model to be applied as intended. If a prediction model is to be applied in daily clinical practice it stands to reason that the definition of data variables collected must align with the variable definitions used during prediction model development, validation and updating – the processes that precede implementation of the prediction model.

When developing clinical prediction models one should consider how the model may be implemented in a reliable, valid and useful way, and whether applying the model would have any impact on perioperative care. To ensure that prediction models are appropriately used, ongoing data collection, analysis and reporting is crucial to enable updating of prediction models as practices change. It is pragmatic to define a core set of measures which include appropriate predictors and standardised outcomes or endpoints, to allow for ongoing data collection.

Evidence that is currently available regarding perioperative care in South Africa was generated during participation of academic centres in large multicentre international studies.[1,2] Generating evidence is crucial in guiding efforts enabling access to safe, affordable perioperative care in South Africa. This fact has been recognised by healthcare policy makers and decision leaders in the South African government.[3]

3 Surgery and health

The benefit of a surgical intervention should outweigh the risk associated with the intervention. Surgical decision making is therefore based on the balance between benefit and risk. A surgical intervention may benefit a patient once he/she has recovered from surgery. Carlisle[4] states that the survival curve after scheduled surgery takes more than one year to equal the survival of patients who did not have surgery. Appropriate perioperative planning takes risk into account, and may serve to modify or decrease risk to ensure optimal outcome after surgery.

In the developing world, where surgery is often performed to save lives, and where the burden of disease is different from the developed world, it is difficult to determine whether a surgical intervention decreases or increases the patient's chance of long-term survival. This is particularly true when access to surgery and healthcare resources is so poor that neither a patient nor a provider have much choice in planning when a patient presents with surgically treatable disease. A patient may present late for a surgically treatable condition, and therefore be at higher risk for a poor postoperative outcome.

The South African 'rainbow nation' population varies greatly not only in the burden of disease, but also in accessible resources to treat this disease burden. Fair and equitable distribution of resources to provide a standard of safe affordable care to the whole population is the only solution.

An abundance of literature exists on perioperative risk factors associated with poor postoperative outcome. Orkin presents these aspects schematically (Figure 1).[5]

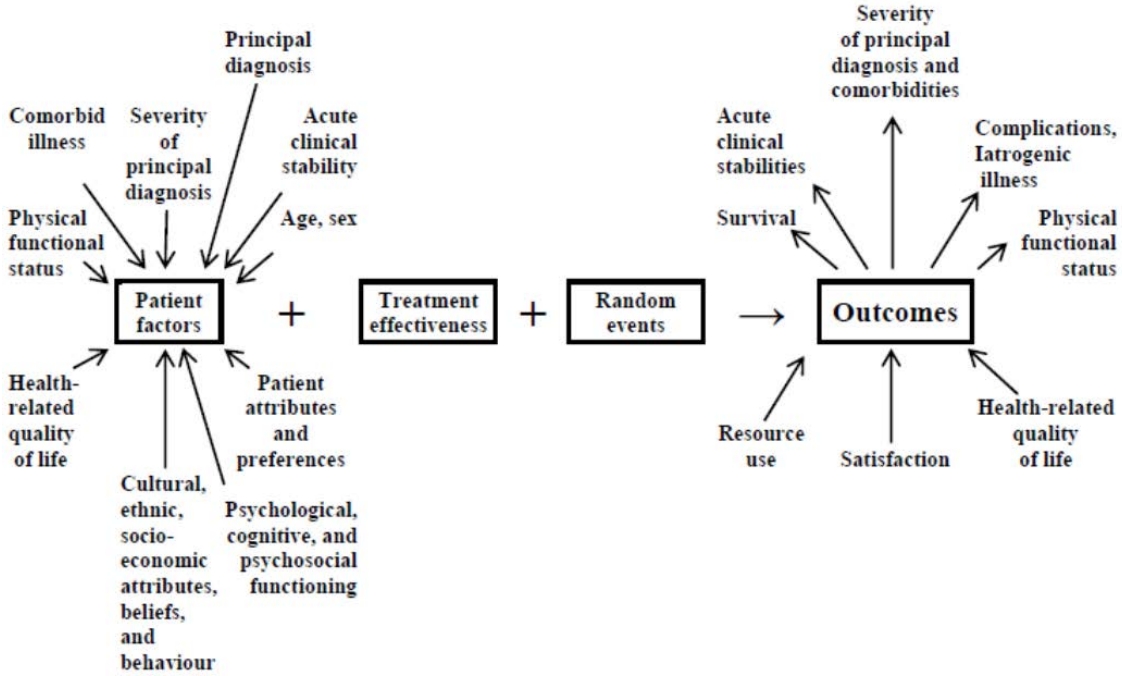

Figure 1: Risk factors for postoperative complications

Orkin points out that there has to be a clear understanding of why one would like to identify predictors for postoperative outcome and how knowledge on the predictors would be used.[5] It is also important to understand the relationships between predictors and how their interaction will influence the outcome.

4 Clinical prediction models in perioperative care

An observational study to identify predictors for postoperative outcome is a research application of clinical prediction modelling.[6] Clinical prediction models can be used in various ways (e.g. scores or computer algorithms) to risk stratify patients with regards to patient-related risk factors, while adjusting for risk inherent to surgical procedure itself, such as the type of surgery, the timing of surgery, the indication for surgery and the severity of surgery.

A book on clinical prediction models by Steyerberg offers a practical approach to the development, validation and updating of prediction models.[6] Publications on clinical prediction models (or clinical prediction rules/calculators/tools, prognostic models or normograms) have increased markedly over recent years. The TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statement was published in 2015,[7] and the associated Explanation and Elaboration document is a valuable resource to researchers. In a publication by Steyerberg and Vergouwe[8], seven steps in model development further simplifies the process and serves as a useful framework when considering model development. The seven steps are summarized as follows:

1. Problem definition and data inspection
2. Coding of predictors
3. Model specification
4. Model estimation
5. Model performance
6. Model validation (and impact analysis)
7. Model presentation

Considerations during the important first step of model development are summarized as follows in this publication:

i. What factors predict the endpoint and how can a combination of the factors be used to estimate risk relating to the endpoint?
ii. What is already known about the predictors?

iii. How patients were selected – was the data collected for the purpose of developing a clinical prediction model, and is the data representative of the population where the model will be applied?

iv. Do the subjects in the development cohort ‘mimic the clinical setting’?

v. Were the predictors reliably and completely measured?

vi. Is the endpoint of interest? The frequency of interest also determine the sample size.

Once a model has been developed and validated in the development cohort, it has to be validated in different populations and settings before it can be broadly applied. Janssen et al proposed ‘a simple method to adjust clinical prediction models to local circumstances’ – the method involves updating of a model intercept to ensure adequate calibration during temporal, geographical or transmural (subjects in a different level of care) validation of a model.[9] It is however important that the definitions of both predictor and outcomes variables are standardised in the populations where the model will be validated and implemented.

Clinical prediction models should be presented in a clinically useful way. Computerised models presented during electronic data capturing can be useful if the calculations from data captured are done ‘at the bedside’. Risk scores (derived from coefficients of predictors in the model) are easier to use than risk models, since it can be calculated by hand, but may not be as accurate to predict individual risk.[10] A clinician should understand the limitation of a clinical prediction model and know the incidence of important outcomes for using tools to calibrate the instrument or model.[11]

Periodic re-evaluation and adaptation of a clinical prediction model once it is in use, is essential, but only possible if data collection of predictors and outcomes is reliable and consistent. Defining a minimum dataset to be captured therefore becomes crucial in low resource settings. The minimum dataset must support a parsimonious model, which is pragmatic, easy to use and reliable.

4.1 Problem definition and data inspection

Reports on the development and validation of clinical prediction models as perioperative risk stratification tools are common in the literature, yet these models, tools and scores are not consistently used in clinical practice. While developing a model it is important to not only have a clear understanding of the research question to be addressed, but also how and where implementation and adoption is envisaged. A clinical prediction model to enable retrospective institutional comparisons may be different from a tool to predict individual patient risk for preoperative decision-making – for example, the predictors and the source of predictor data may be different for patient and procedural risk factors. Simple models mostly addressing procedural risk factors for in-hospital mortality related to the surgery is unlikely to be useful during preoperative individual patient conversations aiming at shared decision-making, where long-term survival is an important consideration.[12] While aiming for a parsimonious model (to avoid over-fitting) one may be required to enter a limited number of variables during model specification. How much of the variation in outcome is explained by the model (the predictors and their interactions) is, for example, expressed as R^2 in linear regression modelling. Should one choose to use a relatively larger number of procedure- specific predictors (e.g. timing of surgery, type of surgery, severity of surgery) in relation to patient-specific predictors,

chances are that the model would perform well and explain a larger amount of variation, but would not contain many patient-specific predictors. To enable development of a model that contains more patient-specific factors (which may be needed for patient conversations around individual risk stratification) one has to either develop procedure-specific models (e.g. for emergency laparotomy) or use a single procedure-specific predictor that defines all the outcomes associated with that predictor (such as that used in the Universal American College of Surgeons National Quality Improvement Programme – ACS NSQIP- Surgical Risk Calculator[13]). Patient predictors seem to, in general, contribute less to risk and outcome after surgery than procedure-specific predictors.[14,15]

4.1.1 Data source and variable definitions

Administrative data is often used to develop clinical prediction models. Sessler et al used administrative data on diagnostic- and procedure codes to develop and validate a broadly applicable risk stratification index for in-hospital mortality and length of hospital stay from more than 35 million case records.[16] It is based on data acquired in hospital and preoperative predictors are not included. It is useful for *post hoc* clinical audit and to compare outcomes between providers or institutions.

Clinical prediction models often include physiological and laboratory measurements with established diagnoses. Fritsch and colleagues performed a study in an Austrian secondary care hospital and found that abnormal laboratory and radiological tests failed to predict outcome reliably, but medical history, age and invasiveness of the procedure did.[17] The outcome variables studied included cardiovascular, cerebrovascular, and respiratory

complications and bleeding (the need for transfusion). The authors concluded that routine laboratory testing should be abandoned in favour of selective ordering, and that further research is needed to identify predictors from the medical history. Recently, objective assessment using the Dukes Activity Status Index questionnaire, preoperative cardiopulmonary exercise testing and biomarkers were shown to contribute to risk stratification in patients undergoing major non-cardiac surgery.[18]

4.1.2 Endpoints, or outcome after surgery

It is important to standardise the definitions of endpoints, not only to enable comparisons between sectors or development of universal datasets, but also to allow consistent reporting and the generation of research that can be reliably used in systematic reviews and meta-analyses.[19] A European taskforce published a statement on the standards for definitions and use of perioperative outcomes in 2015.[20] These standards were used in the international observational surgical outcomes studies, described below. Concerns were raised that such efforts to guide researchers were not in line with published guidelines on health research reporting, and did not take into account the psychometric properties of measures, namely validity, reliability, utility and responsiveness.[19] A group of experts (Standardising Endpoints in Perioperative Care or StEP-group) are currently working on standard definitions for endpoints, with working groups on:

- Patient comfort – published[21]
- Clinical indicators: Perioperative hypothermia; Perioperative iatrogenic injury (nerve injury, postoperative visual loss, pressure sores, dental damage, postdural puncture headache); Medical emergency team/rapid

response calls, cardiorespiratory arrest, unplanned intensive care unit admission; Unplanned hospital readmission, discharge destination

- Cognition and stroke
- Cardiovascular
- Respiratory - published[22]
- Sepsis
- Renal – published a review on planned process[23]
- Bleeding and transfusion – published a scoping review[24]
- Organ failure and survival - Mortality measures (cause/time point); Composite morbidity scales (e.g. PostOperative Morbidity Score or Clavien–Dindo grading: as described by Jammer et al[20])
- Cancer and long-term survival – published for cancer[25]
- Patient centred outcomes - Patient satisfaction; Health-related quality of life; Disability-free survival; Return to work/normal functioning; Functional status/mobility/6 min walk test, other; Home days (days alive and out of hospital)
- Healthcare resource utilisation including length of stay (hospital/ICU)

The Core Outcomes Measures in Perioperative and Anaesthetic Care (COM-PAC) initiative is running in parallel with StEP to define a core outcomes set to guide researchers in selecting appropriate outcomes measures.

Some evidence on postoperative outcomes from selected studies, relevant to the outcomes used in the analyses reported in this thesis, are discussed below.

4.1.2.1 Organ failure and survival measures

In-hospital measures from large multicentre cohort studies can be summarized as follows:

Table 1: The Surgical Outcomes Studies

Study	Measures	Result
European Surgical Outcomes Study[26] 2011	Primary: in-hospital mortality (Censured at 60 days)	4%
International Surgical Outcomes Study[27] 2014	Primary: in-hospital complications*	16.8%
	Secondary: death following complication*	2.8%
	Secondary: in-hospital mortality*	0.5%
South African Surgical Outcomes Study[28,29] 2014	Primary: in-hospital mortality*	3.1%
African Surgical Outcomes Study[30] 2016	Primary: in-hospital complications*	18·2%
	Secondary: in-hospital mortality*	2.1%
	Composite severe complications and death[14]	4.8%
*Data censured at 30 days for patients remaining in hospital		

Data from the American College of Surgeons' National Surgical Quality Improvement Program (ACS NSQIP) showed variation of hospital mortality in inpatient surgery of between 3.5% and 6.9%.[31]

It is clear that a 'snapshot' of postoperative mortality and complications does little to inform on which factors influence the outcome – which is the rationale behind statistical risk-adjustment of outcome using clinical prediction models.

4.1.2.2 Patient-centred outcomes and patient reported measures

"Understanding the patient perspective on healthcare is central to the evaluation of quality"[32]

Short-term anaesthesia-related outcomes often relate to patient satisfaction,[33,34,35] and a good outcome includes avoiding dental damage, sore throat, postoperative nausea and vomiting (PONV), and poor pain control. Although factors relating to patient dissatisfaction usually do not impact on

morbidity and mortality as defined above; they may, however, incur extra cost since they may necessitate prolonged hospitalisation; e.g. PONV and pain.

The recommended endpoints to define patient comfort in the perioperative period,[21] are:

- postoperative pain intensity at rest and on movement at 24 hours
- incidence of postoperative nausea, vomiting/retching, and nausea and vomiting
- postoperative quality of recovery[36,37]
- time to gastrointestinal recovery, defined by time to tolerate oral diet (e.g. soft food or light meal)
- time to mobilisation
- sleep disturbance, using the PROMIS[38] scale

4.1.2.3 Healthcare resource use

Experts* categorize healthcare resource use as follows:

- Intraoperative measures: Duration of surgery as from arrival to departure in operating room
- Duration of care measures: Length of hospital stay; Duration of post-anaesthesia care unit stay; Duration of mechanical ventilation; Duration of ICU stay
- Unplanned events: Unplanned ICU admission; Unplanned emergency room visit; Unplanned readmission (at 30 days); Cumulative length of stay at 1 year after surgery
- Unplanned procedures: Intervention required for a complication

*Personal communication, unpublished. These experts did not consider methods for health economic analyses.

In an opinion piece on evaluation of outcomes and costs in perioperative care, Neuman and Fleisher[39] point out that the higher cost of healthcare delivery in the United States, as compared to other developed countries such as the United Kingdom, may in fact reflect better care to patients at risk, with improved outcomes. They refer to the low rate of critical care admission following surgery in high-risk patients, as reported from studies in the United Kingdom and Europe.

A report on a study on critical care admission after major gastro-intestinal surgery,[40] concluded that the fact that neither planned nor unplanned admission constituted survival benefit, probably indicate appropriate use in high-risk patients. The finding was supported in a report on the International Surgical Outcomes Study.[41]

Boltz and colleagues studied the economic impact of mortality, length of stay and total cost of nineteen postoperative surgical complications captured in the ACS NSQIP database.[42] Cerebrovascular accident and cardiac arrest requiring cardiopulmonary resuscitation were the only events that were significantly associated with increased mortality. Ventilator dependence, pneumonia, sepsis, venous thromboembolism, and surgical site infections, in that order, were significantly associated with both cost and length of stay. Since postoperative complications are associated with increased cost, it seems reasonable to assume that surgical quality improvement will reduce cost.[43]

From the ACS NSQIP data, Davenport et al found that preoperative risk factors were more predictive of hospital costs than complications were.[44] Risk factors predicted 33% ($p<0.001$) of cost variation, work Relative Value Units (RVUs) predicted 23% ($p<0.001$), and complications predicted 20% ($p<0.001$). Risk factors and work RVUs together predicted 49% ($p<0.001$) of cost variation or 16% more than risk factors alone. Adding complications to this combined model modestly increased the prediction of costs by 4% for a total of 53% ($p<0.001$).

Quantifying healthcare resource use can also contribute to weighing the risk versus the benefit of surgery if cost-effectiveness of a procedure is defined. Cost-effectiveness is commonly described as the cost of an intervention in relation to the disability-adjusted life years (DALYs) for a population.[45] DALYs are used to identify gaps in healthcare coverage, representing the sum of years of life lost (YLLs) due to premature mortality and years lived with disability (YLDs). YLLs quantify the gap between observed mortality and a normative life expectancy, and YLDs capture the prevalence of conditions that lead to non-fatal health loss while accounting for the severity of those conditions. The components of health gap measures can be examined to define contributions of relative morbidity and mortality, individual diseases, injuries, and attributable risk factors.[46] Since the United Nations' announcement of the Millennium Development Goals, focussing on maternal and child health and communicable diseases, surgical care has emerged as a priority to treat the growing global epidemics of non-communicable disease and injury. The burden of these diseases are expressed in DALYs. DALYs for a disease can be interpreted or evaluated against a socio-demographic index (SDI) for a country. The SDI takes into consideration the income per capita, schooling, and fertility rate of a

population. The top ten causes for DALYs in South Africa, with the ratio of observed versus expected based on SDI, has been published as follows:[46]

1. HIV 16.28
2. Diabetes 2.67
3. Violence 7.21
4. Lower respiratory infections 2.39
5. Tuberculosis 17.11
6. Road injuries 1.7
7. Ischaemic heart disease 0.76
8. Lower back and neck pain 1.04
9. Stroke 0.92
10. Diarrhoea 7.09

If the DALY for a specific surgical condition is high, a surgical intervention will almost always be cost-effective. If surgical treatment for a condition is known to be successful, there exists little controversy as to whether the risk outweighs the benefit. These have been described as priority 1 conditions and procedures for treatment include hernia repair and external fixation and exploratory laparotomy for trauma.[47,48] Priority 2 conditions however, are a moderate public health burden, *or* surgery for it is moderately successful *or* moderately cost-effective. Procedures include hysterectomy and surgery for breast- and colon cancer. In most instances, cost-effectiveness may be the deciding factor on whether to operate or not, since the individual patient may perceive the burden of the disease differently than how it is prioritised in a population, and surgical care is often suggested as the best treatment option whatever the evidence supporting it.

4.2 Adjustment for surgical risk

A study on the frequency of surgical treatment and related hospital procedures in the United Kingdom (UK),[49] highlighted important questions that have to be answered before interpreting perioperative outcomes such as mortality rates and care, e.g.: ‘What is surgery?’ and ‘What is major surgery?’

Postoperative length of hospital stay, intensive care admission and length of stay, and total cost of admission will vary between procedures. Therefore, ‘procedure mix adjustment’ is necessary.[50] Although both surgery and comorbidity influence outcome, two external factors or variables are difficult to adjust for in outcome models. These external factors act on their own irrespective of preoperative evaluation and optimisation; they are intraoperative care (quality of surgery and anaesthesia) and quality of care in a particular hospital. When surgeons and anaesthetists cooperate in the perioperative period, quality and outcome may improve.[51]

It is interesting that, until recently, the number, cost and mortality of surgical procedures performed in a developed country such as the United Kingdom was unclear. The authors reporting on a study to address this lack of information, used Office of Population Censuses and Surveys version 4 (OPCS4) codes to categorise surgical procedures as follows:[49]

- “Inclusive” category: “procedures that might be considered surgery, including minor surgery, interventional radiology procedures and diagnostic endoscopies, but excluding non-invasive diagnostic procedures (e.g. diagnostic imaging)”.

- “Intermediate” category: “procedures routinely undertaken in an operating theatre and/or under general or regional anaesthesia”.
- “Restrictive” category: “major procedures that due to duration or complexity may often result in tissue injury.”

Based on the report, there where instances where consensus regarding the category of procedure was not possible.

Surgical risk is related to the procedure, which is dependent on surgical skill and availability of resources (which may be influenced by the timing of surgery). The surgeon should weigh the risk-benefit ratio of a given procedure before advising a patient to undergo the procedure. Performing surgery to improve the functional status of individuals – e.g. those with moderate to severe osteoarthritis undergoing joint replacement – may decrease the risk of mortality from cardiovascular events,[52] but the follow-up time to determine the incidence of events would be much longer than the length of a hospital stay.

Minimally invasive procedures are done more frequently. Surgical risk may decrease with minimally invasive surgery to such an extent that anaesthetic risk becomes more important. More procedures occur outside of the operating room, which may increase surgical risk to the patient.[53]

In a study on improving outcome after major surgery, Banz et al point out that “high-risk surgery” is a term rarely explicitly defined.[54] It is possible that outcomes after surgery are worse in low resource settings. Surgery which would not be considered high risk in the developed world, may carry significant risk in a different environment.

There are various systems for surgical risk classification, e.g.:

- The Hohn system classifies procedures into minor-, moderate- and major surgery, and is commonly used in Germany and Europe. The American College of Cardiology/American Heart Association also uses three categories, while authors at Johns Hopkins University have developed a 5-tier system.[55] A three-tier system was used in the South African and African Surgical Outcomes Studies,[28,56] since variables collected were based on the European- and International Surgical Outcomes Studies:[26,27] The definition of the variable severity of surgery according to that used in the Surgical Outcomes Studies is as follows:
    - Minor surgery would include procedures lasting less than 30 minutes performed in a dedicated operating room which would often involve extremities or body surface or brief diagnostic and therapeutic procedures e.g. arthroscopy without intervention, removal of small cutaneous tumour, diagnostic proctology, biopsy of small lesions, etc.
    - Intermediate procedures are more prolonged or complex that may pose the risk of significant complications or tissue injury. Examples include laparoscopic cholecystectomy, arthroscopy with intervention, bilateral varicose vein removal, tonsillectomy, inguinal hernia repair, breast lump resection, haemorrhoidectomy, appendectomy, partial thyroidectomy, cataract surgery, uvuloplasty, minimally invasive repair of vaginal prolapse, vaginal hysterectomy, tendon repair of hand, fixation of mandibular fracture, etc.

- Major surgical procedures are expected to last more than 90 minutes and include major gut resection, major joint replacement, mastectomy, extensive head and neck tumour resection, abdominal aortic aneurysm repair, major vascular bypass procedure, procedures involving free flap to repair tissue defect, amputation, total thyroidectomy, cystectomy, trans-urethral resection of prostate, resection of liver tumour, carotid endarterectomy, nephrectomy, total abdominal hysterectomy, spinal discectomy, etc.

- Fritsch and colleagues used the guidelines for preoperative evaluation of the Austrian Society of Anaesthesiology, Resuscitation and Intensive Care Medicine when classifying surgical procedures in their study on the utility of laboratory tests in predicting outcome.[17] These researchers classified the procedures into minor- and major surgery based on the following definitions:

    - Definition of minor surgery (all of the following): duration of procedure < 2 h, expected blood loss < 500 ml and no opening of visceral cavity (except in case of diagnostic laparoscopy, laparoscopic cholecystectomy and laparoscopic appendectomy).

    - Definition of major surgery (any of the following): duration of procedure > 2 h, expected blood loss > 500 ml, opening of visceral cavity, potential massive respiratory or hemodynamic effects because of surgery.

Cohen et al in 2013 elucidated efforts to optimise the American College of Surgeons National Surgical Quality Improvement Project (ACS NSQIP) modelling.[50] In this report procedure, mix adjustment was addressed. A continuous variable ("CPT – Clinical Procedural Terminology - category linear risk") was added to better adjust for the complexity and risk profile of surgical procedures. This variable was derived using a machine learning process to describe inherent risk for each of the more than 3000 Clinical Procedural Terminology (CPT) codes, and then categorizing CPT codes in about 300 clinically relevant categories. This work was followed in the same year by the development of a universal calculator when transitioning from CPT category risk to individual CPT code risk.[13] The calculator uses 21 preoperative predictors and is not procedure specific. The preoperative predictors are: Age group, sex, functional status (dependency), emergency case, American Society of Anaesthesiologists' Physical Status (ASA PS) class, steroid use for chronic condition, ascites within 30 days preoperatively, systemic sepsis within 48 hours preoperatively, ventilator dependency, disseminated cancer, diabetes, hypertension requiring medication, previous cardiac event, congestive heart failure within 30 days preoperatively, dyspnoea, current smoker within 1 year, history of chronic obstructive pulmonary disease (COPD), dialysis, acute renal failure and body mass index (BMI) class.

The work relative value unit (RVU) as published with the Clinical Procedural Terminology (CPT) surgical code was previously used in the North American literature to stratify surgical risk.[50,57] The SA Medical Association published the CCSA (Complete CPT for South Africa) based on the American Medical Association CPT coding system. Without significant resources and millions of

cases in a system such as in the ACS NSQIP, it seems reasonable to use work RVU as a factor to describe surgical risk in prospective studies for preoperative risk stratification. Satiani, a vascular surgeon, does however warn against the misuse of Work RVU as a measure of productivity.[58]

Surgical expertise influences surgical outcome, and may be quantified using intraoperative measures such as blood loss and duration of surgery.[59] A recent meta-analysis demonstrated a 14% increase in the likelihood of complications for every thirty minute increase in operative time.[60] Patient-, anaesthesia and other factors may however also influence duration of surgery, for example.

4.2.1 Timing of surgery

Urgent or emergent surgery is associated with worse postoperative outcome, and in the South African public sector most procedures (approximately 58%) done are urgent or emergent.[14,30]

4.2.2 Indication for surgery and type of surgery

Other authors have used ACS NSQIP data to build smaller models with more accessible variables for risk prediction, the aim being quality-of-care comparisons. The ASA PS classification is part of the limited variables in such a small model (other variables were surgical procedure code, age and hospitalisation-related variables).[61]

4.3 Intra- and postoperative factors influencing surgical outcomes

A large part of the variation in outcomes for surgery is not explained by the surgery performed or patient risk factors that are captured. Other factors that may account for variation in outcome after surgery are the way in which care was delivered (structure and processes of practice). Intraoperative care,

including anaesthesia, is referred to by Fleisher [53] as the “black box” influencing outcome. Interventions and events influencing postoperative outcome should be recorded even if it does not form part of a risk stratification process.

4.3.1 Quality indicators

“Anaesthesiologists will need to engage in creating quality and competency metrics, or these instruments will be created for us” *Miller’s Anesthesia, 7th edition*

It is important to define quality indicators that can explain the variation in surgical outcomes, and outcome measures that are appropriate in driving quality improvement.

Citron and colleagues recently published the description of tools to assess surgical quality in low resource settings.[62] The group identified measures after establishing a framework – the Donabedian framework (structure, process and quality measures) was combined with the Institutes of Medicine framework (measures classified as safe, effective, patient-centred, timely, efficient or equitable).

It is internationally accepted that professional societies and training institutions have the mandate – if not legal then at least ethical – to define, capture and report quality indicators and outcome measures, in order for clinicians to receive feedback to drive the necessary quality improvement in a team or a facility. A recent systematic review on perioperative structure and process indicators however revealed that the majority of such quality indicators being used do not have the evidence ascribed to them.[63] Furthermore, a patient’s perspective on quality of care may be different to that of a provider.

Failure to rescue, defined as the hospital rate of death following a complication, has been used in international studies and said to be a useful measure of healthcare quality in perioperative care.[64]

4.4 Model estimation

It is possible that a prediction model describes the data under study well, but that the predictions are not valid for new subjects. This ‘overfitting’ can cause ‘optimism’ when externally validating the prediction model. ‘Shrinkage’ is a technique to paradoxically introduce biased estimates of coefficients to address overfitting, so that a prediction model predicts better.[6,8]

4.5 Model performance

Model performance should be assessed during development, and re-assessed when fitted in populations other than the one in which it was developed. When updating or adjustment of the model is required during this external validation, the updated model will require further assessment regarding performance. It seems intuitively reasonable to expect that any newly developed model is still in its infancy, and that continuous intermittent updating is essential for it to stay, or become, clinically relevant.

Prediction model performance is assessed regarding calibration, discrimination and using decision-curve analysis.[8,]

Calibration refers to the agreement between the observed outcome and the predictors. It can be graphically visualised when the predictions are plotted on the x-axis and the observed value on the y-axis. Perfect predictions would show a straight line with an intercept of 0 (comparing the mean of all the predictions with the mean observed risk) and a slope of 1.

Discrimination refers to the ability of the prediction model to differentiate between a patient with and without the outcome. A wide spread between predictions indicate a model that discriminates well. Discrimination is expressed as a concordance statistic (c-statistic) or a measure of the area under the Receiver Operating Characteristic curve (a plot of sensitivity over 1 – specificity).

Decision-curve analysis[65,66] can be used to assess the clinical usefulness of a prediction model – it visually displays whether the predictions produced by a prediction model improves the capacity of a clinician to decide whether a patient should receive treatment, based on the predicted probability for that patient to have the outcome. The decision threshold is a cut-off where patients are classified as high risk versus not high risk. Because this point may vary as a result of not having all the information available to weigh the risk versus the benefit of a decision, and a patient may also choose to take the risk of treatment, we should consider a range of threshold probabilities. By plotting the net benefit a treatment or intervention will have against a range of threshold probabilities, the ability of the prediction model to predict the outcome for a threshold of intervention is illustrated. No intervention/treatment will be of zero net benefit for all patients at all threshold probabilities. A line representing intervention in all patients would cross the y-axis (from positive net benefit to negative net benefit) at the prevalence of the outcome. The ‘no’ and ‘all’ treatment graphical display is shown in Figure 2. The incidence of the outcome in the data used for the illustration was 2.5%.

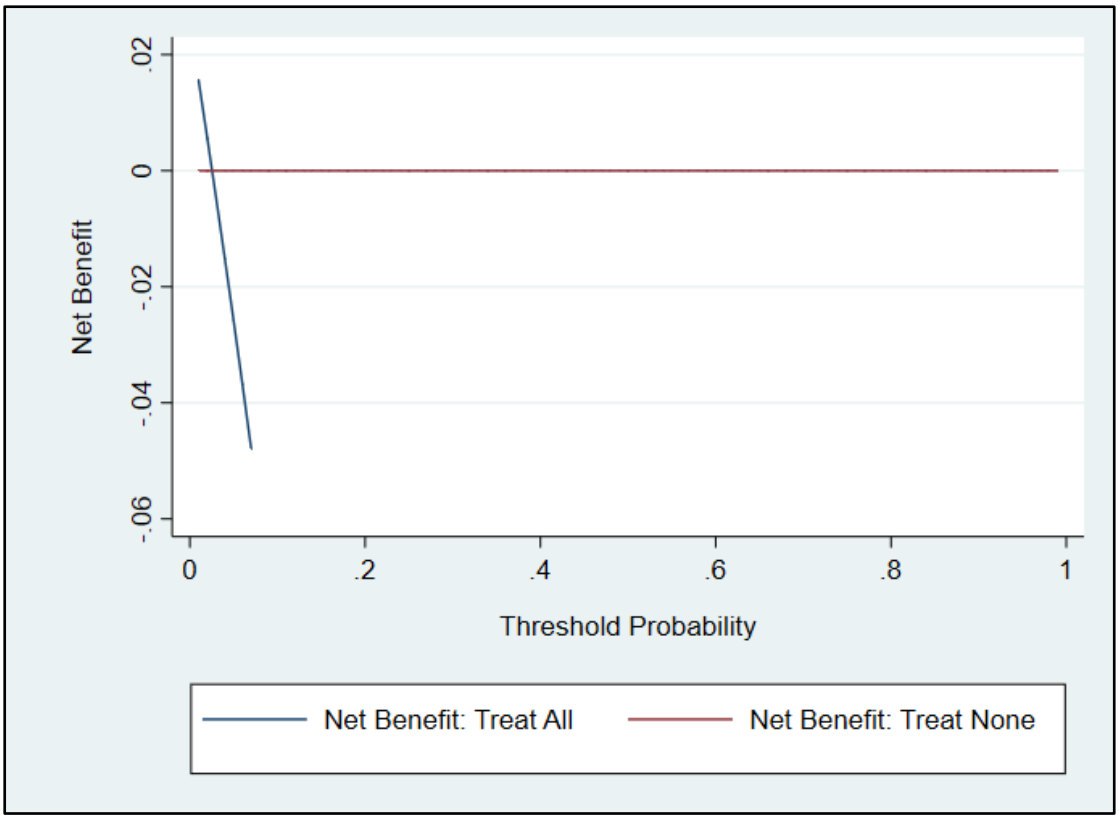

Figure 2: Graphical display of decision curve analysis when either all patients (blue line) or no patients (red line) are treated.

A model performing well would be the 'highest line' on the decision curve – that is, if patients identified as being at risk using the prediction model are treated, it would result in the highest net benefit. (See application of prediction models to decision curve analysis graphs in Chapter Two and Three). Decision curve analysis can also be used to compare the clinical usefulness of different prediction models for the same data.

4.6 Generalisability

Implementation and clinical utility of prediction tools is dependent upon the extent to which the model's data is representative of the population where the tool will be applied.[5,16]'Generalisability' refers to the external validity of a

prediction model.[6] It depends on both the quality of the prediction model, and the characteristics of the population where it is applied.

The performance of the model in the validation cohort is assessed with regards to its calibration, discrimination and clinical usefulness, as above. The model should then be updated for the new setting. Calibration may be unsatisfactory if the incidence of the endpoint is different in the validation cohort than in the derivation cohort. It may be relatively simple to adjust the model intercept in such a case in order for the calibration to improve (re-calibration). However, if the model does not perform well with regards to discrimination, the relative weights of predictors (regression coefficients) may have to be adjusted, or new predictors have to be added.

5 Timing of risk stratification in the perioperative pathway

Preoperative risk prediction and outcomes measurement in perioperative care is deemed necessary to allow for patient-centred decision-making, planning individualized care and identifying opportunities for quality improvement in processes of care for patients identified as being at risk of adverse outcome.[10,67] Preoperative risk prediction or stratification does not take into account intraoperative or postoperative factors contributing to outcomes.

It remains difficult to predict individual risk of adverse outcomes after surgery for a patient.[54] Biccard and Rodseth reiterate this point in a review on the utility of clinical predictors for cardiovascular risk prediction.[68] Overall mortality after surgery may be low, so that identification of high-risk patients is difficult.[69] To precisely determine an individual's risk of death or complications is fundamental to improving postoperative outcome, but it is important that studies to identify predictors use vigorous methods in doing so.[69] If a patient is identified as at high risk for adverse outcome, and a clinician alters clinical management to alleviate the risk, the test used to identify the patient may lose its significance in subsequent observational studies. Once a prognostic test is defined, it should be further investigated in well-designed trials to assess its utility.

In contrast, when intra- and postoperative predictors are used in risk stratification, it allows for retrospective clinical audit of the perioperative process, and refining of quality of care to patients identified to be at risk preoperatively. A comparative audit of providers or institutions is a common application in the first instance, and managing cardiovascular risk a well-researched application of the second.[70]

5.1 Clinical audit and quality improvement initiatives

Lo! In that house of misery
A lady with a lamp I see
Pass through the glittering gloom,
And flit from room to room.
- Santa Filomena by Henry Wadsworth Longfellow

Florence Nightingale's name is well known and is associated with compassionate caring and tireless nursing. What is less well known is that she managed to bring about health reform through her use of statistics, particularly the graphic display of statistical results. The portrayal, to Queen Victoria, of mortality rates and its causes using coxcomb diagrams, convinced the monarch to act. This brought about change in the ways in which injured British soldiers were cared for during the Crimean War and subsequent wars. She became the first female member of the Statistical Society of London in the same year (1858) that she wrote 'Notes on matters affecting the health, efficiency and hospital administration of the British army.' She campaigned for uniform use of hospital and surgical statistics so that the 'laws which regulate diseased action should become better known, the results of particular methods of treatment, as well of special operations, would be better ascertained than they are at present.'[71]

This account on the early use of reporting data in an appropriate manner explains clearly the benefit of clinical audit to identify areas of quality improvement. When reported outcomes are risk adjusted to account for 'case-mix' or 'procedure-mix', comparisons can be made.[72,50,73] Many of the studies published on predictors of postoperative outcome, and the models developed to do so, have the purpose of 'provider profiling', as referred to by Steyerberg in chapter 2, 'Applications on clinical prediction modelling', of his book on

clinical prediction models.[6] The quality of the care for providers is compared to the outcomes, which are considered performance indicators.

Reporting of comparative measures must be sensitive to the benefit as opposed to the risk of such comparisons. Although there is evidence that public reporting of healthcare outcomes may incentivise providers to improve on quality of care,[74] the risk of establishing a 'blame culture' in a socially unsophisticated setting is real.[75]

The Perioperative Quality Improvement Programme (PQIP) is a collaborative UK initiative organised through the National Institute of Academic Anaesthetists' Health Services Research Centre.[76,77] Key to this project is a) finding ways to reduce the burden of data collection and b) working on evidence-based methods of improving quality through data feedback. The initiative also, most importantly, includes the collection of patient-reported outcomes.

5.2 Perioperative planning of clinical care

It may be safe to assume that the most relevant application of preoperative risk stratification tools for individual clinicians in daily practice, is that of it allowing for planning of perioperative care.

5.2.1 Preoperative care

Goal-directed preoperative evaluation and management of disease may prevent mortality and morbidity associated with surgery. In fact, 'prehabilitation' with a programme designed to improve preoperative functional capacity of patients at risk may lead to improved postoperative outcome.[78,79] In a recent supplement of *Anaesthesia,* dedicated to patient optimisation before surgery,

Scheede-Bergdahl and colleagues discuss a multimodal approach to exercise training, and the role nutritional optimisation and psychological wellbeing play in adherence to and the outcome of training.[80] 'Integrated care coordination' with collaborative intervention by a multidisciplinary team was shown to improve outcome after elective surgery in older patients.[81]

5.2.2 Intraoperative care and the anaesthetist's role

Surgery is performed to improve the health status of a patient. Anaesthesia should be administered in such a way as to mitigate the immediate risk of the surgical procedure, within the context of the patient's preoperative health status. Therefore, anaesthesiologists must appreciate the risk factors that may influence mortality and morbidity attributed to perioperative processes. To improve postoperative outcome, anaesthesiologists must define outcomes relevant to anaesthetic care and identify risk factors related to these outcomes.[82] The influence of anaesthesia can be twofold: it can either adversely affect outcome – e.g. loss of airway – or it may improve outcome, such as by taking comorbidities into account.

Risk may not only manifest in the outcome of the immediate postoperative period. Anaesthesia management (technique and management of intraoperative complications) may also influence long-term outcome after surgery.[83,84] Surgical site infections may be influenced by anaesthetic technique, such as thermoregulation, supplemental oxygen, sympathetic block, and pain control to improve tissue-oxygenation which may reduce the risk of infection. Attenuation of the immunosuppressant effect of surgery through non-opioid analgesia and regional techniques may reduce cancer spread. Several intraoperative factors may also affect outcome, including blood product

transfusion, glycaemic control, and perioperative fluid management. Complications that are often overlooked are postoperative cognitive dysfunction and the possible neurotoxicity of volatile anaesthetics in children. These complications may be directly related to the anaesthetic technique as well as to intraoperative management, irrespective of the anaesthetic technique.

The objectives of the pre-operative consultation are the assessment of coexisting conditions, their complications and management, as well as their impact on the foreseen intervention and vice versa. The anaesthesiologist must also consider co-morbidities that have not been identified and that may influence perioperative management. These may include a difficult airway or obstructive sleep apnoea. The preoperative findings define the perioperative management, including the anaesthetic plan. The findings at the preoperative assessment, perioperative plan, as well as financial considerations contribute to the obtaining of informed consent.

In order to plan appropriate perioperative care, it is crucial for anaesthesiologists to identify preoperative risk factors in a timely fashion. In the 2002 report, The American Society of Anesthesiologists' Task Force on Preanesthesia Evaluation states that:

The Task Force believes that it is the obligation of the healthcare system to, at a minimum, provide pertinent information to the anesthesiologist for the appropriate assessment of the severity of the medical condition of the patient and invasiveness of the proposed surgical procedure well in advance of the anticipated day of the procedure for all elective patients.[85]

The recommendations are that the anesthesiologist should evaluate and prepare patients preoperatively. This evaluation applies particularly to those with more severe medical conditions and those undergoing more invasive procedures. The evaluation

should preferably take place the day before surgery in order to allow appropriate evaluation and optimisation.

Although anaesthesiologists play a vital role as perioperative physicians, the health system framework, locally and internationally, does not support the optimal expression of this role. Holt and Silverman[55] point out that day-of-surgery admissions and outpatient procedures make it very difficult for face-to-face conversation among clinicians at the patient's bedside. The anaesthesiologist is no longer assured access to the patient (or detailed information about the patient) before the day of surgery. Preoperative clinics have been established in an effort to enhance preoperative communication, but the designated intraoperative clinician may not see the patient at the clinic.

A report on inadequate preoperative evaluation and preparation from the Australian Incident Monitoring System's database comments that poor airway assessment, communication problems and inadequate evaluation are the most important factors contributing to poor outcome.[86]

5.2.3 Postoperative care

Preoperative risk stratification can assist in planning appropriate postoperative care based on predicted risk and available resources.[87,81] An important finding in international observational studies on surgical outcomes has been that intensive care admission is often not planned for high-risk patients undergoing major surgery.[26] This may mean that patients at risk for poor outcome are not recognised as such; but, of course, this also depends on available resources.

5.3 Patient engagement

The quality and outcome of an encounter between a sick or injured person and a health professional depends on the integrity of the exchange of information.
- Stephen Leeder, Foreword to Talley & O'Connor's 'Clinical examination: a systematic guide to physical diagnosis.'

An important part of preoperative preparation is providing information to the patient. In an early consensus review on optimal perioperative care for colorectal surgery by the Enhanced Recovery After Surgery (ERAS) group,[89] it is stated that a clear explanation of expectations during hospital admission facilitates early recovery and discharge. Knowing and communicating estimates of risk may contribute to obtaining informed consent.

Patient-centred care is achieved by building partnerships between the patient, their families and their healthcare providers.[90] Patient-centric care is said to happen when the information and interaction emanate from the patient through digital technology or eHealth.

Sturgess and colleagues provide a narrative review on the evolution of shared decision-making, particularly as it pertains to anaesthesia.[91] Shared decision-making is quoted as being the "pinnacle of patient-centred care". They state that "shared decision-making aims to bring together the patient's values and preferences with the physician's expertise to determine the best bespoke care package for the individual." They also discuss barriers to the process – time constraints being an important consideration for anaesthetists.

The rationale for developing the Surgical Outcomes Risk Tool (SORT)[15] include the recommendations from the 2011 National Confidential Enquiry into Patient

Outcome and Death (NCEPOD) Knowing the Risk report: that a mortality risk assessment must be communicated with the patient and recorded. The estimate for mortality must be taken from a national system to identify patients at high risk for mortality.

Carlisle, though, argues that estimates for mortality calculated from a perioperative risk prediction model should not be used in shared decision-making, since it does not adequately reflect long-term outcome after surgery in a way that guides patients to an appropriate decision regarding a surgical intervention.[12] It seems reasonable however that a patient should have some idea of the risk of dying shortly after a surgical procedure, is assured that all efforts have been made to optimise his/her physical status before the intervention, and is informed on how the chosen hospital or perioperative team's performance compares to others.

Patient reports on their health status, mobility, self-care, and other measures[92] can be valuable if recorded through-out the perioperative period. These are commonly called patient-reported outcomes measures (PROMs), but may include measures other than outcome measures after a health intervention. It is also a valuable method to determine endpoints such as those defined for patient comfort.[21,35,93]

6 Overview of existing perioperative clinical prediction models

Numerous risk prediction models related to perioperative care has been described, but it is difficult to objectively assess the impact the application of these tools have had on the care of individual patients or on surgical populations. Existing prediction models are however worth investigating, since the history of development and adaptation, the methodology, the aim and endpoint, and definition of the predictors identified, contribute to clearly defining these issues when developing a model using limited available data. It is sometimes difficult to standardise the definition of variables, particularly predictors, from data generated in different global populations. An example of this is the definition of 'severity of surgery', or to answer the question as to what constitutes 'major surgery' - and how (or if) such a variable should be defined in a risk prediction model.

The section that follows therefore includes descriptions of predictor variables in well-known prediction models or –tools, even though the risk-adjusted outcomes of the prediction models differ from those in the models developed and reported on in this thesis.

6.1 Mortality and/or morbidity risk

United Kingdom developments include a report on the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM), published in the British Journal of Surgery in 2003.[94] The Score was developed to enable a comparative audit of surgical practices. The POSSUM consists of a physiology score (age, cardiac signs, respiratory signs, physiological- and biochemical variables and EKG result) and an operative

score (incorporating blood loss, peritoneal soiling, surgery for malignancy and timing – elective/urgent/emergent). In calculating a percentage risk, the score needs to be used in a regression equation, with different constants and weighted value for mortality and morbidity. There have been problems with the application of POSSUM, in the form of mistakes made in data collection and analysis. A Portsmouth group developed a different regression equation using linear analysis instead of exponential analysis. It was called the Portsmouth POSSUM, and developed because the original equation overestimated risk in the Portsmouth population. Other British authors used a combination of the Confidential Enquiry into Perioperative Deaths (CEPOD) grade, American Society of Anesthesiologists' Physical Status (ASA PS) classification and British United Provident Association (BUPA) operative grade to create a tool for a comparative surgical audit instead of POSSUM – the Surgical Risk Scale.[95] This tool reinforces the broad application and endurance of the ASA PS to classify preoperative physical status, as a predictor variable.

The United Kingdom's National Confidential Enquiry into Patient Outcome and Death (NCEPOD) audited all patients in the UK over 16 years who were undergoing surgery during a one-week period in August 2010.[96] The authors supported the development of a risk assessment tool to guide informed consent, but noted considerable variation in what was considered to be a high-risk patient. In the audit, anaesthesiologists considered 20% of patients to be at high risk. The authors found that 18% of high-risk patients did not attend a pre-assessment clinic, and that these patients had a higher 30-day mortality rate (4.8% compared to 0.7%).

A systematic and qualitative review on risk stratification tools by Moonesinghe et al, published in 2013,[10] identified the following validated and most commonly reported tools at the time: the American Society of Anesthesiologists' Physical Status (ASA-PS) classification, the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system, the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM), the Portsmouth POSSUM, the Surgical Risk Scale, the Surgical APGAR Score, the Charlson Co-morbidity Index and Donati's Surgical Risk Score.

Subsequent to the review the Surgical Outcomes Risk Tool (SORT)[15] was developed. The SORT was developed from NCEPOD Knowing the Risk data, to enhance informed consent and shared decision-making, as well as to enable targeted intervention.

The Surgical Mortality Probability Model developed by Glance et al found the ASA PS classification to be the strongest predictor in the model.[97] Other variables in this simple model are procedure risk and emergency. The objective of the study was to develop a 30-day all-cause mortality risk index for noncardiac surgery that is easy and economical to use at the bedside. The authors felt that the full ACS NSQIP model was not practical and risk indices such as the Revised Cardiac Risk Index of limited value, as they only predict a single organ specific outcome group e.g. adverse cardiac events.

In the United States, publications and reports emanating from the American College of Surgeons National Surgical Quality Improvement Programme (ACS NSQIP) database shed some light on how pre-operative severity of illness influences the outcome of surgical care. This database was developed from the

National Veterans' Affairs Surgical Risk Study prior to 1997.[98] The programme was developed to assess and enhance the quality of surgical care in different institutions. As referred to by ACS NSQIP authors, key features to the success of ACS NSQIP are support by surgeons, consistent clinical definitions, reliable data collection, a uniform nationwide informatics system and the support of administration and management staff. Numerous studies using data sets from ACS NSQIP have been published. Information about variables included in the database is available online for downloading as a user guide.[99]

The retrospective audit and feedback design of NSQIP models prompted Glasgow and colleagues to develop software for a Decision Support for Safer Surgery (DS3) system.[100] The rationale was to enable prospective risk identification and mitigation. The authors compared previously developed models using a variety of endpoints, with surgeons' estimation of risk. They found a fair correlation in risk prediction between the models, surgeons' estimates and observed outcome. Apart from age, gender, race and BMI, selected comorbidities in the model were hypertension, current smoker, partial or totally dependent functional status, COPD, history of percutaneous coronary intervention, chronic steroid use, previous cardiac surgery, metastatic cancer, peripheral vascular disease, congestive heart failure, bleeding disorder and on dialysis.

The ASOS Surgical Risk Calculator,[14] developed from the African Surgical Outcomes Study (ASOS) cohort,[30] is a preoperative risk stratification score for predicting a composite endpoint of death and severe postoperative complications. Its envisaged application is to identify patients that may benefit from intervention by increased postoperative surveillance prior to the

development of severe complications. It is intended for use in a pragmatic interventional trial in Africa to assess the benefit of such an intervention to decrease ‘failure to rescue’ and hence improve postoperative outcome.

6.2 Cardiovascular risk

Perioperative risk prediction models with organ system-specific endpoints are some of the most well-known applications available. The rationale for developing these models are, in general, different from those developed with all-cause postoperative mortality as endpoint – it usually serves to risk stratify patients preoperatively in order to institute clinical management processes or pathways that modify or manage risk in the high-risk patients identified using these tools. Predictors identified in such tools, and the relationship of predictors in the multivariate analysis, may inform the definition of predictors during new prediction model development.

The Revised Cardiac Risk Index (RCRI) was derived and validated by Lee and co-workers in 1999,[101] and replaced the well-known Goldman and Detsky tools[102] in clinical practice. The following risk factors were identified for postoperative cardiac events in major elective non-cardiac surgery:

1. High-risk type of surgery – includes any intra-peritoneal, intra-thoracic or supra-inguinal vascular surgery.

2. Ischemic heart disease – includes any of the following: history of myocardial infarction or pathologic Q waves on electrocardiogram, history of a positive exercise test, current chest pain considered to be ischaemic, or the use of sublingual nitro-glycerine. Does not include the following: prior coronary artery bypass grafting or percutaneous

coronary intervention unless the other features mentioned above are present.

3. History of congestive heart failure (CHF) – includes any of the following: history of CHF, pulmonary oedema, paroxysmal nocturnal dyspnoea, rales or S3 on physical examination, or a chest radiograph consistent with CHF.

4. History of cerebrovascular disease – includes any history of a transient ischaemic attack or stroke.

5. Insulin therapy for diabetes.

6. Preoperative serum creatinine > 2.0 mg/dL (160 μmol/L).

If each of the RCRI predictors are counted as one point, the risk of cardiac events (including myocardial infarction, pulmonary oedema, ventricular fibrillation or cardiac arrest, and complete heart block) can be predicted as follows: 0 predictors = 0.4-0.5%; 1 predictor = 0.9-1.3%; 2 predictors = 4-6.6%; and 3 or more predictors = 9-11%.

In patients undergoing major noncardiac surgery it seems that the clinical predictors in the RCRI cannot improve on a risk stratification model based on B-type natriuretic peptides.[103] Kertai and colleagues modified the RCRI for vascular surgical patients by including more information in the 'customized' index about the vascular procedure, clinical predictors, and medication use. The model identified additional predictors of mortality; that is hypertension and COPD. Beta blocker- and statin use were associated with decreased mortality.[104]

The preoperative risk factors for myocardial injury after noncardiac surgery (MINS) described by the VISION (Vascular events In noncardiac Surgery patIents cOhort evaluation) group are: age above 65 years, urgent/emergent surgery, cancer, history of COPD, history of stroke, history of peripheral vascular disease and recent high-risk coronary artery disease.[105]

Biccard and Pooran developed and validated a preoperative and postoperative model of all-cause mortality in South African vascular surgical patients from retrospective data.[106] These authors conclude that the preoperative model may predict in-hospital mortality and the postoperative model may identify patients whose risk increases as a result of perioperative surgical or physiological factors. The preoperative predictors in this study were age, serum creatinine > 180 mmol/L, chronic beta-blocker therapy and the absence of chronic statin therapy. The contribution of cardiac events to all-cause mortality was not mentioned.

6.3 Pulmonary outcome

A systematic review undertaken on behalf of the American College of Physicians refers to the fact that postoperative pulmonary complications contribute as much to morbidity and mortality as do cardiac complications.[107] The risk factors referred to in this review incorporate surgical site and laboratory values such as serum albumin and urea. Risk factors with good evidence to predict pulmonary-related outcome include advanced age, ASA PS ≥ II, congestive heart failure, functional dependency and chronic obstructive pulmonary disease. There exists fair evidence for cigarette- and alcohol use as predictors, but good evidence that asthma and obesity do not contribute to postoperative pulmonary risk. Three years after this review, one of the authors

collaborated on another review of the identification and evaluation of a patient with lung disease.[108] Here, Sweitzer and Smetana claim that postoperative pulmonary complications are more costly than thromboembolic, cardiovascular or infectious complications. Weight loss, impaired sensorium, and perioperative transfusion are added as risk factors with evidence to increase risk for postoperative pulmonary complications.

A multicentre study group published risk factors for a patient developing postoperative acute respiratory distress syndrome (ARDS) after high-risk surgery.[109] The group tested and refined a previously reported model for surgical lung injury prediction (SLIP). The risk factors derived from this multicentre cohort study were sepsis, high-risk aortic vascular surgery, high-risk cardiac surgery, emergency surgery, cirrhosis, admission location other than home, increased respiratory rate (20 to 29 and ≥ 30 breaths/min), FIO_2 greater than 35%, and SpO_2 less than 95%.

The following predictors were identified from ACS NSQIP data for unplanned postoperative intubation in elderly patients:[110] Sex (male), emergency case, octogenarian, ASA PS≥ IV, functionally dependent, current smoker, recent severe weight loss, dyspnoea, COPD, diabetes mellitus, active CHF, preoperative ascites, renal failure (dialysis), intra-operative transfusion, work RVU, reoperation, medical diagnoses ≥ 3.

According to the ACS NSQIP and AGS guidelines for assessment of the elderly,[111] patient-related risk factors for postoperative pulmonary complications are:

Age > 60 years, COPD, ASA II or greater, functional dependence, congestive heart failure, obstructive sleep apnoea, pulmonary hypertension, current cigarette use, impaired sensorium, preoperative sepsis, weight loss > 10% in 6 months, serum albumin < 3.5 mg/dL, blood urea nitrogen ≥ 7.5 mmol/L, serum creatinine > 133 μmol/L. Obesity, well-controlled asthma, and diabetes were not found to be risk factors for pulmonary complications.

7 The South African context

South Africa is rather unique in the sense that it is in the process of developing universal healthcare coverage yet the distribution of healthcare delivery is unequal and fragmented. Furthermore, there is no existing national programme across sectors (private and public) for the collection, aggregation and analysis of data on surgery and anaesthesia. Regulation of healthcare expenditure, improving access to essential surgical care in rural parts of the country, and increasing data on perioperative care and resource distribution will be critical to improving anaesthesia and surgical care in South Africa.

7.1 Socio-economic circumstances of the SA population

Socio-economic development has a huge impact on a population's health. South Africa is home to approximately 56.5 million people of diverse ethnicity and culture.[112] Since the first democratic election in 1994 and the adoption of the South African Constitution in 1996, the country has been struggling to address its inequalities. In healthcare, there have been successes such as decreasing incidence of HIV infections and increasing life expectancy (from 55.2 years in 2002 to 62.4 years in 2016). South Africa has a gross national income per capita of $5,480 (Upper Middle-income Country), yet approximately 19% of the population live below the World Bank poverty line (US$1.90 per day), and only 17% of the population has private medical insurance.[113] The proportion of the population living below the extreme poverty line is much higher than that of many other middle-income countries. A recent collaborative report by the World Bank denotes South Africa as "one of the most unequal countries in the world."[114] The South African Department of Health is working toward

universal health coverage and a draft National Health Insurance Bill was published in June 2018.[115]

Socio-economic circumstances influence population health. In a publication in the Lancet Global Health, Basu and colleagues[116] report on recent data illustrating the high prevalence of hypertension, dyslipidaemia and diabetes in South Africans, with a disproportionately high prevalence in the male, black and poor subpopulations. They simulated the impressive cost-effectiveness of addressing cardiovascular risk using established medical intervention guidelines.

7.2 Fragmentation in the SA healthcare system

Fragmentation in the healthcare system in South Africa causes great difficulty for the healthcare community in dealing with challenges in the quality of patient care on a national, institutional and individual level. There is the perception amongst healthcare practitioners of a great divide between the private and the public sector, and between the nine provinces' departments of Health functioning autonomously from the National Department of Health. Workforce shortage further complicates matters: for example, the South African population receives attention from only 2 to 3 anaesthesia specialists per 100 000.

Anaesthetists in private practice in South Africa are not hospital based, and travel between hospitals according to demand from surgical colleagues. The South African Society of Anaesthesiologists (SASA) therefore plays a significant role in the private sector as a representative body for clinician interaction with other stakeholders. In contrast, all public sector anaesthetists are employed by the provincial Departments of Health at specific hospitals.

The already limited specialist anaesthesia workforce is also unequally distributed between the private and the public sector, and between rural and urban areas in South Africa. For example, approximately 1800 specialist anaesthesiologists were registered with the Health Professions Council of SA (HPCSA) in 2017, of which around 1100 specialists are SASA members (information on practice therefore available). The majority (790) work in the private sector, providing anaesthesia services to an estimated 9 million patients.[117] Unsatisfactory working conditions and -remuneration are the most commonly quoted reasons for anaesthetists leaving the public sector for the private sector after registering as specialists.

7.3 Data sources

Information on anaesthesia-related outcomes is not available on a national level, but some useful data are obtained through reports from the National Committee for the Confidential Enquiry into Maternal Deaths.[118] Surgical outcomes for South Africa and Africa have been reported following recent multicentre studies.[30]

7.3.1 Public sector

The SA National Health Research Database, administered by the Health Systems Trust, allows access to national healthcare information to researchers on submission of documents confirming a data user's agreement, a research proposal and ethics clearance as appropriate. The available databases contain information on public health indicators and primary healthcare, and include the District Health Information System (DHIS), National Department of Health (NDoH) electronic Tuberculosis register, the National Institute of Communicable Diseases, the National Injury Mortality Surveillance System and

databases on HIV. Of these, information in the DHIS, which collects information on all public health facilities in SA, may potentially be of most relevance to healthcare providers in the perioperative field. However, the system does not include data elements or indicators specific to surgical- and anaesthesia care and outcomes. Furthermore, an evaluation of the system reported significant problems with, amongst others, data collection and feedback reporting to providers on the ground.[119] Although the inadequate performance of a health information system is not unique to developing countries such as South Africa, there is a significant need for policy-makers and government officials to understand the importance of surgical outcomes as public health indicators. Perioperative Mortality Rate (POMR) a WHO Global Core Health Indicator, is not captured by any of the current SA health information systems.[120]

The South African[28] and African Surgical Outcomes Studies[30] and the South African Paediatric Outcomes Study[121] contributed massively to our understanding of outcomes after surgery in South Africa and the predictors of risk for poor outcomes. It is possible that the information gathered during these studies can continue to inform strategies to improve surgical- and anaesthesia care for some time to come, particularly with regards to decisions on requirements of a dataset for ongoing data collection and reporting (such as in a registry).

7.3.2 Private sector

The SA private healthcare sector is a data-rich environment. Unfortunately most of this data is not accessible to clinician groups in aggregated, de-identified form – unless such clinicians are affiliated to a specific hospital, in which case discussions about performance may take place at an institutional

level. The Health Professions Council of SA's policy document on business practice does not allow the employment of healthcare professionals by organisations in the private sector – primarily in the interest of clinical independence.[122]

Anaesthetists submit information (administrative data) to funders for billing purposes. This information includes patient demographic information already captured by hospitals and funders, procedural information on date and duration of surgery, and procedural codes used in South Africa. The procedural coding system (Medical Doctors Coding Manual) was developed by the SA Medical Association (SAMA), and they have copyright and require a licensing agreement for its use. SAMA also publishes Clinical Procedural Terminology (CPT) codes which is based on the American Medical Association's coding system and includes Relative Value Units (RVU). For financial authorisation purposes, it is required to add the diagnostic code (using the International Classification of Diseases (ICD) system) to identify the indication for surgery. Both these sets of codes are communicated to the patient on scheduling of the procedure in order to obtain payment authorisation. Private hospital groups use CPT codes and in certain instances diagnosis-related groups to categorize data on hospital procedures.

7.4 Global context

The Millennium Development Goals (MDGs) were the eight international development goals for the year 2015 that had been established following the Millennium Summit of the United Nations in 2000, following the adoption of the United Nations Millennium Declaration. All 191 United Nations member

states at that time, and at least 22 international organizations, committed to help achieve the following Millennium Development Goals by 2015:

1. To eradicate extreme poverty and hunger
2. To achieve universal primary education
3. To promote gender equality and empower women
4. To reduce child mortality
5. To improve maternal health
6. To combat HIV/AIDS, malaria, and other diseases
7. To ensure environmental sustainability
8. To develop a global partnership for development

The Sustainable Development Goals replaced the MDGs in 2016 – 17 goals, including Goal 3 – good health and well-being for people with universal health coverage as an aim; and Goal 17 – partnerships for the goals.

Global Burden of Disease is a World Health Organisation topic, and global epidemiological assessments revealed a decline in child, maternal, HIV and tuberculosis mortality, while non-communicable disease and injuries gained prominence as causes of death, disability and ill-health since the turn of the century. Based on the prevalence of diseases, the need for surgery was estimated on a global level, and found to be significant.[123]

The Lancet Commission on Global Surgery was launched in 2014, which is one of several commissions on global health topics initiated by The Lancet since it started focussing on such topics in 2003. Numerous publications on studies

regarding global surgery and anaesthesia have originated from the commission participants in various countries.

The World Health Assembly passed a resolution on the strengthening of emergency and essential surgery and anaesthesia care as part of universal health coverage in 2015. Developing national surgery, obstetrics and anaesthesia plans (NSOAPs) is part of the proposed surgical systems strengthening, as published by the WHO in collaboration with the Program in Global Surgery and Social Change at Harvard Medical School.[124]

South Africa, designated an upper-middle income country by the World Bank, has been targeted as a potential recipient of assistance by members of the global surgery community. Within the country, the fact that most specialists in the perioperative environment function outside of the academic- and public sector sphere has caused these approaches to have minimal impact on clinicians and their practice.

The NSOAP programme has gained political traction in so far as a task team has been set up by the SA National Department of Health to advise on strategy to institute a programme in SA.

7.5 Clinician initiatives to generate evidence on perioperative care

Safe Surgery South Africa (SSSA), a not for profit company (NPC), is an initiative of the SA Society of Anaesthesiologists (SASA), supported by the Federation of SA Surgeons (FoSAS). SSSA aims to create the opportunity for perioperative clinicians and their patients to collect data using electronic platforms. Within platforms it is possible for clinicians to compare data captured on patients cared for by them, to de-identified data captured by others. SSSA,

by aggregating de-identified data, and analysing and reporting on it appropriately, can inform programmes to improve access, quality and safety of perioperative care. The Perioperative Shared Health Record is a custom-made interoperable platform with a patient focus, developed by SSSA. It can be used to drive data collection with regards to specific research questions, surgery or outcomes, since it has the ability to incorporate numerous data fields with relatively low additional cost. Lessons learnt in establishing the company and the platform are briefly reviewed in the following paragraphs.

Advances in health information technology make it possible for groups of clinicians to participate in data collection, keep registries, analyse it appropriately and share this information with decision-makers on national healthcare programmes. A recent data simulation study demonstrated that relatively small sample populations can be used to estimate values for indicators such as perioperative mortality rate in low-resource settings.[125] This means that any effort to collect reliable quality data may be enough to allow for appropriate interpretation and use. Apart from clinicians' contributions to data collection, they also have the obligation to define variables in line with international requirements, based on current evidence.

A growing understanding on how access to safe and affordable surgery can influence the SA population's burden of disease, combined with pressure from global initiatives to provide population data, is creating the political will to establish or adapt health information systems and hopefully include data on surgical- and anaesthesia care. Proposals on national health data management review and strengthening has been made in the Draft National Health Insurance Bill 2018, by the Office of Health Standards Compliance in the National Core

Standards and by the Competition Commissioners' Health Market Inquiry into the private sector.

However, the urgent nature of the need for perioperative data to plan care is sufficient motivation for clinicians to participate in more than just defining the measures and advocate for its use in national data management systems.

In essence, the initiatives discussed here aim to establish registries and registry participation by clinicians, with a registry being defined as 'an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.'[126]

The coding of variables according to national consensus for classification is important for registry platforms to be interoperable.[127,128] Furthermore, development of registry platforms must take into account the South African eHealth Strategy.[129]

To require clinicians to collect data during the perioperative period may be seen as an additional burden, particularly in the SA setting where electronic data capture by clinicians is uncommon. A recent study (as yet unpublished) highlighted the high level of burnout amongst anaesthetists in South Africa, and the relationship to their areas of work-life. Burnout may be alleviated by a sense of personal achievement. It is possible that participation in registries may balance or outweigh the perceived burden because of the personal satisfaction achieved.

Participation may also be increased by a sense of community, specifically by harnessing the contributions made in the spirit of 'citizen science'.[14] The SA Perioperative Research Group (SAPORG) members where invaluable in their contribution to ASOS. There may exist an underlying motivation for participating in collaborative research of this type, with the resulting gratification in seeing results published.

Complex and expensive health information systems are doomed to fail if workflow is not incorporated into usual processes. Interoperability of systems is crucial to allow integration from data sources with minimal additional effort on the part of clinicians. It is also crucial to harness patients' participation in data collection – it adds value to the information, it saves clinicians time and effort, and it provides the opportunity to provide and receive feedback on perioperative care to patients.

Data available to the international community interested in furthering the cause of global surgery and anaesthesia is produced by multicentre collaborative studies.[27,56,130] It has been shown that by using appropriate research software, data for such studies can be collected relatively easily. These studies also serve to inform decisions on appropriate measures to be captured to estimate values for important indicators of healthcare delivery.[125,131]

It is important that the smallest number of variables are required in a national perioperative dataset. It is also possible that with repeated relatively small sampling, good estimates of outcome in the total surgical population can be predicted.[125] An example of an existing core dataset is that of the Swedish Perioperative Registry (SPOR).[132] European registry governance aligns with

the South African legal requirements regarding the protection of private information in data repositories.

Finally, when establishing platforms for data collection by clinicians and/or patients, consideration should be given to data governance and data security issues. The protection of Private Information (POPI) Act was passed in 2013.[133] Although it has not yet been fully enforced, it is important to give due consideration to issues raised in the Act[134] when setting up databases containing patient identifiable data which may be used in research at a later stage. Research in perioperative care, however, seldom requires patient identification in datasets. Patients need to be identified in the database to allow linking sets of data on different surgical events, but data extraction for research purposes should be de-identified.

8 Clinical prediction models for South Africa

The lack of data on surgical outcomes for heterogeneous surgical procedures in a population that is representative of the larger South African population, limits the utility of clinical prediction models in this setting. It is unlikely that any newly developed or existing adapted model or risk stratification tool will be implemented in clinical practice, at least not without significant further research on the predictors that can be identified from currently available data, and how information about these predictors can be used to improve perioperative care.

When following Steyerberg's 'seven steps' in prediction model development for South Africa, one should be cognisant, particularly when coding predictors and during model specification, of defining a dataset for ongoing data collection in circumstances where limited data is available.

The data on perioperative care used for prediction model development were collected from two different population subgroups of South Africa. The data in the two cohorts differ with regards to the patient characteristics, distribution of surgery-specific risk and the endpoints or outcomes. The healthcare resources available to the patients in the two cohorts differ. The differences stem from the inequality still existing in the socio-economic circumstances of South Africans, both with regard to burden of disease and access to surgical resources. It also differs in the way data was collected: patient participation was not required in one cohort, while it was integral to data collection in the other.

Chapter Two: Development of a Clinical Prediction Model for Perioperative Mortality in the South African Public Healthcare Sector

1 Introduction

1.1 Background

Information on risk-adjusted perioperative mortality is important to identify gaps and opportunities in delivery of surgical care, as the South African healthcare system struggles to address inequality on the way to universal health coverage. Generating evidence on risk-adjusted outcome after surgery has the potential to massively impact on efforts to improve access to, and the quality of perioperative care in South Africa.[1]

The South African Surgical Outcomes Study (SASOS), the first national multi-centre study investigating surgical outcomes and associated predictors, was published in 2015.[28] Subsequently, the SA Perioperative Research Group published national priorities for perioperative research.[135] The research priority ranked tenth in a Delphi consensus process was 'Development and validation of a risk stratification tool for SA surgery based on the SASOS data'. The African Surgical Outcomes Study superseded the development of a South African tool,[30] and an ASOS Risk Calculator was developed.[14] Since South African patients contributed 60.4% of the representative data used to develop the calculator, it seems reasonable that the tool should perform well in the South African public sector. However, the endpoint used in developing the calculator was a composite of severe complications and death, so that it can

preoperatively identify patients at risk of severe complications in which ‘failure to rescue’ can contribute to mortality. Recording postoperative complications in addition to mortality significantly increases the number of variables in a data set, and the associated burden of data collection.

Two temporally distinct cohorts are therefore available for prediction model development and validation. The settings in which the data were collected are similar. Since no further data are available for external validation, the model may not be generalizable and predict well in different settings.[136] The predictors specified in the model may be compared regarding definition with predictors in another prediction model, such as the Surgical Outcomes Risk Tool (SORT).[15]

A previous decision to not validate the SORT in ASOS data was made because of the limited amount of predictor data available in ASOS.[14] Assessing performance of a model such as SORT, a prediction model used in a developed country, can provide valuable information regarding the reliability of selected predictors in a prediction model developed in South African surgical patients, in anticipation of further validation and updating.

1.2 Objectives

To develop a preoperative clinical prediction model for in-hospital mortality after surgery using the South African cohort from the African Surgical Outcomes Study (ASOS).

To perform temporal validation using a cohort from the South African Surgical Outcomes Study (SASOS).

To validate the Surgical Outcomes Risk Tool (SORT) in an appropriate subpopulation of the South African cohort of ASOS

2 Methods

2.1 Source of data

The source of the data used for model development is the South African contribution to the African Surgical Outcomes Study.[56] This was a seven day, international, multicentre, prospective observational cohort study of patients ≥18 years undergoing any form of in-patient surgery in hospitals in African countries. Recruitment of South African patients to the study took place during a week in March to April 2016. This study was registered on the South African National Health Research Database (KZ_2015RP7_22), and on ClinicalTrials.gov (NCT03044899). Regulatory approval varied between countries, with some requiring ethics approval and others only data regulatory approval. The primary ethics approval was from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, South Africa (BE306/15).

2.2 Participants

All patients undergoing elective and non-elective surgery with a planned overnight hospital stay following surgery during the recruitment week where eligible for inclusion. Exclusions included planned day surgery, or radiological procedures not requiring anaesthesia.

The representative sample for South Africa included case data for 51 hospitals, where data was collected on at least 90% of eligible patients. The total number of cases in the representative sample for South Africa was 5273.

The number of participating sites per province are displayed in Table 2. Each hospital lead investigator was requested to submit site information, including information regarding hospital category and population served by the hospital.

The information received was, on face value, unreliable, and is not reported here. All central teaching hospitals participated in ASOS. There are three universities located in Gauteng, one each in Limpopo, KwaZulu-Natal, Free State and Eastern Cape, and two in the Western Cape province.

Table 2: The number of South African hospitals participating in ASOS, per province.

Province	Number of participating hospitals
Gauteng	9
KwaZulu-Natal	15
Limpopo	2
Free State	2
Eastern Cape	6
Northern Cape	1
Mpumalanga	1
Western Cape	17
North West	2
Total	54

2.3 Outcome

The primary outcome of the main study was in-hospital complications, which was censored at 30-days for patients who were still in-hospital. Secondary outcomes were rate of mortality on the day of surgery and in-hospital mortality rate for patients undergoing surgery in Africa, censored at 30-days.

2.4 Predictors

Data on predictors captured in ASOS included data on the patient (age, gender, smoking status, ASA Physical Status classification, comorbid disease, available laboratory values), the surgical procedure (type, timing of surgery, severity of surgery, indication for surgery, duration of surgery, anaesthetic technique, intra-operative blood loss, intra-operative events, completion of the WHO safe surgery checklist) and the seniority of the attending anaesthetists and surgeons. Additional information was collected for obstetric surgical cases.

Variables were selected for the model by initially analysing the univariate association of all variables including sex, smoking status, comorbidities (coronary artery disease, congestive heart failure, diabetes mellitus, cirrhosis, metastatic cancer, hypertension, stroke or transient ischaemic attack, chronic obstructive pulmonary disease/asthma, human immunodeficiency virus/acquired immunodeficiency syndrome, and chronic renal disease) and procedure related variables during logistic regression with the primary outcome.

Non-communicable disease was used as reference category for the variable indication for surgery, since this indication was the most common. For the same reason, orthopaedic surgery was used as reference category in type of surgery. Surgery type categories were further reduced by grouping types with similar association with outcomes together. The timing of surgery variable was reduced to two categories: elective and not elective. Age was included as a continuous variable.

2.5 Sample size and missing data

There was no pre-specified sample size in the African Surgical Outcomes Study, from which the cohort for model development is taken. The aim was to recruit as many participating sites as possible using convenience sampling. Sites not including more than 90% of eligible patients during the recruitment date, where excluded. The estimated mortality rate to be expected was 4% for the continent. A sufficient number of records were obtained to enable development of a robust regression model.

No imputation for missing data was done because the data were complete for the predictors considered in the model. Missing data for predictors not

considered in the model is reported in Table 4. An ‘available case analysis’ was done.

2.6 Statistical analysis

Categorical variables were described as proportions and compared using Fisher’s exact test. Continuous variables were described as mean and standard deviation and compared using t-tests.

A multivariable logistic model was developed with in-hospital mortality as the dependent variable. Preoperative risk variables were considered as predictors when the variable was significantly associated with the outcome using univariate logistic regression. Forward stepwise regression technique was then employed to select for possible predictors prior to model specification. An observed mortality rate of 2.5%in ASOS, when considering an event per variable rate of 10, allows for the entering of up to 13 binary variables or categories from nominal variables.[137]

Model estimation using biased regression coefficients was not performed because the large development cohort decreases the risk of overfitting.

Model performance was evaluated by assessing the calibration (plotting observed against expected outcome) and discrimination (calculation of area under the receiver operator characteristic or c-statistic) of the model. When considering clinical usefullness, model performance was assessed by using decision curve analysis as explained previously by Vickers, Steyerberg and others. (The resource used can be found at www.decisioncurveanalysis.org.) Since specificity and sensitivity “can only be used as a naïve summary indicator of usefullness”[8], net benefit was used as a summary measure. The net benefit

can only be determined once a threshold probability for decision-making has been decided on. However, this threshold may differ between patients, so the graph illustrates a range of threshold probabilities.

The SASOS cohort was used to temporally validate the model, with subjects in this cohort being temporally distinct from the ASOS cohort. The data in the validation cohort was collected in the same clinical setting as the data in the derivation cohort. In-hospital postoperative mortality was a primary outcome in SASOS and a secondary outcome in ASOS. Predictors were similarly defined, but SASOS did not include obstetric- or cardiac surgery. No further external validation of the model was done because of the lack of available data from a different setting in South Africa.

Finally, the Surgical Outcomes Risk Tool was validated in the cohort, after comparing the definition of the predictor variables in the developed model and the SORT.

All data were analysed using Stata®/IC 15.1 for Windows, StataCorp LLC, Texas, USA.

3 Results

3.1 Participants

Data were collected on 5522 patients in 54 hospitals and captured in REDCap[138] by the hospital lead investigators. Each hospital lead investigator was responsible for verifying the data for their site. Thirty-one records (0.56%) had missing mortality data. Exclusion of the data resulted in the exclusion of a hospital from the study. Records from two hospitals did not fulfil the criteria for

per-protocol inclusion, which required that more than 90% of eligible patients during the recruitment week are recruited to the study and data captured on these patients. Most of the exclusion was a result of investigators being unable to trace records of patients to complete outcomes variables during the postoperative follow-up.

The number of records excluded during prediction model development to allow analysis of data from complete records, was 26 (0.49%). This was considered sufficiently low to not influence the ability of the model to reliable predict outcome. Figure 3 describes the flow of patients through the study.

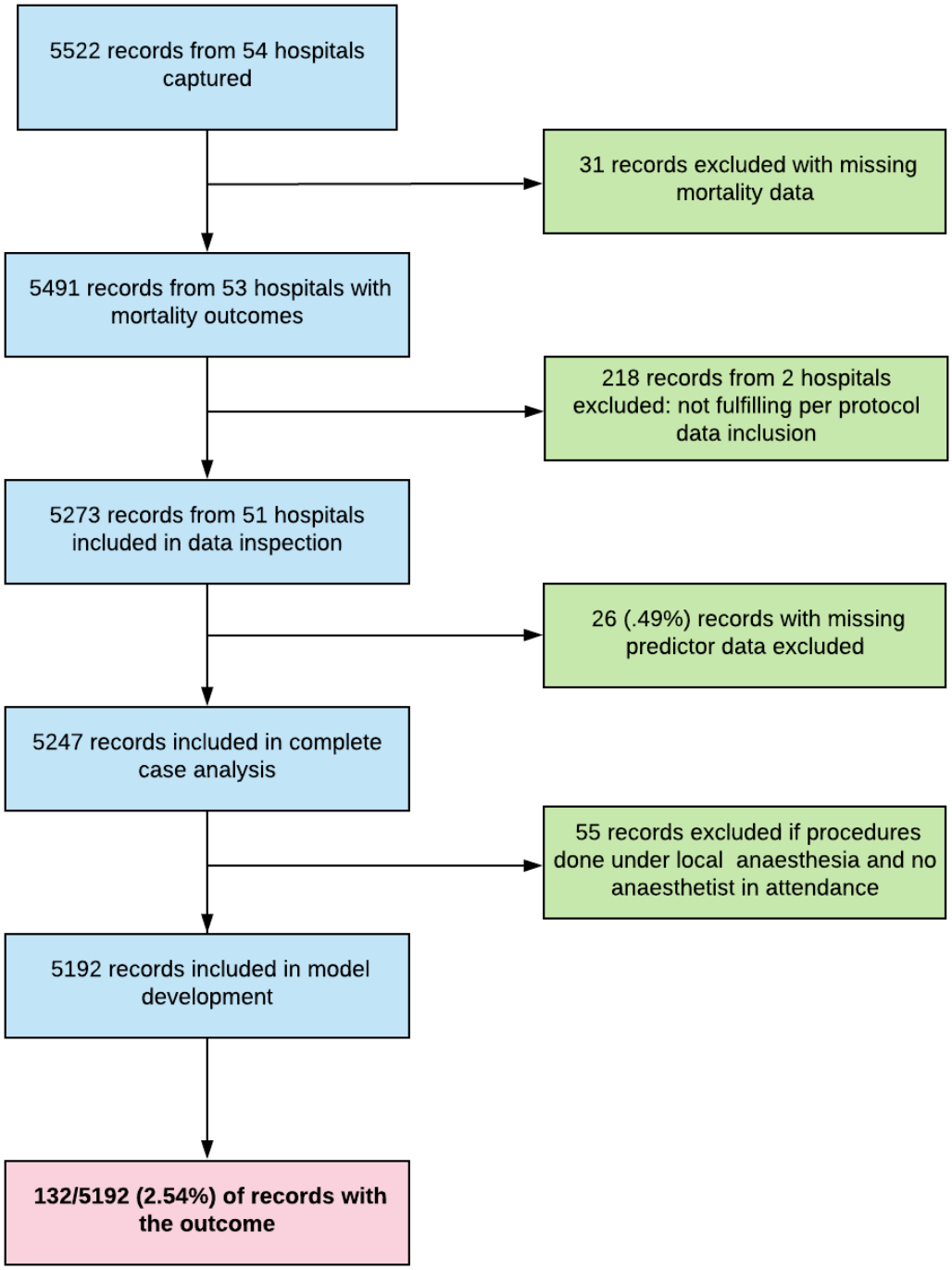

Figure 3: Diagram illustrating recruitment of the prediction model derivation cohort.

The patient characteristics for the derivation (ASOS) and validation (SASOS) cohorts are described in Table 3. Data are mean (standard deviation) or n/N (%). Mortality for each characteristic variable is summarised as number of patients with the characteristic per total number of cases where data is

available, in percentage. Missing data are reflected per variable in the total number for that variable.

Table 3: Patient characteristics of the derivation and validation cohorts.

	SA ASOS cohort (derivation cohort)		SASOS cohort (validation cohort)	
	All patients (n=5247)	Mortality (n=132)	All patients (n=3927)	Mortality (n=123)
Age (yrs.)				
<30	1804/5247 (34.38)	20/132 (15.15)	1062/3927 (27.04)	13/123 (10.57)
>=30	3092/5247 (58.93)	87/132 (65.91)	2481/3927 (63.18)	85/123 (69.11)
>=70	351/5247 (6.69)	25/132 (18.94)	384/3927 (9.78)	25/123 (20.33)
Male	1923/5247 (36.65)	72/132 (52.55)	1994/3925 (50.80)	71/123 (57.72)
Female	3324/5247 (63.35)	60/132 (45.45)	1931/3925 (49.20)	52/123 (42.28)
Current smoker	1225/5241 (23.37)	27/129 (20.93)	1083/3837 (28.23)	26/113 (23.01)
ASA Physical Status				
I	2194/5247 (41.81)	22/132 (16.67)	1743/3898 (44.72)	12/122 (9.84)
II	2188/5247 (41.70)	31/132 (23.48)	1347/3898 (34.56)	29/122 (23.77)
III	718/5247 (13.68)	44/132 (33.33)	663/3898 (17.01)	40/122 (32.79)
IV	143/5247 (2.73)	31/132 (23.48)	131/3898 (3.36)	37/122 (30.33)
V	4/5247 (0.08)	4/132 (3.03)	14/3898 (0.36)	4/122 (3.28)
Preoperative co-morbidity				
Coronary artery disease	115/5247 (2.19)	8/132 (6.06)	160/3869 (4.14)	8/119 (6.72)
Congestive heart failure	58/5247 (1.11)	6/132 (4.55)	55/3869 (1.42)	3/119 (2.52)
Diabetes Mellitus	453/5247 (8.63)	32/132 (24.24)	394/3927 (10.03)	19/123 (15.45)
Cirrhosis	3/5247 (0.06)	0	7/3869 (0.18)	1/119 (0.84)
Metastatic cancer	65/5247 (1.24)	4/132 (3.03)	101/3869 (2.61)	12/119 (10.08)
Hypertension	1177/5247 (22.43)	48/132 (36.36)	-	-
Stroke or transient ischaemic attack	30/5247 (1.14)	4/132 (3.03)	55/3869 (1.42)	8/119 (6.72)
COPD/Asthma	245/5247 (4.67)	10/132 (7.58)	240/3869 (6.20)	10/119 (8.40)
HIV positive/AIDS	958/5247 (18.26)	14/132 (10.61)	509/3869 (13.16)	11/119 (9.24)
Chronic renal disease	108/5247 (2.06)	10/132 (7.58)	-	-
Severity of surgery				
Minor	1384/5247 (26.38)	18/132 (13.64)	1403/3885 (36.11)	16/121 (13.22)
Intermediate	2946/5247 (56.15)	58/132 (43.94)	1672/3885 (43.04)	45/121 (37.19)
Major	917/5247 (17.48)	56/132 (42.42)	810/3885 (20.85)	60/121 (49.59)
Urgency of surgery				
Elective	2204/5247 (42.0)	23/132 (17.42)	1795/3915 (45.85)	25/123 (20.33)
Urgent	1301/5247 (24.80)	42/132 (31.82)	1290/3915 (32.95)	42/123 (34.15)
Emergent	1742/5247 (33.20)	67/132 (50.76)	830/3915 (21.20)	56/123 (45.53)
Indication for surgery				
Non-communicable disease	2202/5247 (41.97)	47/132 (35.61)	1881/3914 (48.06)	49/123 (39.84)
Infection	769/5247 (14.66)	41/132 (31.06)	736/3914 (18.80)	30/123 (24.39)
Trauma	1127/5247 (21.48)	40/132 (30.30)	1297/3914 (33.14)	44/123 (35.77)
Caesarian section	1149/5247 (21.90)	4/132 (3.03)	-	-
Type of surgery				
Orthopaedic	1019/5247 (19.42)	18/132 (13.64)	1112/3922 (28.35)	12/123 (9.76)
Breast	113/5247 (2.15)	2/132 (1.52)	109/3922 (2.78)	1/123 (0.81)
Obstetrics	1442/5247 (27.48)	4/132 (3.03)	-	-
Gynaecology	570/5247 (10.86)	3/132 (2.27)	525/3922 (13.39)	2/123 (1.63)
Upper gastro-intestinal	135/5247 (2.57)	11/132 (8.33)	154/3922 (3.93)	18/123 (14.63)
Lower gastro-intestinal	397/5247 (7.57)	26/132 (19.70)	400/3922 (10.20)	24/123 (19.51)
Hepatobiliary	85/5247 (1.62)	1/132 (0.76)	88/3922 (2.24)	4/123 (3.25)
Urology & Kidney	237/5247 (4.52)	5/132 (3.79)	225/3922 (5.74)	4/123 (3.25)

Vascular	162/5247 (3.09)	14/132 (10.61)	134/3922 (3.42)	9/123 (7.32)
Head and neck	204/5247 (3.89)	11/132 (8.33)	222/3922 (5.66)	6/123 (4.88)
Plastics/Cutaneous	310/5247 (5.91)	6/132 (4.55)	242/3922 (6.17)	7/123 (5.69)
Cardiac	42/5247 (0.80)	4/132 (3.03)	-	-
Thoracic (lung & other)	88/5247 (1.68)	5/132 (3.79)	65/3922 (1.66)	1/123 (0.81)
Thoracic (gut)	9/5247 (0.17)	1/132 (0.76)		
Neurosurgery	122/5247 (2.33)	14/132 (10.61)	133/3922 (3.39)	11/123 (8.94)
Other	312/5247 5.95)	7/132 (5.30)	513/3922 (13.08)	24/123 (19.51)

About two thirds of all cases in the derivation cohort were attended to by non-specialist physicians (anaesthetists and surgeons). In 29.55% (39/132) of deaths the most senior anaesthetist in the operating room was a specialist, and in 34.85% (46/132) of deaths the most senior surgeon was a specialist. Intraoperative procedures/events and workforce characteristics for the derivation cohort are summarized in Table 4 as frequency and proportion. The univariate association for these variables with mortality are also shown. Intraoperative event and workforce characteristics in the validation cohort are not described.

Table 4: Intra-operative events and workforce characteristics in the derivation cohort data.

Variable (N=5247)	Missing n	Frequency n (%)	Proportion (95%CI)	Mortality (N=132)		
				n (%)	Odds ratio (95% CI)	P value
Most senior anaesthetist	5					
Specialist		1381 (26.34)	0.263 (0.252-0.275)	39 (29.5)	Reference	
Non-specialist physician		3756 (71.65)	0.716 (0.704-0.728)	93 (70.4)	0.874 (0.598-1.276)	0.485
Non-physician anaesthetist		37 (0.71)	0.007 (0.005-0.010)	0	-	
No anaesthetist		68 (1.3)	0.013 (0.010-0.016)	0	-	
Most senior surgeon	5					
Specialist		1687 (32.18)	0.3218 (0.309-0.335)	46 (34.8)	Reference	
Non-specialist physician		3545 (67.63)	0.676 (0.663-0.689)	86 (65.1)	0.887 (0.617- 1.275)	0.517
Non-physician surgeon		10 (0.19)	0.002 (0.001-0.003)	0	-	
Anaesthetic technique	2					
General		2666 (50.83)	0.508 (0.495-0.522)	105 (79.5) -10 day of surgery	Reference	
Spinal		1998 (38.09)	0.381 (0.368-0.394)	19 (14.3)	0.234 (0.143-0.383)	<0.001
Epidural		47 (0.90)	0.009 (0.007-0.012)	0	-	
Sedation		107 (2.04)	0.020 (0.017-0.024)	1 (0.01)	0.230 (0.032-1.664)	0.146
Local		228 (4.35)	0.043 (0.038-0.049)	4 (3.03)	0.435 (0.159-1.193)	0.106
Other regional		199 (3.79)	0.038 (0.033-0.043)	3 (2.27)	0.373 (0.117-1.187)	0.095
Anaesthetic complications	11					
None of the below		5,202 (99.35)	0.993 (0.991-0.995)	124 (93.9)	Reference	
Failed intubation		5 (0.10)	0.001 (0.000-0.002)	0	-	
Aspiration		4 (0.08)	0.001 (0.000-0.002)	0	-	
Cardiac arrest		5 (0.10)	0.001 (0.000-0.002)	3 (2.27) -2 day of surgery	61.427 (10.174-370.887)	<0.001
Hypoxia		4 (0.38)	0.004 (0.002-0.006)	5 (3.79) -3 day of surgery	13.650 (4.885-38.147)	<0.001
Surgical checklist used	6					
Yes		4268 (81.43)	0.814 (0.803-0.825)	104 (78.8) -8 day of surgery	.843 (.552-1.287)	0.429
No		973 (18.57)	0.186 (0.175-0.196)	28 (21.2) -2 day of surgery	Reference	
Blood loss in ml	16	Mean (SD): 291 (373)	Min: 5 Max: 6000	Mean (SD): 411 (753)	1.000 (1.000-1.001)	<0.001
Duration of surgery in min	10	Mean (SD): 76 (64)	Min: 9 Max: 695	Mean (SD): 133 (113)	1.007 (1.006-1.009)	<0.001

3.2 Model development

3.2.1 Participants and outcome events

Twenty-six patients had missing data and were not included during model development. Fifty-five cases were done under local anaesthetic only, with no anaesthetist in attendance. These cases were excluded from the derivation cohort. Of the 5192 patients included in model development, 132 (2.54%) had the primary outcome of in-hospital death.

The day-of-surgery death ratio for the study period was 10/5192 cases: 0.19%. The mean age of the patients that died on the day of surgery was 47.3 years (95 % confidence interval 39.412 - 55.187). Of the ten patients, one was classified as ASA PS I (an obstetric surgical case), one as ASA PS II, one as ASA PS III, and seven as ASA PS IV or more. The WHO safe surgery checklist was not completed in two of these patients. Seven where classified as emergency cases, two as urgent and one (a cardiac case) as elective. Three patients experienced hypoxia and cardiac arrest. Two patients were reported to have had cardiac arrest not associated with hypoxia. No failed intubation or aspiration were reported in any of the ten cases. Two of the ten patients were transferred to a critical care unit after surgery.

Duration of the procedure and blood loss where associated with mortality, but these variables were not included in the model specification because of the known association with severity of surgery. Spinal anaesthesia was associated with reduced mortality during univariate analysis. Due to the high proportion of obstetric surgery in healthy patients done under spinal anaesthesia,

anaesthetic technique was not included as a predictor. None of the intra-operative variables were therefore included during model specification.

The association of predictors with the outcome during univariate analysis is described in Table 5. Data are mean (SD) or n/N (%).

Table 5: Association of candidate predictors with mortality in univariate analysis.

	All patients (n=5192) (%)	Patients died (n=132) (%)	Patients alive (n=5060) (%)	Odds ratio (95% CI)	P-value
Age (yrs.)	39.5 (16.36)	51.5 (19.06)	39.15 (16.16)	1.039 (1.030-1.049)	<0.001
ASA Physical Status					
I	2169/5192 (41.78)	22/132 (16.67)	2147/5060 (42.43)	Reference	
II	2164/5192 (41.68)	31/132 (23.48)	2133/5060(42.15)	1.418 (.818-2.457)	0.213
III	713/5192 (13.73)	44/132 (33.33)	669/5060 (13.22)	6.418 (3.819-10.786)	<0.001
IV	146/5192 (2.81)	35/132 (26.52)	111/5060 (2.19)	30.772 (17.465-54.215)	<0.001
Preoperative co-morbidity					
Coronary artery disease	115/5192 (2.21)	8/132 (6.06)	107/5060 (2.11)	2.986 (1.425-6.260)	0.004
Congestive heart failure	58/5192 (1.12)	6/132 (4.55)	52/5060 (1.03)	4.586 (1.934-10.874)	0.001
Diabetes Mellitus	443/5192 (8.53)	32/132 (24.24)	411/5060 (8.12)	3.620 (2.401-5.458)	<0.001
Hypertension	1150/5192 (22.15)	48/132 (36.36)	1102/5060 (21.78)	2.052 (1.431-2.944)	<0.001
Stroke or transient ischaemic attack	59/5192 (1.14)	4/132 (3.03)	55/5060 (1.09)	2.844 (1.015-7.966)	0.047
HIV positive/AIDS	953/5192 (18.36)	14/132 (10.61)	939/5060 (18.56)	0.521 (0.297-.910)	0.022
Chronic renal disease	108/5192 (2.08)	10/132 (7.58)	98/5060 (1.94)	4.150 (2.113-8.151)	<0.001
Severity of surgery					
Minor	1349/5192 (25.98)	18/132 (13.64)	1331/5060 (23.60)	Reference	
Intermediate	2926/5192 (56.36)	58/132 (43.94)	2868/5060 (56.68)	1.495 (.878-2.548)	0.139
Major	917/5192 (17.66)	56/132 (42.42)	861/5060 (17.02)	4.809 (2.808-8.236)	<0.001
Urgency of surgery					
Elective	2157/5192 (41.54)	23/132 (17.42)	2134/5060 (42.17)	Reference	
Urgent	1294/5192 (24.92)	42/132 (31.82)	1252/5060 (24.74)	3.1125 (1.8631-5.1997)	<0.001
Emergent	1741/5192 (33.53)	67/132 (50.76)	1674/5060 (33.08)	3.7135 (2.3025–5.9891)	<0.001
Indication for surgery					
Non-communicable disease	2152/5192 (41.45)	47/132 (35.61)	2105/5060 (41.60)	Reference	
Infection	769/5192 (14.81)	41/132 (31.06)	728/5060 (14.39)	2.522 (1.645-3.867)	<0.001
Trauma	1122/5192 (21.61)	40/132 (30.30)	1082/5060 (21.38)	1.656 (1.079-2.540)	0.021
Caesarian section	1149/5192 (22.13)	4/132 (3.03)	1145/5060 (22.63)	0.156 (0.562-0.435)	<0.001
Type of surgery					
Orthopaedic, other	1287/5192 (24.79)	25/132 (18.94)	1262/5060 (24.94)	Reference	
Breast & Plastic	421/5192 (8.11)	8/132 (6.06)	413/5060 (8.16)	0.978 (0.438-2.184)	0.956
Obstetrics & Gynaecological	2012/5192 (38.75)	7/132 (5.30)	2005/5060 (39.62)	0.176 (0.076-0.409)	<0.001
Gastro-intestinal & Hepatobiliary	617/5192 (11.88)	38/132 (28.79)	579/5060 (11.44)	3.313 (1.981-5.540)	<0.001
Urology & Kidney	236/5192 (4.55)	5/132 (3.79)	231/5060 (4.57)	1.093 (.414-2.883)	0.858
Cardiothoracic & Vascular	300/5192 (5.78)	24/132 (18.18)	276/5060 (5.45)	4.389 (2.470-7.801)	<0.001
Neuro	119/5192 (2.29)	14/132 (10.61)	105/5060 (2.08)	6.731 (3.397-13.337)	<0.001
Head & Neck	200/5192 (3.85)	11/132 (8.33)	189/5060 (3.74)	2.938 (1.4226.069)	0.004

3.2.2 Model specification

During coding of the predictors categories within variables were collapsed for the variable of the urgency of surgery. When applying forward stepwise regression technique, primary indication for surgery was not selected. Including this predictor during model specification did however improve model performance. The full prediction model is presented in Table 6, with all regression coefficients and the model intercept. CI = confidence interval

Table 6: Full clinical prediction model for in-hospital mortality.

Risk predictor	Coefficient	95% Confidence Interval	Standard error	z	P-value
Intercept	-7.2242	-8.2300 to -6.1488	0.5487	-13.17	<0.001
Age	0.0241	0.0123 to 0.0359	0.0060	4.00	<0.001
ASA Physical Status classification					
ASA I	Reference				
ASA II	0.2448	-0.3362 to 0.8257	0.2964	0.83	0.409
ASA III	1.0272	0.4273 to 1.6271	0.3061	3.36	0.001
ASA IV and more	2.0857	1.4362 to 2.7353	0.3314	6.29	<0.001
Urgency of surgery					
Elective surgery	Reference				
Urgent & emergent surgery	1.2328	0.7155 to 1.7500	0.2639	4.67	<0.001
Severity of surgery					
Minor	Reference				
Intermediate	0.4047	-0.1632 to 0.9726	0.2897	1.40	0.162
Major	1.0350	0.4166 to 1.6533	0.3155	3.28	0.001
Primary indication for surgery					
Non-communicable disease	Reference				
Infection	0.4941	-0.0152 to 1.0035	0.2599	1.90	0.057
Trauma	0.5324	-0.0395 to 1.1043	0.2918	1.82	0.068
Caesarian section	0.0526	-1.4350 to 1.5403	0.7590	0.07	0.945
Type of surgery					
Orthopaedics	Reference				
Plastics & breast	0.1744	-0.7154 to 1.0642	0.4540	0.38	0.804
Gynaecology/obstetrics	-0.9978	-2.2847 to 0.2890	0.6566	-1.50	0.001
Gastro-intestinal & hepatobiliary	1.0383	0.4186 to 1.6580	0.3162	3.28	0.003
Urology	0.6916	-0.3652 to 1.7484	0.5392	1.28	0.411
Cardiothoracic & vascular	0.7182	0.0370 to 1.3994	0.3475	2.07	0.099
Neuro	1.4268	0.6647 to 2.1890	0.3888	3.67	0.001
Head & Neck/ENT	1.3329	0.5209 to 2.1450	0.4143	3.22	0.003

3.2.3 Model performance

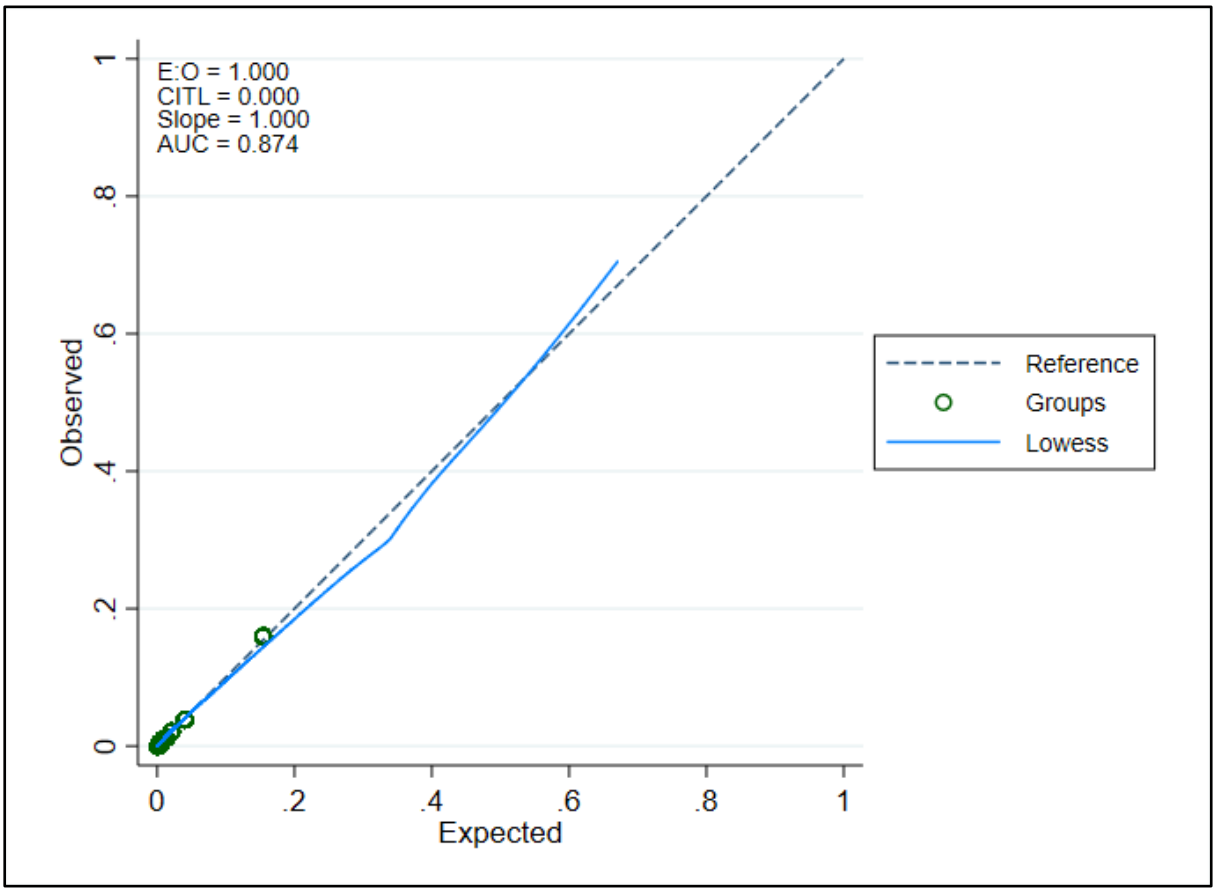

Figure 4: Calibration plot for prediction model of in-hospital mortality.

The area under the receiver-operating curve (AUROC) or c-statistic was 0.8737 (95% confidence interval: 0.84331 - 0.90402) for the full model. The Hosmer-Lemeshow statistic was found to be non-significant (p=0.9938).

The validation plot of observed against expected outcomes using Lowess smoothing is shown in Figure 4. E:O = Expected : Observed, CITL = Calibration-in-the-large, AUC = Area Under Curve.The agreement between the expected predictions and observed mortality is not perfect at higher predictions, as indicated by the blue line. The

observed outcomes in groups with similar risk (indicated by green circles) all fall below this point, and is close to the ideal dashed line indicating perfect calibration.

The distribution of the subjects is displayed in a histogram (Figure 5). The spread of predictions are better in the subjects with the observed outcome than in those without. The distribution indicates that the prediction model performs fairly well with regards to discrimination.

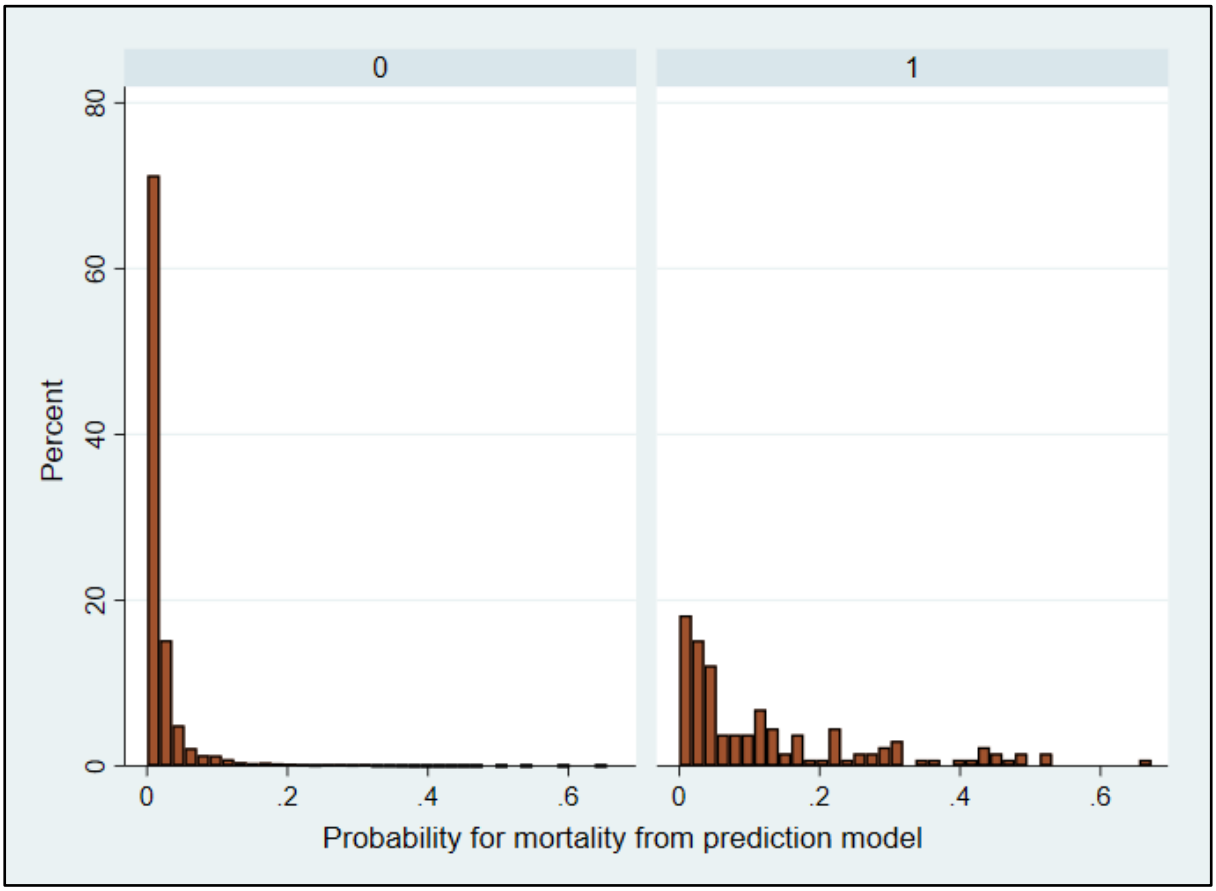

Figure 5: Histogram illustrating the distribution of predictions of patients that lived (0) and died (1)

Using a probability cutoff of 0.025, sensitivity and specifity were as follows:

		Actual		Total
		Positive	Negative	
Predicted	Positive	104	1023	1127
	Negative	28	4037	4065
Total		132	5060	5192
Sensitivity		78.79%	Specificity	79.78%

Positive predictive value	9.23%	Negative predictive value	99.31%
False negative rate	21.21%	False positive rate	20.22%

The decision-curve analysis is shown in Figure 6. It is meant to be an illustration of the performance of the model as a tool in clinical decision-making, compared to other options (for example treating patients on the basis of one predictor only). The green line in the figure represents the probability for mortality as calculated when the prediction model is fitted. The probabilities as calculated when single predictors would be used is also shown: red line for neurosurgery as predictor, orange for non-elective surgery, and light blue for trauma patients. The curve illustrating net benefit for treating all patients crosses from positive to negative on the y-axis at the prevalence of mortality in the cohort, shown as 2.5%. The graph shows that intervening in some way to decrease mortality in neurosurgery will always be of benefit, no matter the threshold for decision-making. This does not apply for the other two single predictors, where no benefit for intervention is indicated at a threshold probability of around 0.04. The graph illustrates that the prediction model will always perform better than when basing decision making on the probability calculated when using a single predictor.

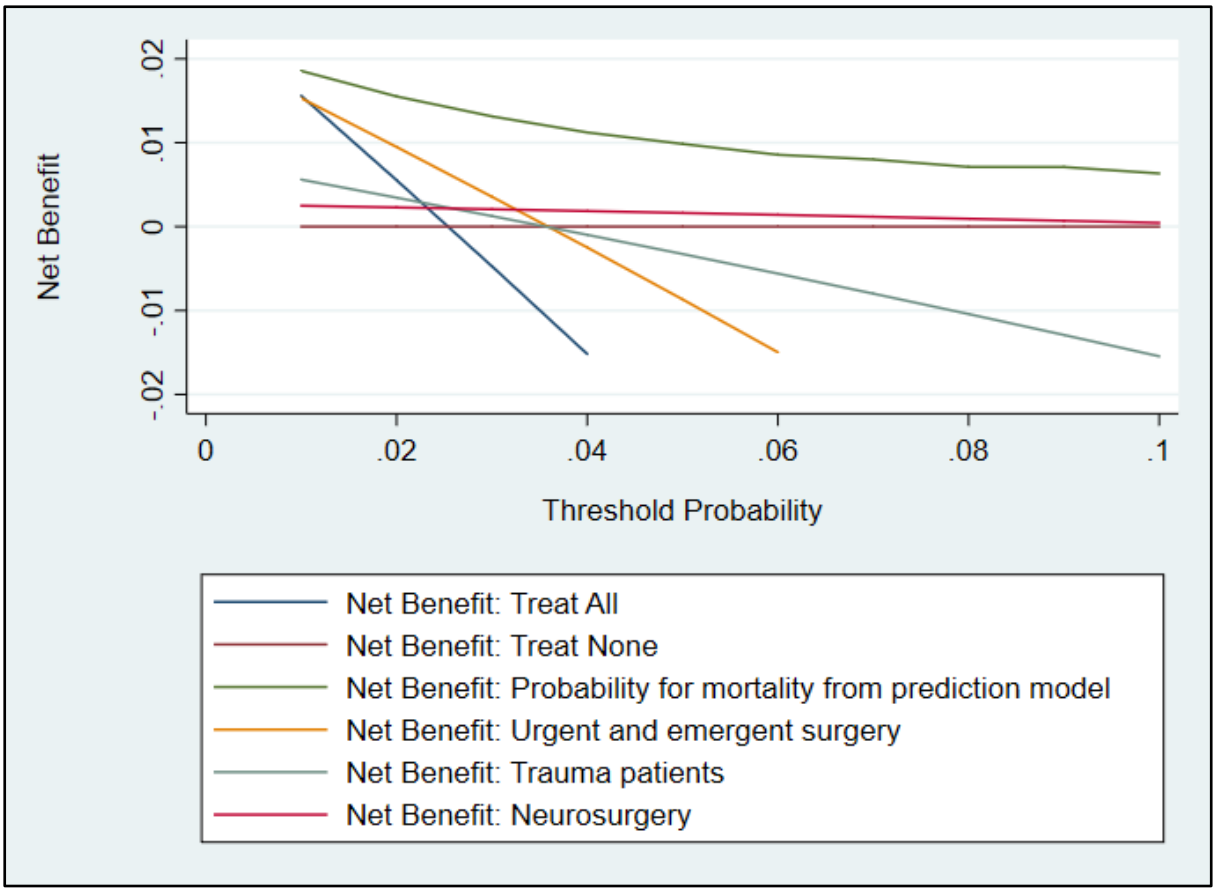

Figure 6: Graph for decision curve analysis illustrating net benefit for a range of threshold probabilities for mortality.

The prediction model was internally validated by fitting to a bootstrap sample. The resulting AUROC was found to be 0.8805 (95% confidence interval :0.8491 - 0.9119) and the calibration plot is shown in Figure 7. In this particular sampling procedure with 94 replications performed from 100 iterations requested, the prediction model discriminates well, but the validation plot shows variance in the agreement between predictions and observations. The slope of the calibration was however 1.000.

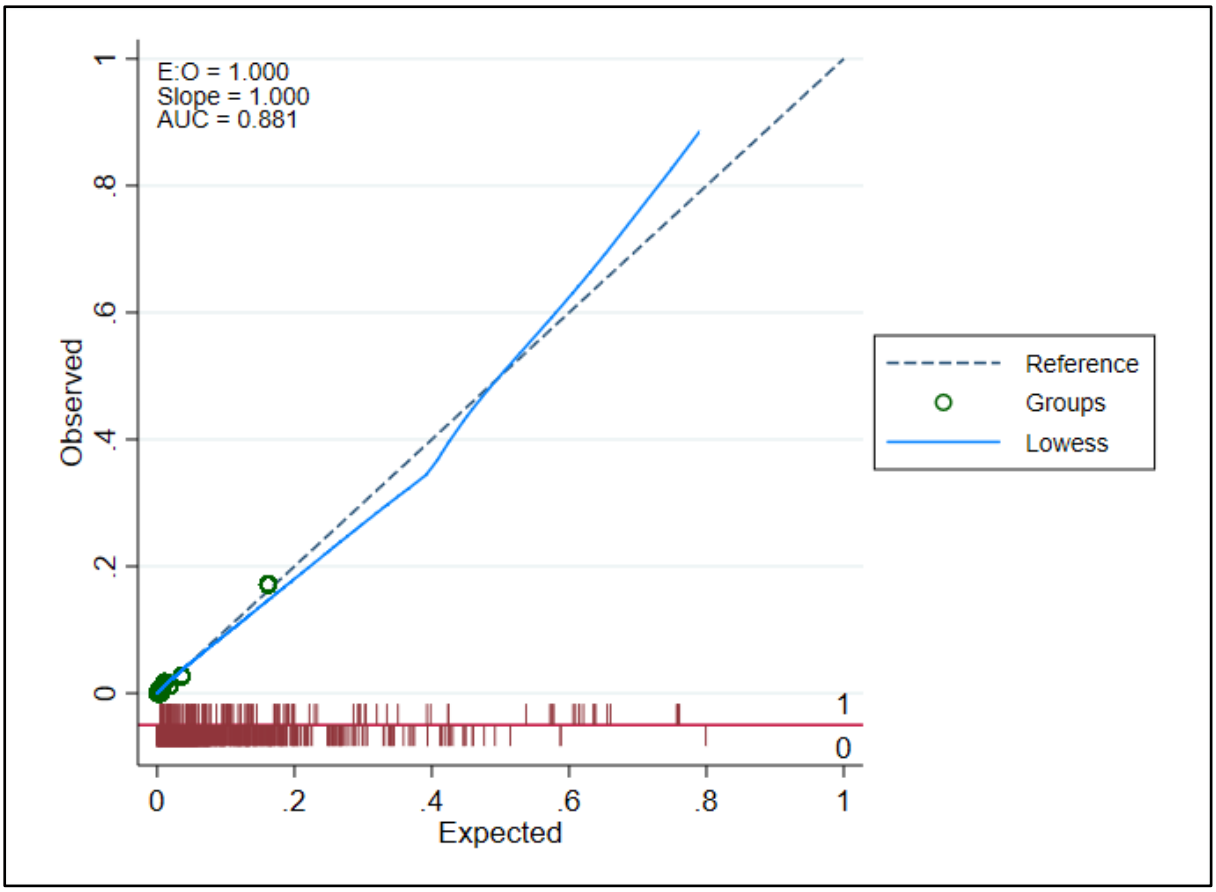

Figure 7: Validation plot for prediction model fitted to a bootstrap sample.

During validation of the prediction model using the SASOS cohort, the c-statistic (AUROC) was found to be 0.8639 (95% CI 0.82810 - 0.89963) in 3842 observations. The Hosmer-Lemeshow statistic was 14.23 (p= 0.0760). The validation plot is shown in Figure 8. The prediction model performance was similar in the validation cohort when compared to the derivation cohort. Importantly, the coefficients for predictors and the intercept during validation in the SASOS cohort were similar, and no updating of the model is required following validation.

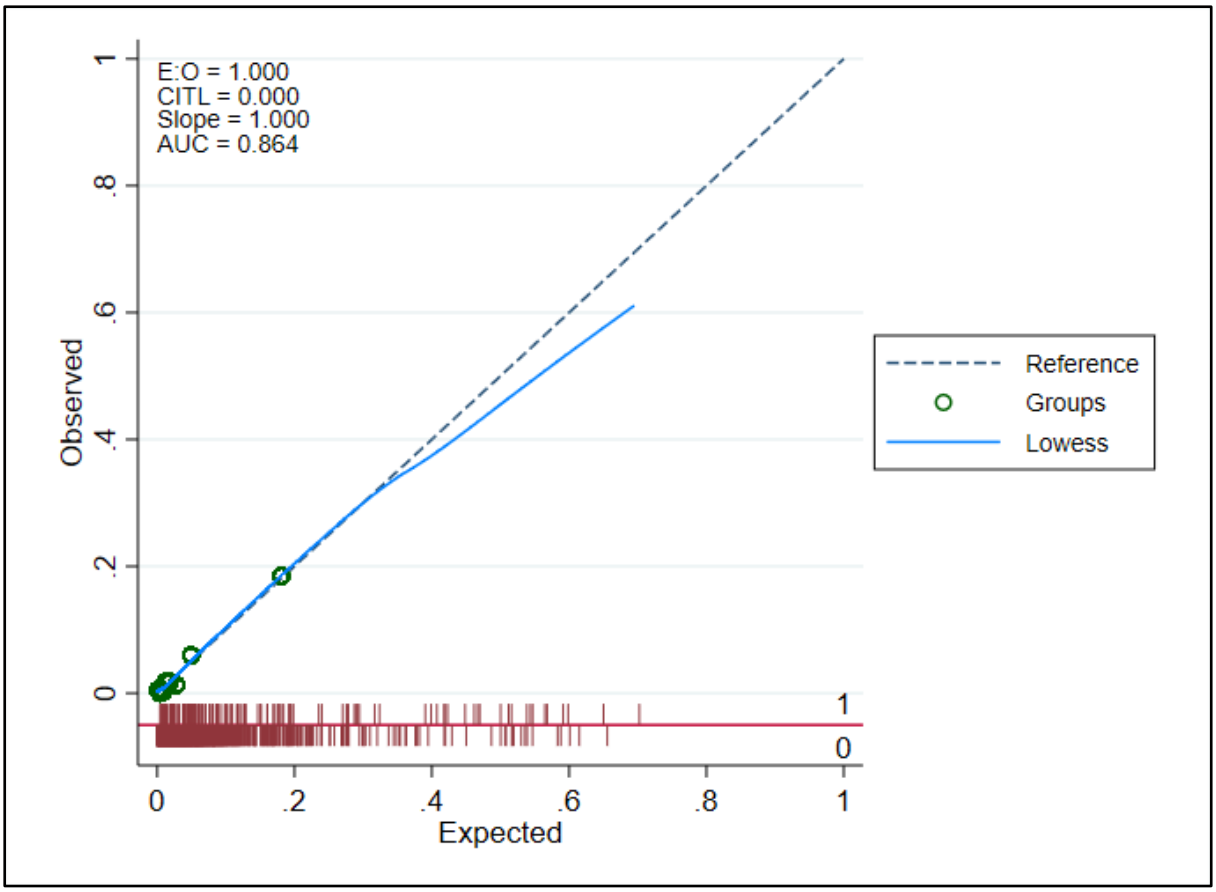

Figure 8: Validation plot for prediction model fitted to SASOS cohort data.

A restricted model was specified as described in Table 7, to enable predictor comparisons with the Surgical Outcomes Risk Tool.

Table 7: Restricted prediction model for in-hospital mortality.

Risk predictor	Coefficient	95% Confidence Interval	Standard error	z	P-value
Intercept	-6.4730	-7.2275 to -5.7184	0.3850	-16.81	<0.001
Age	0.0259	0.0146 to 0.0371	0.0057	4.52	<0.001
ASA PS III	0.9715	0.5163 to 1.4267	0.2322	4.18	<0.001
ASA PS IV and more	2.0938	1.5632 to 2.6245	0.2708	7.73	<0.001
Urgent surgery	1.1936	0.6592 to 1.7279	0.2726	4.38	<0.001
Emergent surgery	1.6820	1.1470 to 2.2171	0.2730	6.16	<0.001
Major surgery	0.7182	0.3128 to 1.1237	0.2069	3.47	0.001
Obstetric surgery	-1.8496	-2.9011 to -0.7982	0.5364	-3.45	0.001
Lower gastro-intestinal surgery	0.6817	0.1675 to 1.1960	0.2624	2.60	0.009
Neuro surgery	1.0887	0.4072 to 1.7701	0.3477	3.13	0.002
Head & Neck surgery	1.0542	0.3450 to 7.7634	0.3618	2.91	0.004

The area under the receiver-operating curve (AUROC) or c-statistic was 0.8643 (95% confidence interval: 0.83063 - 0.89799) for the restricted model. The Hosmer-Lemeshow statistic was found to be non-significant (p=0.7679).

The validation plot of observed against expected outcomes using Lowess smoothing is shown in Figure 9. E:O = Expected : Observed, CITL = Calibration-in-the-large, AUC = Area Under Curve.

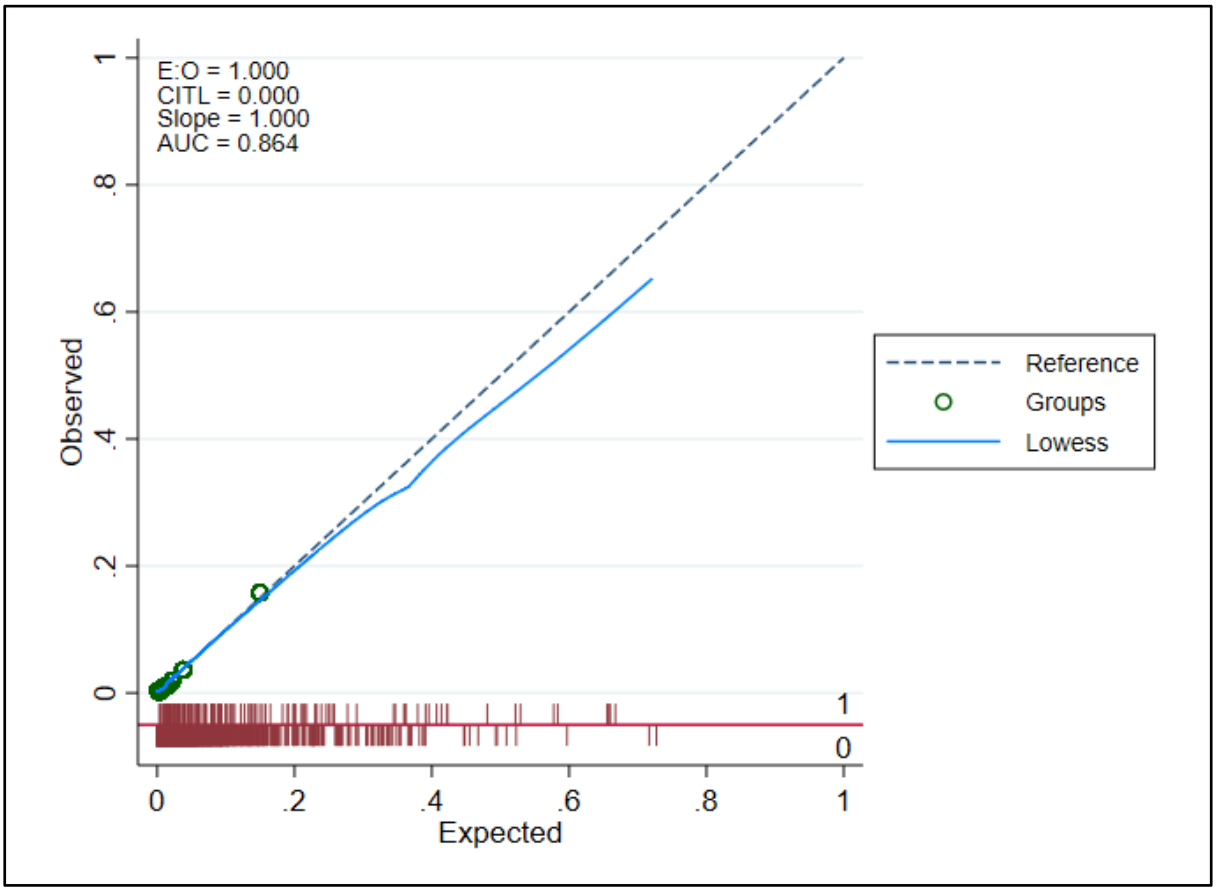

Figure 9: Calibration plot for restricted prediction model.

When fitting the SORT to the available data a comparison of variable definitions was required. The variables in the restricted prediction model that was developed from the SA cohort of ASOS differ from the predictors in SORT. Expedited surgery is not

available as a separate category in South African data. Other variable definitions that may not align are cancer in SORT (metastatic cancer was used as a predictor in ASOS), and high-risk surgery (defined as gastro-intestinal, cardiothoracic and vascular surgery in SORT). Lastly, the definition of extra major or complex surgery was assumed to align with the ASOS definition of major surgery. Of note is that the severity of surgery classification in the SORT is derived from pre-defined categorisation of the surgical procedure. In ASOS the classification was done by physicians based on definitions primarily related to duration of surgery.

SORT was developed in adult patients (16 years of age or older) receiving in-patient non-neurological non-cardiac surgery. Before the SORT model was fitted to the dataset, neurosurgical and cardiac surgery cases were excluded from the cohort. There were 5031 records in the resulting cohort.

The predicted probability was generated as follows (using Stata®):

```
generate SORT = 1.411*(ASAIII) + 2.388*(ASAIV) + 4.081*(ASAV) + 1.236*(Sexp) +
1.657*(Surgent) + 2.452*(Semerg) + 0.712*(Stype) + 0.381*(major) + 0.667*(MetCa) +
0.777*(Sage1)  + 1.591*(Sage2)-7.366

generate pSORT=inlogit(SORT)
```

ASA = ASA Physical Status III/IV/V, Sexp = Expedited surgery, Surgent = Urgent surgery, Semerg = Emergency surgery, Stype = Type of surgery, major = Major surgery, MetCa = Metastatic cancer, Sage1 = Age 65 – 79 years, Sage2 = Age >= 80 years, pSORT = Predicted probability

Performance of the SORT was evaluated and the calibration plot is displayed in Figure 10. The c-statistic was 0.7531 (95 % confidence interval 0.70515 to 0.80101).

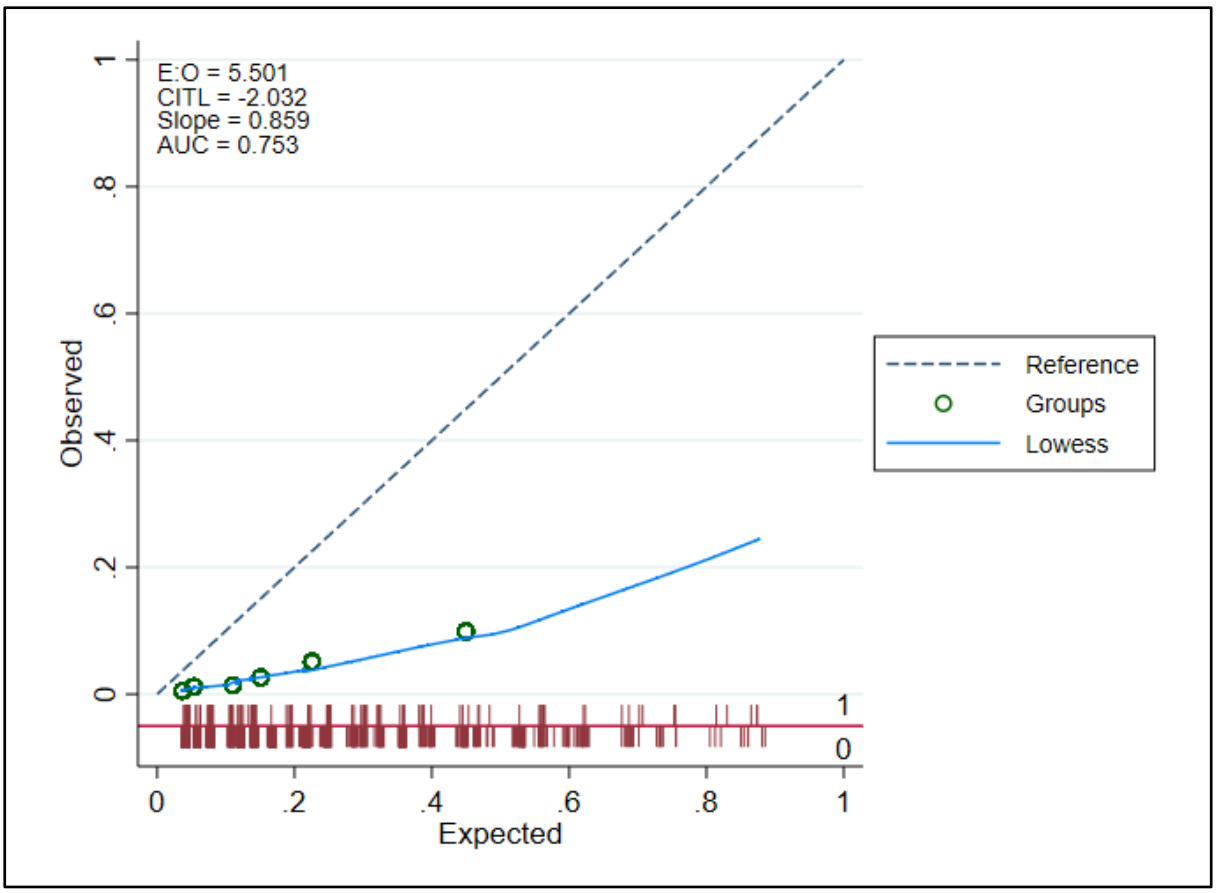

Figure 10: Validation plot for the SORT fitted to South African cohort.

4 Discussion

4.1 Principal findings

The prediction model developed from a large South African cohort, temporally validated, identifies the most important predictors of perioperative mortality and their relative contribution to the outcome in a defined (regional and central public sector hospital) subgroup of the SA surgical population. This prediction model was not externally validated in a different setting.

4.2 Limitations

Temporal validation is considered external validation in time, but evaluates model performance in patients from the same centres.[136] It does not truly reflect the generalisability of a prediction model.

The SASOS and ASOS data were collected in the public sector. The population represented by the sample may differ from the private sector population regarding burden of disease, access to surgery and anaesthesia care, resource (particularly workforce) allocation.

Some of the predictors related to patient-specific risk and procedure-specific risk were not classified according to established systems commonly used in the SA healthcare system. These classifications need to be considered when validating the model further. This will then require model updating regarding predictor definitions, and re-calibration.

A further limitation of the study is that updating of the SORT was not attempted at the time of submission of the thesis, since it may require more than just simple re-calibration measures.

4.3 Interpretation

The prediction model described provides a useful indication of priority areas in which quality improvement initiatives are likely to have the largest effect, such as emergency- and urgent surgery, and specific types of surgery such as neurosurgical procedures.

In a prediction model for mortality such as this, quality improvement initiatives can cause harm only when resources are allocated to patients that are not at high risk for poor outcome. Theatre efficiency and optimal theatre utilisation are even more important resource measures when considering surgery other than elective surgery.

By applying the model to estimate individual patient risk, such decisions regarding intervention (prioritising care) are easier to make. Model performance regarding decision support for patients with a higher probability of mortality is important. The fact that the positive predictive value of the model is 9.23%, means that a large number of patients considered to be at risk may receive an intervention, while only about 1 in 10 patients will benefit from the intervention. This may have cost implications for the healthcare system. In practice, the prediction model would however predict a probability of dying for each patient. The question is at what threshold of probability, between 0 and 1, one would decide to withhold intervention when the possible harm or benefit is not known or measured.

4.4 Implication

It has been proposed that definitions and processes for measurements are standardised.[139] Perioperative mortality rate (POMR) has been recommended as an indicator of access to safe surgery and anaesthesia,[131] and is an important measure to understand and improve surgical outcomes.[2,140] POMR is listed as a Global Core Health Indicator by the World Health Organization (WHO)[120] as a service quality and safety indicator. POMR may be defined as all-cause death rate prior to discharge among patients having one or more procedures in an operating theatre during the relevant admission. The denominator is the total number of surgical procedures (or surgical volume as number of procedures per 100 000 population). Mortality has two components: death on the day of surgery and in-hospital mortality.[131] Neither the numerator nor the denominator are currently captured in the South African District Health Information System, a system capturing information from all public sector hospitals in South Africa. A recent data simulation study suggests that estimates of

institutional POMR can be produced by relatively small sampling of the surgical population, depending on the surgical procedure.[125]

Validating a clinical prediction model with all-cause postoperative in-hospital mortality as endpoint in geographically different populations, and in alternate levels of surgical care to where it was developed, can contribute to nationally representative estimation of postoperative death rate. Updating the risk-adjusted model in such diverse populations can be informative – resource allocation to areas of need is important during development of universal health coverage. Furthermore, postoperative death rates for specific procedures, e.g. the Bellwether procedures, can be benchmarked nationally with relatively small sample cohorts.

Information on risk-adjustment for an outcome that can be used in calculating nationally representative estimated values for an indicator used in global health evaluation, will probably contribute significantly in mapping the path to universal health coverage in South Africa.

Updating of the model after further external validation will make the prediction model more useful, since benchmarking exercises can then be applied. Benchmarking will imply standardisation of clinical care pathways for patients with similar risk, undergoing procedures carrying similar risk.

4.5 Future research

The global surgery movement has gained enormous traction in Africa since the publication of the results of the African Surgical Outcomes Study in the Lancet. South Africa is leading the way in pragmatic trials developed subsequent to ASOS.[141] Yet in our own country there is still much to learn on what and how to improve in perioperative care. Expanding the local investigator network, gathering data across sectors, and

interpreting and using that data to drive change and strengthen the healthcare system, should be priorities for South African clinicians. To enable this, however, a dataset of predictors that are appropriately defined and coded is crucial. External validation of the prediction model in different settings is needed. Such validation may expose the need for significant updating due to a problem with the quality of the prediction model as well as the characteristics of the validation cohort population.

Chapter Three: Development of a Patient-Centric Clinical Prediction Model for Cost in patients admitted for Elective Non-cardiac surgery to a South African private hospital

1 Introduction

The healthcare 'climate' in South Africa is rapidly changing, and the private healthcare sector, perceived as relatively well-resourced but overspending on delivery costs, is under increasing scrutiny.[142] It is important that, in this climate, healthcare providers participate in assessing and reporting on the value of healthcare they deliver. Value is the quality of care or outcome divided by the cost of healthcare delivery.[143] Anaesthesiologists can demonstrate value by being part of a perioperative team that shares outcomes.[144]

Some global advances have been made in challenging the perception that surgical care is expensive and only available to the affluent.[130] Preoperatively identifying patients at increased risk for high healthcare resource use may enable appropriate planning of allocation of resources for intra- and postoperative care.[87,145] It may also serve to identify patients in whom preoperative efforts such as aerobic exercise training may be a safe, feasible and cost-effective intervention.[146]

Defining predictors of outcome after surgery using variables derived from a preoperative self-assessment questionnaire has several advantages: the possibility of early risk stratification (if the questionnaire is completed as soon as the proposed surgery is discussed), obtaining more granular and detailed information, and by being 'patient-centric' – involving patients in decision-making and enabling the reporting of endpoints by patients after surgery (e.g. patient-reported outcomes measures).

Although this study does not attempt to report on value or cost-effectiveness, it is a step towards quantifying cost of surgery, and patient factors that influence cost in South Africa, from a clinical perspective. By quantifying the economic value of surgical procedures in the South African private sector, the information may be used to evaluate cost-effectiveness of surgery using appropriate outcomes measures such as disability-adjusted life years (DALYs).[46,116,147] This would be of benefit to plan delivery of universal health coverage to the larger South African population.[48,148]

1.1 Background

1.1.1 Healthcare resource use as surgical outcomes measures

There is an increasing understanding amongst clinicians that healthcare resource use plays an important part in clinical decision-making. It is also an important measure for patients, contributing to their part in shared decision-making, since it impacts on their expectations regarding time spent away from work recovering, the level of care to be anticipated, and the risk of paying for healthcare out of pocket. Often the impact of surgical interventions on an individual patient's socio-economic circumstances and home life is not fully recognized by clinicians.

Measures for healthcare resources use include length of stay (intensive care unit/hospital), healthcare costs and fitness for discharge/delayed discharge.[19]

1.1.2 Preoperative predictors

It is clear that preoperative risk factors play a role in postoperative outcome in general. Anaesthesiologists rely on diagnoses made by their surgical colleagues and primary physicians. The diagnoses may be captured in administrative data with the use of ICD10 codes. Accurate diagnosis is important for the reliability of risk prediction models. Certain co-morbid diseases may yet be undiagnosed in patients presenting

for surgery; e.g. obstructive sleep apnoea. Healthcare professionals other than anaesthesiologists may not have elicited risk factors specifically related to anaesthesia. The ASA PS classification as evaluated by an anaesthesiologist is in itself an important predictor for outcome. It is therefore important that the anaesthesiologist gather relevant reliable information on the medical history of the patient in a timely fashion. The earlier this information is available to the anaesthesiologist, the smoother and more efficient preoperative assessment can take place.

Reliable identification of risk factors with a self-assessment tool depends on the literacy of the patients in the study population. Literacy has important health implications and has been associated with health status and mortality. Doctors are often not aware of low literacy in a patient, and patients are often too ashamed to admit to it. Health literacy is defined as “the degree to which individuals can obtain, process, and understand basic health information and services needed to make appropriate health decisions.”[149] Powers et al reviewed the use of single-item questions to quickly identify limited health literacy and found some to be moderately effective (e.g. LR 5.0 if little confidence in filling out medical forms).[149] Including such an item in a questionnaire may identify patients requiring further engagement to ultimately ensure appropriate shared decision-making.

Logistically speaking, the options available to an anaesthesiologist regarding the taking of medical history are to do so during the first face-to-face consultation with the patient, to use a self-administered questionnaire before the meeting, or to have the questionnaire administered by a representative, such as a nurse in a preoperative clinic or an administrative person. It is important to take the history as soon as possible

after scheduling of the surgery, because this will determine the requirements regarding the rest of the preoperative evaluation and planning of perioperative care.

Anaesthesiologists in the South African private healthcare sector act on referral of patients from surgeons and often do not have direct patient contact until shortly before the procedure. Unfortunately, there are very few preadmission or preoperative clinics run by anaesthesiologists in South Africa, and communication between the healthcare team may be suboptimal. In order to demonstrate the cost-effective implementation of such clinics it is important that only patients at risk for poor postoperative outcome are seen at such a clinic: those undergoing high-risk surgery or those with high risk related to their preoperative health status. Thilen et al[150] evaluated the factors contributing to increased billing for preoperative consultation in (low-risk) cataract surgery. Although co-morbidities were associated with increased consultation, nonmedical factors contributed mainly to the phenomenon. This study highlights the importance of ensuring the cost-effectiveness and appropriateness of scheduled pre-operative consultation, particularly for low-risk surgery.

1.1.3 The potential of patient-generated data in preoperative assessment

The technological advances in wearable devices that allows ‘self-tracking’ of health-related measures, have resulted in patient-generated data on physical status and activity. Although it seems intuitively possible to use such data in preoperative screening, challenges regarding the quality of data remain.[151]

1.1.4 The preoperative anaesthesia questionnaire

A preoperative anaesthesia questionnaire may be useful in various ways – it can be used as a screening tool to alert anaesthesiologists of patient factors that can influence preoperative optimization, intra-operative care and outcome after surgery. Intra-

operative care can be tailored to individual patient needs at relatively short notice in most cases, such as managing the risk of postoperative nausea and vomiting. To understand and manage the risk of patients for an adverse outcome not specifically related to anaesthesia care only, such as morbidity due to surgical site infections, is not as straight-forward. Even where sufficient evidence exists to enable risk stratification of a patient for a particular outcome based on certain variables, timing of access to this information should allow for appropriate intervention aiming at risk modification. In this case, data from a completed preoperative questionnaire is most useful in planned or elective surgery.

In an editorial on 'Risk stratification, risk adjustment and other risks' by Orkin, published in *Anesthesiology,* he discusses the advantages and the disadvantages associated with using either clinical data or administrative data in identifying risk predictors.[5] Clinical data inherently already suffers from poor reliability (e.g. terminology poorly defined), lack of objectivity (e.g. biased or subjective information) and lack of completeness (missing data). Aylin, Bottle and Majeed[152] compared an administrative database with three clinical databases by using predictive models for three common procedures. These researchers found that the administrative database could predict death with comparable discrimination. They suggest that administrative and clinical databases should function together.

The problems with reliability, objectivity and completeness may be augmented when attempting to identify predictors from a survey or questionnaire completed by a patient. Part of such a survey may have been validated as a tool (see reference to for example STOP-bang), but it is unknown what the quality of data would be from administering a questionnaire in the South African population sampled by this study. It is also possible

that a different disease profile in a South African population may point to different predictors.

Although there are options available to anaesthesiologists to access administrative data from patients belonging to certain medical aid groups, comorbidities tend to be underreported in administrative data, as described by Quan et al, when clinical chart data and administrative data are compared.[153] For some individual comorbidity variables, the ability to predict in-hospital mortality is less reliable than the use of summarised scores.

It is not known what the impact will be of a study that involves the patient in a more structured fashion in preoperative communication with anaesthesiologists in the South African private healthcare setting, but this may point to the non-clinical influence on post-operative outcome, as referred to by Orkin.[5]

Grant et al evaluated the utility of guided self-assessment using an electronic questionnaire by comparing it to face-to-face interviews with an anaesthesiologist.[154] The authors concluded that self-assessment could produce quality health information. Boissonnault and Badke, two physical therapists, evaluated the accuracy of self-administered questionnaires in reporting important medical history by comparing self-assessment to responses received by an experienced healthcare practitioner and reports found in the medical record.[155] These authors found self-reporting to be accurate.

1.1.4.1 Self-assessment questions to identify and define predictors

There is evidence available on patient factors that may influence postoperative morbidity and mortality. How these predictors influence healthcare resource use, is not as evident, particularly from a clinician's perspective. It seems reasonable to

expect that, if risk stratification is done based on evidence of mortality and morbidity outcome, high-risk patients may need more resources to modify that risk. To use resources optimally, it may be more important to identify what is over-utilization of resources (where patient risk stratification does not warrant increased resource use). An example of such thinking are the current guidelines for preoperative testing – in general, 'less is more' regarding testing, unless individual patient risk factors warrant investigation to enable active management of the risk.

It is imperative when developing a prediction model to accurately define the variables. The definition must include the measurement scale of the variable; e.g. the duration of exposure to a variable may be more relevant than simply its presence in a model. Variables may also be coded categorically or combined to create a parsimonious model. What follows here is a discussion on predictors that may be defined from a self-assessment questionnaire.

1.1.4.1.1 Health status or physical status

1.1.4.1.1.1 American Society of Anaesthesiologists Physical Status (ASA-PS) classification

Since its introduction in 1941, the ASA physical status classification has been used widely as a basis for comparison of pre-operative health status.[156] The original seven classes were reduced to five in 1963, and further minor modifications made over the years:[157]

Table 8: ASA Physical Status classification

Class	Description
I	Healthy patient
II	Mild systemic disease - no functional limitation
III	Severe systemic disease - definite functional limitation
IV	Severe systemic disease that is a constant threat to life
V	Moribund patient unlikely to survive 24 h with or without operation
VI	A declared brain-dead patient whose organs are being removed for donor purposes

The risk for postoperative complications is mainly influenced by ASA PS III and IV,[157] so it is important to distinguish between ASA PS II and III.

Although there is variance in the ASA PS class assigned by different clinicians – particularly between clinicians from different specialities – it has been almost universally used as a predictor of postoperative outcome. It is included in the current ACS NSQIP data set but, according to certain ACS NSQIP authors, it is "inconsistently used" and "clinically imprecise".[158] These authors propose the use of ACS NSQIP-derived risk factors to validate ASA PS classification. The robustness of the ACS NSQIP database enables this exercise. This study demonstrated:

- Once again, a significant relationship between ASA PS and surgical outcomes
- A strong interdependence between ASA PS (itself a ACS NSQIP variable) and other ACS NSQIP variables
- The twenty most influential ACS NSQIP preoperative variables predicting ASA status, are in descending order of odds ratio:

Preoperative coma, dyspnoea at rest, preoperative impaired sensorium (according to the variable definition the patient is acutely confused and/or delirious), on ventilator, morbid obesity (Body Mass Index/BMI > 39 kg/m^2), totally dependent functional status, previous percutaneous transluminal coronary angioplasty, previous cardiac operation, current smoker, history of cerebro-vascular accidents without neurologic deficit, dyspnoea with moderate exertion, history of hypertension, insulin-dependent diabetes, COPD, orally treated diabetes, age (10-yr increment), low haematocrit, high white blood cell count, albumin < 3.5 mg/dL, obesity (25 < BMI < 39).

- A comparison of ACS NSQIP prediction with assignment by anaesthesiologists: “In general, the ACS NSQIP risk factors tended to upgrade assigned level Is to level IIs and tended to downgrade assigned level IVs to IIIs and level Vs to IVs and IIIs.”

However, the purpose of the ASA PS classification is less to predict surgical outcome, which is also dependent on other variables, than to create a common understanding of preoperative status and identify patients eligible for preoperative intervention. The anaesthetist would decide on ASA PS during the pre-operative consultation. Should the patient be graded ASA PS III, a decision would have to be made whether this risk was modifiable; that is, if surgery should be postponed while the systemic disease is being treated.

1.1.4.1.2 Fitness, functional status/performance/capacity

The objectives to classify activity / functional status/capacity / performance are as follows:

1. To classify functional status in the management and the monitoring of established cardiovascular disease; e.g. the New York Heart Association (NYHA) and Canadian Cardiovascular Society (CCVS) classification.
2. To classify functional disability in management and monitoring of diseases affecting mobility; e.g. rheumatoid arthritis.
3. To classify activity in monitoring and improving physical activity in geriatric patients; e.g. the LASA Physical Activity Questionnaire (LAPAQ).
4. To risk stratify patients during preoperative evaluation; e.g. the American College of Cardiologists/American Heart Association (AHA/ACC) and European Society of Cardiology/European Society of Anaesthesiology

(ESC/ESA) guidelines on perioperative evaluation and management in noncardiac surgery.[45,89]

Functional status, as assessed by the NYHA classification, varies because of the impact of not only cardiac disease but also environmental, social and psychological factors.[159] The New York Heart Association (NYHA) classification was developed to identify and communicate gross changes in severity of illness based on the assessment of limitations in physical activity as a result of cardiac disease. The NYHA is a valid measure for functional status, but not for functional performance or functional capacity. These concepts and their application are defined in a review on the use of the NYHA in research.[159] Patients' self-assessment of NYHA class has been shown to predict hospitalisations, quality of life and mortality.[160] It is argued that self-assessment of functional status may be the 'gold standard' for using such a complex tool, which is subject to inter-observer variability. *Functional performance* is the amount of function a person actually chooses to perform. The Specific Activity Scale (SAS) as designed by Goldman in 1981 aimed to define the approximate metabolic costs of a variety of activities. Bennett et al believes this scale to be an appropriate instrument for measuring functional performance.[159]

Functional capacity, which integrates cardiorespiratory, circulatory, and musculoskeletal function, is the difference between basal and maximal function. Activity level or exercise tolerance as determined by direct questioning is a subjective estimate of functional capacity.

Jette et al describe metabolic equivalents (METs) in the context of prescribing intensity level of exercise.[161] It is common to use 4 METs, or the ability to climb a flight of stairs to mark 4 METs, as a cut-off value for decision making. Byrne and colleagues question

the widespread use of the MET system as a scientific convention and review the variable definitions and application thereof.[162] These authors warn that it is important to use an expression of METs as it was intended; that is, as an activity classification system in survey research. Others have questioned the use of MET's terminology in cardiopulmonary exercise testing.[163]

Impaired preoperative functional capacity is associated with poor postoperative outcome.[164,165] Dosluoglu et al divided patients categorised as ASA PS III into two groups: one group was shown to achieve METs of 4 and greater and the other less than 4.[102] The latter group had significantly more severe comorbid disease and poorer postoperative outcome than the former.

The subjective evaluation of functional capacity was also defined by the Duke Activity Status Index (DASI) in 1989.[166] The DASI was adapted by the authors of the 2007 ACC/AHA and ESC/ESA guidelines on preoperative evaluation to allow risk stratification based on a cut off of 4 METs functional capacity.

Table 9: Duke Activity Status Index

Activity	Score
Take care of self (e.g. eating, dressing, bathing, using the toilet)	+2.75
Walk indoors	+1.75
Walk 1–2 blocks on level ground	+2.75
Climb a flight of stairs or walk up a hill	+5.5
Run a short distance	+8.0
Do light work around the house (e.g. dusting, washing dishes)	+2.7
Do moderate work around the house (e.g. vacuuming, sweeping floors, carrying in groceries)	+3.5
Do heavy work around the house (e.g. scrubbing floors, lifting or moving heavy furniture)	+8.0
Do yardwork (e.g. raking leaves, weeding, pushing a power mower)	+4.5
Have sexual relations	+5.25
Participate in moderate recreational activities (e.g. golf, bowling, dancing, doubles tennis, throwing a baseball or football)	+6.0
Participate in strenuous sports (e.g. swimming, singles tennis, football, basketball, skiing)	+7.5
Maximum	+58.2

The DASI was found to be valid in predicting capacity in COPD patients.[167] It has also been found to reliably predict capacity in patients with chronic kidney disease.[168] Arena et al, on the other hand, found the DASI to be of limited value in determining perceived functional capacity in heart failure patients.[169]

The DASI outperformed a Patient Reported Outcomes Measurement Information System (PROMIS) physical activity short-form in predicting results of exercise testing.[170]

Simple walk tests or cardiopulmonary exercise testing can give an objective estimate of functional capacity, identify ischaemia or arrhythmias, and estimate risk more accurately. On the basis of a meta-analysis by Kodama et al,[163] cardiopulmonary fitness was however not included as a predictor in the 2013 AHA/ACC Guideline on the Assessment of Cardiovascular Risk. The Measurement of Exercise Tolerance before Surgery (METS) study[171,18] results report on using the 6 minute walk test to

predict disability-free survival after major surgery.[172] It was found safe and compared well with cardiopulmonary exercise testing.

It is important to note that the DASI score required to identify patients at high risk of having poor cardiovascular outcome or other morbidity, has not been defined.[173] It still remains important to not rely only on a single predictor of outcome, but to identify how a combination of factors influence outcome (as defined in a prediction model).

In a review of the relationship between the inability to climb two flights of stairs and outcome after major noncardiac surgery,[174] Biccard points out that the selection of a test for functional capacity should be tailored to the clinical scenario and anticipated outcome. To prove the point, Biccard points out that the inability to climb two flights of stairs predicts outcome in thoracic surgery and in patients with comorbidity. It does not, however, predict the aerobic capacity to survive the stress response after major noncardiac surgery. Biccard argues that a screening test for aerobic capacity should allow for warm up and be of sufficient duration. Biccard also advocates for prospective comparison of a screening test with cardiopulmonary exercise testing.

Struthers et al compared the incremental shuttle walk test (ISWT), the Duke Activity Status Index (DASI) questionnaire and cardiopulmonary exercise testing (CPET) to assess fitness for surgery in patients presenting for general surgery.[175] Postoperative outcome was not considered because of the low mortality rate and insufficient sample power. Neither the ISWT nor the DASI distinguished adequately between low- and high-risk patients, as defined by a VO_2peak threshold of 15 ml O_2 kg^{-1} min^{-1}. Importantly, many patients that performed poorly with the DASI and ISWT had adequate functional capacity demonstrated with the CPET.

The Veterans Specific Activity Questionnaire categorises patients according to METs, and was validated in patients referred for exercise testing.[176]

Dronkers et al studied the association of *physical fitness and physical activity* with outcome after major scheduled abdominal surgery.[177] These authors defined functional status according to the WHO International Classification of Functioning, Disability and Health. This classification distinguishes between activity as reported by questionnaire and observed ability. These authors found the result of a questionnaire to be the strongest predictor of outcome in their study population of patients older than 59 years. The questionnaire used was the LASA Physical Activity Questionnaire (LAPAQ). This was derived from two other questionnaires on activity in older people compiled by the Longitudinal Aging Study Amsterdam (LASA).[178]

The ACS NSQIP and the American Geriatric Society (AGS) developed well-referenced guidelines for the optimal preoperative evaluation of the geriatric patient.[111] The societies developed a checklist on which the guidelines are based. These include attention to cognitive ability, depression, risk factors for developing postoperative delirium, alcohol and other substance abuse/dependence, cardiac evaluation according to the ACC/AHA algorithm for patients undergoing noncardiac surgery, risk factors for postoperative pulmonary complications, functional status, frailty score, nutritional risk, poly-pharmacy, goals and expectations, and family and social support system. The guidelines advocate use of a very simple screening instrument to determine which patients should receive further attention in this regard. The following questions are asked during assessment:

- Can you get out of bed or chair yourself?
- Can you dress and bathe yourself?

- Can you make your own meals?
- Can you do your own shopping?

If NO is the response to any of these questions, more in-depth evaluation should be performed, including full screening of activities of daily living.

The following points are part of the definition used for the ACS NSQIP variable "functional health status prior to surgery":[99]

- The patient's ability to perform activities of daily living (ADLs) in the 30 days prior to surgery is reported.
- The best functional status demonstrated by the patient within the 30 days prior to surgery is reported.

The levels are:

- Independent: The patient does not require assistance from another person for any activities of daily living.
- Partially dependent: The patient requires some assistance from another person for activities of daily living.
- Totally dependent: The patient requires total assistance for all activities of daily living.
- Unknown: If unable to ascertain the functional status prior to surgery, report as unknown.

1.1.4.1.3 Age

Comprehensive preoperative assessment in geriatric patients improves outcome.[179] The components of such an assessment reflect the areas of risk for poor outcome in

older patients and include severity of co-morbid conditions, nutritional status, cognition and mood, functional capacity and social circumstances and environment.

Turrentine et al used ACS NSQIP data for the University of Virginia Health System to assess the impact of increasing age on surgical mortality and morbidity.[180] The authors reached the conclusion that although several risk factors increase with age, age itself remains an important risk factor. There is an exponential increase in mortality and morbidity in relation to age. Mortality reached 6% in the decade after 80 years of age. The risk factors most frequently associated with poor outcome in this decade were shown to be hypertension, dyspnoea, diabetes, previous cardiac operation and smoking.

In a report on the ethical and legal aspects regarding anaesthesia for the elderly, White argues that healthcare to the elderly should be prioritised,[181] in order to lessen the impact of unnecessary poor outcome.

The ACS NSQIP and AGS guidelines[111] on assessment of the elderly recommend that cognitive ability is assessed with the Mini-Cog©, which is a face-to-face screening tool. Assessment of gait and mobility is suggested to be done with the Timed Up and Go Test (TUGT), and the frailty score is defined as follows:

Table 10: Frailty score

Criteria	Definition
Shrinkage	Unintentional weight loss ≥ 10 pounds past year
Weakness	Decreased grip strength
Exhaustion	Self-reported poor energy and endurance
Low physical activity	Low weekly energy expenditure
Slowness	Slow walking
The patient receives 1 point for each criterion met: 0 to 1, not frail; 2 to 3, intermediate frail (pre-frail); 4 to 5, frail.	

Kothari et al[182] identified questions from previously validated screening tools to predict outcome (length of stay and discharge destination) in geriatric thoracic surgery cases.

The screening tools used were the geriatric depression scale (GDS), the nutritional screening initiative nutritional health checklist (NSI NHC), the mini mental status exam (MMSE), the brief fatigue inventory (BFI), and activities for daily living (ADLs). The following questions had predictive value: dependency regarding “shopping” from the ADLs; “I have an illness or condition that made me change the type of food I eat”, “Without wanting to, I have lost or gained 10 pounds in the last 6 months” and “I am not always able to physically shop, cook, or feed myself” from the NSI NHC; “Have you dropped many of your activities and interests?” and “Do you feel pretty worthless the way you are now?” from the GDS.

1.1.4.1.3.1 Frailty

Frailty is an expression of population aging.[183] Two reviews reported on frailty assessment and assessment instruments in 2016.[184,185] The Lancet published a study on the development of a score using electronic records in 2018.[186] Frailty and the association with postoperative outcome has been investigated.[187–189] Frailty as assessed by a Risk Analysis Index (RAI) was shown to be associated with failure to rescue after low-risk and high-risk surgical procedures (risk for mortality <=1% or >1%, respectively).[190] The RAI is reported to perform better than other measures of frailty, and include measures for age, sex, cancer diagnosis, weight loss, renal failure, congestive heart failure, shortness of breath, chronic care facility status, cognitive deterioration, and functional status.

1.1.4.1.4 Diagnosed medical comorbidity

A group of authors published the result of a study to determine whether a self-administered questionnaire is beneficial in identifying medical comorbidities and patients at risk for adverse intra- and postoperative events after cataract surgery.[191] Most comorbidity predictors in this study are identified with direct questioning, such

as: “Do you have, or are you being treated for high blood pressure?” Angina is defined by “Within the past year, have you had chest pain or pressure with activity such as walking or climbing stairs?” COPD and asthma are combined as a diagnosis, with the defining question being “Are you currently being treated for asthma, emphysema, wheezing or bronchitis?”

In the South African context, continued exposure to comorbid disease may play a different role in determining postsurgical outcome from what is reported in international literature, possibly as a result of the lack of access to quality primary healthcare and risk modification. Biccard and Nepaul refer to this possibility in a report on a study of risk factors for intermediate (less than one year following surgery) and long-term (more than one year following surgery) mortality after vascular surgery.[192] In the multivariate analysis of their retrospective data, these authors found hypertension to be a predictor. In bivariate analysis hypertension and diabetes were found to be associated with intermediate- and long-term mortality. Wax et al found the magnitude of pre-induction systolic blood pressure in independent risk factors of postoperative myocardial infarction/injury and in-hospital mortality, particularly when it exceeded 200 mmHg.[193] However, hypertension is not consistently associated with poor cardiac outcome in perioperative literature and is not included in commonly used risk stratification tools. Recent studies investigated the relationship of preoperative hypertension with intraoperative haemodynamic changes and postoperative morbidity.[194,195]

The *Charlson score* was developed in 1987 from a cohort of 559 medical patients, and is often quoted in medical literature.[196] It has been used in specific disease states and surgical intervention types to predict postoperative survival.[16] It was, for example, compared with the ASA PS classification in urology, and the ASA PS classification was found to perform better as a predictor.[197] It was developed to classify prognostic

comorbidity in longitudinal studies of mortality. The comorbidities were weighted as seen in Table 11.

Table 11: Charlson weighted index of comorbidity

Weights	Conditions
1	Myocardial infarct
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumour
	Leukaemia
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumour
	AIDS

It is possible that comorbidities may be undiagnosed or inappropriately diagnosed at the time of preoperative assessment. In a paper on the utility of clinical risk predictors for cardiovascular risk prediction, Biccard and Rodseth argue that predictor performance may improve if it reflects "the degree of organ dysfunction rather than a historical diagnosis".[68] The diagnosis of chronic obstructive pulmonary disease (COPD), which may be an important predictor, may be as problematic as diagnosing heart failure – as referred to in the paper. COPD, defined as airflow limitation that is not fully reversible, is diagnosed with spirometry in patients suspected of having the disease after history taking and physical examination. Spirometry alone is not sufficient to make the diagnosis. In a systematic review of the diagnostic value of history and physical examination for COPD, Broekhuizen et al found that a history of dyspnoea (OR 0.9), wheezing (OR 0.9), previous consultation for wheezing or cough

(OR 0.86), self-reported COPD (LR 5.6), age (≥ 45 years; LR 1.5) and current and extensive (> 40 pack years) smoking (LR 11.7) had diagnostic value for COPD.[198] Only six studies were included in the systematic review, since several studies did not use the WHO GOLD (Global Initiative for Obstructive Lung Disease) criteria used in the review.

1.1.4.1.5 Cognitive function

Cognitive dysfunction may be an important preoperative predictor of postoperative cognitive dysfunction and may therefore influence economic outcome. Furthermore, the presence of cognitive dysfunction might affect the reliability of a self-assessment questionnaire.

In a brief review on practical preoperative cognitive screening tools,[199] Long, Shapiro and Leung allude to the significant influence that postoperative delirium has on outcome. The risk factors include cognitive impairment, sensory impairment, older age, ASA PS classification, low education level, psychotropic drug use, poor functional status, dehydration, medical comorbidities (especially cerebrovascular or other brain disease), electrolyte abnormalities, low albumin, and depression. Preoperative cognitive impairment is the strongest predictor and the authors sought a screening tool to identify this in the preoperative clinic.

According to the ACS NSQIP and AGS guidelines for assessment of the elderly, risk factors for postoperative delirium are:

- Cognitive and behavioural disorders – Cognitive impairment and dementia, untreated or inadequately controlled pain, depression, alcohol use, sleep deprivation.

- Disease- or illness related – severe illness or comorbidity, renal insufficiency, anaemia, hypoxemia.
- Metabolic – poor nutrition, dehydration, electrolyte abnormalities.
- Functional impairment – Poor functional status, immobilisation, hearing and vision impairment.
- Other – older age ≥ 70 years, polypharmacy of psychotropic medication, risk of urinary retention or constipation, presence of urinary catheter.

The Nomenclature Consensus Working Group published recommendations in 2018 to align the terminology used in postoperative cognitive dysfunction with that used in cognitive dysfunction in the general population.[200]

1.1.4.1.6 Risk of bleeding and thromboembolism

Arnold, Anderson and Kearon[201] stress that personal and family history are the most important assessments of the patient's individual risk for bleeding and thromboembolism with surgery. Patients taking antiplatelet and/or anticoagulation medication are at risk for surgical bleeding. The ACS NSQIP definition for the variable "bleeding disorders" include patients with any condition that places the patient at risk for excessive bleeding requiring hospitalisation due to a deficiency of blood clotting elements (e.g., vitamin K deficiency, haemophilia, thrombocytopenia, chronic anticoagulation therapy that has not been discontinued prior to surgery.) Patients are not included who are on chronic aspirin therapy.[99]

1.1.4.1.7 Human immunodeficiency virus

In a prospective South African study, Redman et al found that although HIV-positive patients presenting for vascular surgery were younger and had fewer risk factors according to the Revised Cardiac Risk Index, these patients had similar cardiovascular

outcomes to HIV-negative patients.[202] The authors suggest that alternative clinical risk predictors for cardiac outcomes be developed for HIV-positive patients.

In a group of HIV-positive patients assessed for ASA PS classification and CD4 count, Penfold and Lundgren found that severely immune-compromised patients were classified in low-risk ASA PS categories.[203]

1.1.4.1.8 Metabolic syndrome

Obesity, contrary to what is expected, has been shown to be associated with a lower risk of mortality after surgery, but metabolic syndrome impacts negatively on postoperative outcome.[204] Truncal obesity, insulin resistance, dyslipidaemia and hypertension characterise the metabolic syndrome. The modified metabolic syndrome is defined as the presence of obesity, hypertension and diabetes.[204] Although the presence of the syndrome alerts the anaesthetist to specific areas of risk management and intervention, data on best practice is scarce, according to a review published in the British Journal of Anaesthesia.[205] Reports have been published that identify the metabolic syndrome as a predictor for postoperative complications after urological procedures.[206] The definition of metabolic syndrome varies, but at least three factors should be present. These factors are defined by measurements (waist circumference or waist-hip ratio; blood pressure) or biochemical markers (dyslipidaemia, hyperglycaemia). It is estimated that the incidence of obesity may be as high as 34% in certain populations. Metabolic syndrome has been linked to, amongst others, colorectal cancer, so it is possible that the incidence in surgical populations is high. One study reported a 49% incidence of metabolic syndrome in patients undergoing cardiothoracic surgery.[205]

1.1.4.1.9 Postoperative nausea and vomiting

The complications from postoperative nausea and vomiting are seldom life threatening, but may have a significant impact on patient satisfaction and economic measures, particularly regarding unplanned admission in day-case surgery. Several risk scores exist to predict PONV, but limited agreement exists between the scores. None of the scores are based only on patient risk factors such as gender, history and smoking.[207]

1.1.4.1.10 Infectious processes

Sepsis in hospitalised patients is associated with poor postoperative outcome. The patient from the community (that is, not hospitalised when the decision is taken to perform surgery) that presents for elective surgery may have a bacteraemia that may influence the outcome after surgery; e.g. urinary tract infection in a patient presenting for hip replacement. Subjective fever is not an accurate predictor of bacteraemia (positive LR 1.0), but the reporting of chills, particularly shaking chills (positive LR 4.7) may be more predictive.[208]

1.1.4.1.11 Palpitations and cardiac arrhythmia

Palpitations occur in up to 16% of the population.[209] They can be associated with clinically significant cardiac arrhythmia in at least 20% of patients, depending on the presence of cardiac disease. Most demographic and historical features do not influence the likelihood of clinically significant arrhythmia. With recurrent palpitations prolonged electrocardiographic monitoring is indicated.

1.1.4.1.12 Dyspnoea

In a review on patients with lung disease, dyspnoea is discussed in detail.[108] It has been defined as the ‘‘subjective experience of breathing discomfort that consists of

qualitatively distinct sensations that vary in intensity.'' It can be caused by cardiovascular conditions, pulmonary conditions or conditions such as anaemia, renal failure or neuromuscular disease. Dyspnoea may be intermittent (e.g. with asthma), recurrent (e.g. with CHF), or persistent (e.g. with COPD or interstitial lung disease) and may be influenced by body position (e.g. supine, lateral, or upright). Night-time orthopnoea typically occurs in patients with CHF, obstructive sleep apnoea, gastro-oesophageal reflux disease (GERD), or asthma.

On the basis of the Modified Framingham Criteria for heart failure,[210] a patient can be diagnosed with heart failure if he or she admits to either orthopnoea or paroxysmal nocturnal dyspnoea (major criterion) plus two of the minor criteria: ankle swelling, night cough or dyspnoea on exertion. The absence of dyspnoea on exertion (LR 0.48), orthopnoea (LR 0.65) and paroxysmal nocturnal dyspnoea (LR 0.70) decreases the likelihood of heart failure.[211]

1.1.4.1.13 Depression and chronic pain

Preoperative depression has been associated with postoperative delirium, cognitive dysfunction and increased postoperative morbidity and complications.[212] The association of postoperative depression with certain surgical procedures has also been studied. According to Williams,[213] screening for depression with a single question is appropriate during preventative medicine consultations and in response to triggers that increase the likelihood of depression. Patients with chronic pain are at high risk for depression.[214]

1.1.4.1.14 Nutritional status

The European Society for Parenteral and Enteral Nutrition (ESPEN) published a Nutrition Risk Score (NRS) as a screening tool in 2002.[215] Schiesser et al evaluated

the use of the NRS to predict the risk of nutritional complications in gastrointestinal surgery.[216] Patients with higher nutritional risk scores developed significantly more and severe postoperative complications and had a significantly longer hospital stay.

Nutritional risk is evaluated by assessment of nutritional status and severity of disease. Nutritional status is evaluated by body mass index (BMI < 20.5), recent weight loss, and food intake during the week before admission. Regarding severity of disease, this is scored from 1 to 3. If any nutritional status risk factor is present and the patient is severely ill, a further more detailed scoring is done. An age of ≥ 70 years then contributes to the nutritional risk, while a lower BMI (< 18.5) increases the score.[215]

1.1.4.1.15 Alcohol use

Harris et al used the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) as a screening tool in determining the association of the score with postoperative complications in joint replacement in men.[217] The AUDIT-C asks three simple questions, with the score ranging from 0-12:

> "How often did you have a drink containing alcohol in the past year?"
>
> "How many drinks did you have on a typical day when you were drinking in the past year?"
>
> "How often did you have six or more drinks on one occasion during the past year?"

According to Talley and O'Connor,[218] positive scores for unhealthy or excess drinking are:

- Three or more for women (73% sensitivity; 91% specificity)
- Four or more for men (86% sensitivity; 89% specificity)

The definition for alcohol use as a risk factor in the ACS NSQIP database[99] is the patient's admission to more than two drinks per day in the two weeks before admission.

1.1.4.1.16 Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) increases perioperative morbidity significantly.[219] A STOP-BANG score ≥ 3 is associated with a higher rate of ICU admissions.[220] The diagnosis of obstructive apnoea (OSA) is done with polysomnography. However, patients are reluctant to be admitted for this procedure. The STOP questionnaire was developed as a screening tool for OSA.[221] Without the use of this tool, OSA may remain undiagnosed. The STOP-BANG score includes more variables and is more sensitive:[222]

1. Snoring: do you snore loudly (loud enough to be heard through closed doors)? Yes/No

2. Tired: do you often feel tired, fatigued, or sleepy during daytime? Yes/No

3. Observed: has anyone observed you stop breathing during your sleep? Yes/No

4. Blood pressure: do you have or are you being treated for high blood pressure? Yes/No

5. BMI: BMI more than 35 kg/m2? Yes/No

6. Age: age more than 50 years old? Yes/No

7. Neck circumference: neck circumference greater than 40 cm? Yes/No

8. Gender: male? Yes/No

The validity of the STOP-BANG was assessed [223] and found to have fair construct validity when compared to scores such as the ASA PS classification and Charlson Comorbidity Index, but it did not predict postoperative outcome.

The ability of the Berlin questionnaire to predict the presence of OSA has also been assessed.[2245] The questionnaire does not incorporate age, male gender or neck circumference.

1.1.4.2 Predictors

The combination of questions used to define predictors are listed in Table 12. Predictor definitions were changed during model specification to reflect the scale of measurement most appropriate for inclusion in the prediction model. These changes may not be reflected in the Table. Single questions serving to define variables are not listed in the Table. The questionnaire used to define predictors is attached as an appendix to the thesis.

Table 12: Use of self-assessment questions to define predictor variables

Variable	Definition	Question(s)	Scale
Age	Date of birth; ID		Continuous
Gender	Male/Female		Nominal
Frailty[111]	1 = if age >=65 AND (Activities of daily living low + 'yes' to 'When going up the stairs between two floors, do you have to rest in between?'+Depression+ Weight loss) >=2	Can you get out of bed or chair yourself? Can you dress or bathe yourself? Can you make your own meals? Can you do your own shopping or sweep the floor? Can you paint a room or mow the lawn? When going up the stairs between two floors, do you have to rest in between? Have you been feeling sad or depressed much of the time? Have you lost weight or decreased your dress size in the past 6 months, without dieting?	Nominal
BMI	Body mass index as calculated by height in metres divided by mass in kg squared.	What is your weight? What is your height?	Continuous
Questionnaire reliability[149]	Health literacy as measured by confidence in filling forms 0 = Extremely confident 1 = Quite confident 2 = Somewhat confident 3 = A little confident 4 = Not at all confident	How confident are you in filling out medical forms by yourself? Not at all confident A little bit confident Somewhat confident Quite confident Extremely confident	Ordinal
Patient incompletely informed about the procedure[89]	The patient does not know how to prepare for the procedure, what to expect in the operating theatre, what to expect postoperatively in hospital, or what to expect and how to care for him/herself after discharge from hospital. Yes = 0; No = 1; Unsure = 2	Are you satisfied with the information you have received about what to do and what to expect before, during, after the operation, and after discharge? Options: yes, no, or unsure.	Nominal
Cognitive dysfunction[225]	The patient is unable to complete the questionnaire himself or herself, **and** the person filling in the form responds "no" to the question Yes = 0; No = 1	Does the patient have the mental ability to complete the form?	Nominal
ADL: low[111]	Activities of daily living 0 = if 'yes' to all of the questions 1 = if 'no' to any of the first four questions AND 'no' to the last question	Can you get out of bed or chair yourself? Can you dress or bathe yourself? Can you make your own meals? Can you do your own shopping or sweep the floor?	Nominal

Variable	Definition	Question(s)	Scale
		Can you paint a room or mow the lawn?	
ADL: cause	1 = If activity status low = 1 **and** 'Yes' to joint, bone or back problems 2 = If activity status low = 1 **and** 'Yes' to difficult breathing 3 = If activity status low = 1 **and** 'Yes' to pain, pressure or discomfort in your chest, neck or arm 4 = Other reason	Can you not do any of these because of joint, bone or back problems? Can you not do any of these because of difficulty breathing? Can you not do any of these because of pain, pressure, or discomfort in your chest, neck or arm? Can you not do any of these because of a reason not mentioned here?	Nominal
ASA PS self-assessment[226]	Physical status self-assessment as reported by the patient, based on the ASA PS classification. The categories are defined as follows: 1 = ASA I healthy patient 2 = ASA II mildly affected patient 3 = ASA III severely affected patient 4 = ASA IV threat to life	Are you healthy? OR Have you been suffering from a disease for longer than a few months? If yes, Does the disease affect your daily life only mildly; that is, you can continue with your daily life as previously? OR Does the disease affect your daily life severely; that is, the disease does not allow you to continue with your daily life as previously? OR Is the disease a constant threat to life; that is, the disease is so severe that you must stay in bed to survive?	Ordinal
Indication for surgery: effect	0 = 'no' to the question 1 = 'yes' to the question	Is the disease(s) mentioned above the reason for having the operation?	Nominal
Severity of acute diagnosis	Equals self-assessment score if indication for surgery=1, otherwise = 0	As above	Ordinal
Activity status count	Adopted from Duke's Activity Status Index. Higher score = higher activity status to a maximum of 23.45: Take care of self (e.g. eating, dressing, bathing, using the toilet) +2.75 Walk indoors +1.75 Walk 1–2 blocks on level ground +2.75 Climb a flight of stairs or walk up a hill +5.5 Do light work around the house (e.g. dusting, washing dishes) +2.7	Can you dress or bathe yourself? Can you get out of bed or chair yourself? Can you make your own meals? Can you climb two flights of stairs without stopping?	Continuous

Variable	Definition	Question(s)	Scale
	Do moderate work around the house (e.g. vacuuming, sweeping floors, carrying in groceries) +3.5 Do yardwork (e.g. raking leaves, weeding, pushing a power mower) +4.5	Can you do your own shopping or sweep the floor? (2.7 +3.5) Can you paint a room or mow the lawn?	
HT: Diagnosed[192]	If yes, duration in months since diagnosis.	Do you have high blood pressure? If yes, since when?	Continuous
HT: Treatment[13]	Does the patient take the medication regularly? Yes = 0; No = 1	Do you take medication for high blood pressure regularly?	Nominal
Ischaemic heart disease: diagnosed	Duration in months since first of any of events.	Have you ever been told that you have a problem with the blood supply to your heart? If yes, when? Have you ever had a heart attack? If yes, when? Have you ever received a stent in the blood supply to your heart? If yes, when? Have you ever had a bypass or surgery of the blood supply to your heart? If yes, when?	Continuous
IHD: most recent event	Months since most recent MI, stent or bypass		Continuous
Cardiac failure: Diagnosed[101]	If yes, months since diagnosis.	Have you ever been told that you have a weak heart? If so, when?	Continuous
Valvular heart disease	0 = if 'no' to all questions 1 = if 'yes' to any of the questions.	Do you have an abnormal heart valve? Have you had surgery to a heart valve? Have you had rheumatic fever?	Nominal
Important arrhythmia[209]	If yes to palpitations **and** valvular heart disease+cardiac failure+ischaemic heart disease < 1 and no to questions = 0 If yes to palpitations **and** valvular heart disease+ cardiac failure+ ischaemic heart disease ≥ 1 **or** yes to any question = 1	If yes, have you felt dizzy or blacked out when this happens? Have you been diagnosed with abnormal heart rate or rhythm? Do you have an implanted pacemaker or defibrillator?	Nominal
Cardiovascular and neurological alarm[218]	0 = 'No' to all questions 1 = 'Yes' to any question	Have you had blackouts without warning? Have you felt dizzy or blacked out when exercising? Do you have any weakness or numbness in your arms or legs?	Nominal
Framingham heart failure[210]	1 = if 'yes' to either of the first two questions **and** 'yes' to two of the last three questions.	Do you wake up at night because of difficulty breathing? Do you get short of breath when lying flat on your back?	Nominal

Variable	Definition	Question(s)	Scale
	0 = Other than 1	Do your ankles or legs swell? Do you get short of breath when climbing stairs? Do you wake up coughing at night?	
Vascular system compromise[57]	0 = if 'no' to all questions 1 = if 'yes' to symptoms 2 = if 'yes' to diagnosis or surgery (Enter highest number related to 'yes' answer)	Do you have pain in the muscles of your legs during exercise? Do you have cold or blue hands or feet? Have you been diagnosed with disease of the large blood vessels such as the aorta? Have you had surgery to the large blood vessels?	Ordinal
Lung disease	0 = if 'no' to all questions 1 = if 'yes' to previous consultation 2 = if 'yes' to symptoms in last month 3 = if 'yes' to hospitalisation 4 = if 'yes' to home oxygen (Enter highest number related to 'yes' answer)	Have you ever had to see a doctor for lung problems of any kind? If yes, have the lung problems affected you during the last month? Have you ever been admitted to hospital for any lung problems? Are you using oxygen at home?	Ordinal
Current smoker in the past year	0 = 'no' to question 1 = 'yes' to question	Have you been smoking cigarettes in the past year?	Nominal
Pack years smoking	If 'yes' to current smoking and 'yes' to previous smoker then number of packs of cigarettes per day times the number of years the patient has been smoking.	Did you smoke before but stopped? How many years have you been smoking/did you smoke? How many cigarettes per day do you smoke/did you smoke?	Continuous
HIV	If 'yes', duration in months since diagnosis	Do you have HIV? If yes, since when?	Continuous
History of tuberculosis	Previous treatment for tuberculosis Yes = 1; No = 0	Have you ever been treated for tuberculosis?	Nominal
History of malignancy	0 = No to all questions 1 = Previous cancer surgery 2 = Previous chemo- or radiation therapy 3 = Current chemo- or radiation therapy 4 = Metastatic cancer If yes to more than one question, the highest ordinal number for a question where the answer 'yes' is entered.	Have you ever been told you have cancer? Have you ever had an operation for cancer? Have you ever received medication or radiation for cancer? Are you currently receiving medication or radiation for cancer? Have you been told that the cancer is not under control, or has spread?	Ordinal
History of renal dysfunction[101]	0 = No to all questions 1 = Previous renal dysfunction (acute)	Have you ever had any kidney problems? Do you currently have kidney problems?	Ordinal

Variable	Definition	Question(s)	Scale
	2 = Current renal dysfunction (chronic) 3 = Previous dialysis 4 = Current dialysis If yes to >1 question, highest ordinal number for question where answer 'yes' entered.	Have you ever received dialysis? Are you currently receiving dialysis?	
History of liver disease	0 = No to all questions 1 = Jaundice episode as an adult or previous diagnosis liver disease 2 = Current liver disease symptoms 3 = Cirrhosis	Have you ever had jaundice (yellow skin or eyes) as an adult? Have you been told that you have a liver disease? Do have symptoms of the liver disease at the moment? Do you have scarring of the liver or long-term liver damage?	Ordinal
Hypercholesterolemia: diagnosed	If yes, duration in months since diagnosis.	Do you have high cholesterol? If yes, since when?	Continuous
Hypercholesterolemia: management	Duration in months of therapy.	Do you use medication for the high cholesterol? If yes, for how long?	Continuous
Metabolic syndrome risk	Are you fat around the waist? DM: diagnosed; HT: diagnosed Hypercholesterolemia: diagnosed If < 3 of variables listed = 0 If 'yes' to question and >1 variables = 1 If 'no' to the question and 3 variables = 1	Are you fat around the waist?	Nominal
DM: diagnosed	If yes, duration in months since diagnosis.	Do you have diabetes (high blood sugar)? If yes, since when?	Continuous
DM: requiring insulin	If yes, duration in months of insulin therapy.	Do you use insulin for the diabetes (high blood sugar)? If yes, for how long?	Continuous
Nutritional risk	0 = If 'no' to all of the questions. 1 = If 'yes' to any of the questions or BMI < 20.5 2 = if 'yes' to weight loss or BMI < 18.5 3 = If 'yes' to weight loss or BMI < 18.5 **and** age ≥ 70 years or major surgery	Have you eaten less than usual or changed your eating habits in the past two weeks? Have you lost weight or decreased your dress size in the past six months, without dieting?	
VTE risk	0 = if 'no' to all questions and variables other than below 1 = if 'yes' to any question or: Age ≥ 60 years ADL status other than 0 History of malignancy other than 0 Pregnancy other than 0 BMI ≥ 30	Have you had a blood clot in the deep veins or in your lung previously? Do you take female hormones, the pill, or do you receive any contraceptive injections? Do you have a disease that causes your blood to clot abnormally fast?	Nominal

Variable	Definition	Question(s)	Scale
	HIV other than 0	Have you been diagnosed with inflammatory bowel disease?	
Bleeding risk	0 = if 'no' to all questions 1 = if 'yes' to any of the questions.	Do you use any medication to make the blood thin? Do you have a disease that prevents your blood from clotting?	Nominal
Cerebrovascular incidents	0 = if 'no' to all questions 1 = if 'yes' to transient weakness/blindness 2 = if 'yes' to stroke	Have you suffered from short-lived weakness in your arms or legs, or short-lived blindness? Have you had a stroke?	Ordinal
Depression and chronic pain [213]	Depression: 0 = if 'no' to all questions 1 = if 'yes' to question, and 'no' to chronic pain Depression and chronic pain: 1 = if 'yes' to depression question and 'yes' to chronic pain Depression and chronic pain on treatment: 1 = if 'yes' to taking medication	Have you been feeling sad or depressed much of the time? Are you in constant pain for any reason? If yes, are you taking medication?	Nominal
Upper GIT dysfunction	0 = if 'no' to all questions 1 = if 'yes' to any of the questions.	Do you get heartburn? Do you have any difficulty in swallowing?	Continuous
Airway risk	0 = if 'no' to all questions 1 = if 'yes' to any of the questions.	Do you have any narrowing in your mouth, throat, or air pipe that makes your breathing difficult or noisy? Are you aware of any difficulty to place a tube into your windpipe to help your breathing during a previous operation?	Nominal
OSA: risk[224]	0 = Fewer than three of the following: 'Yes' to any of the questions HT: diagnosed = > 0 BMI≥ 35 Age ≥ 50 years Male gender 1 = 3 or more of the factors/questions 'Yes'	Do you snore loudly? Do you often feel tired, fatigued, or sleepy during daytime? Has anyone seen you stop breathing during sleep?	Nominal
OSA: diagnosis	Obstructive sleep apnoea previously diagnosed. If 'yes' to question, duration in months.	Has a doctor diagnosed you with sleep apnoea? If yes, when?	Continuous
Alcohol use[218]	0 = if score < 3 in women, < 4 in men 1 = if score 3 to 6 in women, 4 to 7 in men 2 = if score 6 to 9 in women, 7 to 10 in men 3 = if score > 8 in women, 10 and more in men	How often did you have a drink with alcohol in the past year? 0 = Never 1 = Monthly or less 2 = Two to four times a month	Ordinal

Variable	Definition	Question(s)	Scale
		3 = Two to three times a week 4 = Four or more times a week How many drinks did you have on a typical day when you were drinking in the past year? 0 = None, I do not drink 0 = 1 or 2 1 = 3 or 4 2 = 5 or 6 3 = 7 to 9 4 = 10 or more How often did you have six or more drinks on one occasion in the past year? 0 = Never 1 = Less than monthly 2 = Monthly 3 = Weekly 4 = Daily or almost daily	
History of perioperative anaesthesia-related complications	0 = none 1 = if the patient answers 'yes' to any of the questions.	Have you had an abnormal reaction to an anaesthetic? Are you aware of any difficulty to place a tube into your windpipe to help your breathing during a previous operation? Have you ever had nausea and/or vomiting after surgery? Have you ever had prolonged confusion after surgery? Did you have an unexpected blood transfusion after surgery? Were you ever admitted to ICU unexpectedly after surgery? Were you ever in hospital for longer than expected after an operation?	Nominal
Anaesthetic family history	0 = none 1 = if the patient answers 'yes' to any of the questions.	Do you have a family history of any of the following: Someone died because of anaesthetic problems Someone stayed in hospital for longer because of anaesthesia problems Malignant hyperthermia Scoline Apnoea Porphyria	Nominal

1.2 Aim

To determine which patients presenting for elective non-cardiac surgery are at higher risk for increased healthcare resource use during hospitalisation in a South African private hospital, by developing and internally validating a clinical prediction model or -models.

1.3 Objectives

To develop a clinical prediction model for in-hospital cost after surgery

To develop a clinical prediction model for length of hospital stay after surgery

To develop a clinical prediction model for intensive care stay after surgery

To perform a sub-analysis of type of surgery categories regarding in-hospital cost after surgery

2 Methods

The data to develop a clinical prediction model was collected, for this purpose, at a large private hospital in South Africa during the last six months (July to December) of 2015. Ethics approval for this prospective observational study was obtained from the University of Pretoria, Faculty of Health Sciences Research Ethics Committee. Permission for the study to be conducted was obtained from the hospital manager and the relevant hospital group's Research Operational Committee.

All data were analysed using Stata®/IC 15.1 for Windows, StataCorp LLC, Texas, USA.

2.1 Source of data and participants

Patients 18 years and older presenting to the preadmission administration area for an elective non-cardiac, non-obstetric surgical intervention were eligible for recruitment to the study. Obstetric patients were excluded because of the healthier profile of women of child-bearing age. Data on preoperative variables was prospectively collected from a cohort of patients scheduled for elective non-cardiac disease using a self-assessment questionnaire. Patients were provided with information and consent was implied with completion of the questionnaire. The requirement for written consent was waived. Screening for eligibility took place with the aid of an electronic screening tool that contained questions to determine age of the patient, and whether the scheduled intervention is elective, non-cardiac, and non-obstetric. Patients had a choice to complete the preoperative measurement instrument either as a paper-based- or electronic self-assessment questionnaire. Pilot testing of the questionnaire was performed. The information sheet and form for the printed questionnaire is attached as an Appendix.

In-hospital outcomes data and procedural data was obtained from the hospital database using South African identity number as identifier. The outcomes and procedural data was temporally linked with the completion of the preoperative questionnaire. No data on perioperative care processes or interventions was collected.

Data was stored and managed electronically using REDCap software[138] installed on a Safe Surgery SA[227] server.

2.2 Outcomes

Primarily this study set out to develop a prediction model, based on thirty-nine potential preoperative predictors/determinants (derived from a 141-item self-assessment

questionnaire to be administered preoperatively) of length of stay following surgery in a patient population undergoing elective non-cardiac procedures. (*A priori* primary outcome was defined as length of hospital stay, and secondary outcomes were cost of hospital admission, admission to critical care, critical care length of stay, and postoperative in-hospital mortality).

Predictive models for the outcomes of interest employed regression techniques:

1. Hospital cost outcome analysis was first done using the continuous outcome and linear regression, followed by model development using a binary outcome and logistic regression.
2. Length of hospital- and critical care stay employed Poisson regression
3. ICU admission and mortality employed logistic regression

Post hoc the possibility to use univariate predictor associations for LOS, ICU admission and mortality to assist in identifying candidate predictors for the final model to be developed (which used cost as primary outcome) was explored.

Cost of hospital admission was defined as total cost billed by the hospital minus the fees and prostheses, which reflect the cost risk that the hospital service provider carries (e.g. drug/dispensary costs, disposable costs and other additional costs). Adjustment was made for surgical risk by dividing this cost by the total Work Relative Value Units published in the Complete Current Procedural Terminology for South Africa (CCSA) as associated with the particular procedural codes.

Post hoc a binary outcome was created - high cost cases being those with log transformed adjusted cost of equal to and more than the mean of the transformed variable plus one standard deviation.

2.3 Predictors

Clinical judgment was used to define variables from a self-assessment questionnaire (Table 12) and in selecting potential candidate predictors during data inspection. The potential predictors were coded according to the most relevant clinical evidence on risk factors for adverse postoperative outcomes in general.

2.4 Sample size and missing data

By convention, adequate sample size for regression is 10 – 15 (patients) procedures per predictor/determinant; i.e. at most 460 – 690 for this study. For logistic regression, to achieve an event per variable rate of 10, no more than 13 variables or categories of variables should be entered during model specification.

An “available case analysis” was performed while analysing predictors, and no imputation was done for missing data. The number of records with missing data in predictors are reported in Table 14 and 15.

2.5 Statistical analysis

Categorical variables were described as proportions and compared using Fisher’s exact test. Continuous variables were described as mean and standard deviation, or median and interquartile range (IQR), and compared using t-tests.

After data inspection, coding was adjusted to combine or collapse categories within variables where the incidence in different categories was low. Patient variables were not considered candidate predictors if the incidence were low in the sample population, it showed no association with the outcome during univariate regression, and/or the clinical significance of the predictor was judged to be low (Table 13).

Table 13: Definitions and frequency of variables not considered as predictors.

Variable	Missing n	Frequency n/N (%)	Proportion (95% Confidence Interval)
Recent IHD diagnosis/event	0		
Within the past 3-6 months		2 (0.26)	0.002 (0.001-0.010)
Within the past 3 months		2 (0.26)	0.002 (0.001-0.010)
Liver disease	0		
Diagnosed		8 (1.04)	0.010 (0.005-0.021)
Symptoms		2 (0.26)	0.002 (0.001-0.010)
Scarring or damage		5 (0.65)	0.006 (0.003-0.015)
Framingham heart failure criteria	0	21 (2.72)	0.027 (0.018-0.041)
Hyperthyroidism	1	12 (1.56)	0.015 (0.009-0.027)
Home O_2	0	3 (0.39)	0.004 (0.001-0.012)
Metastatic cancer	0	10 (1.30)	0.013 (0.007-0.024)
Previous or current dialysis	0	12 (1.55)	0.015 (0.009-0.027)

The univariate association of cost with each of the determinants was assessed. Stepwise forward logistic regression was then employed to select variables after univariate testing was done on all variables at a significance level of 0.05. Variables were tested for collinearity during stepwise logistic regression. Certain variables were significant when coded either as continuous or binary, e.g. time since diagnosis of hypertension versus diagnosed hypertension. The decision on which coding to use was made based on the difference either coding type made to model performance. Variables were sequentially dropped from the model during repeated regression analyses at P>0·050.

Type of surgery was inferred from the Current Procedural Terminology codes captured by the hospital administration.

The indication for surgery was inferred from the ICD10 code linked to the CPT codes as non-communicable disease, infection or trauma.

Severity of surgery was categorized as minor (<30 min), intermediate and major (>=90 minutes according to duration of the procedure). Changes were made to the classification after inspection of the associated procedural codes.

The clinical prediction model was developed for the primary outcome of cost using logistic regression technique. The model performance was evaluated for discrimination by determining the area under the Receiver Operating Curve (AUROC), or c-statistic, with 95% confidence intervals, and for calibration by plotting observed against expected outcome with LOWESS (locally weighted scatterplot smoothing). A decision-curve analysis was performed. The model was internally validated (using the same data set) using 50 repetitions of a bootstrap sample.

3 Results

3.1 Participants

Patients admitted more than twenty-four hours prior to surgery were excluded. Cases with missing data in outcomes or more than 10% in predictors were excluded. Two cases were excluded based on exclusion criteria for surgical procedures (cardiac or obstetric surgery). Extreme values for total cost in Rand per Work Relative Value Unit were excluded before univariate analysis (based on clinical interpretation) and the associations with other outcomes were described. The final sample population size was 770 cases. There were 142/770 (18.44%) cases identified with the outcome.

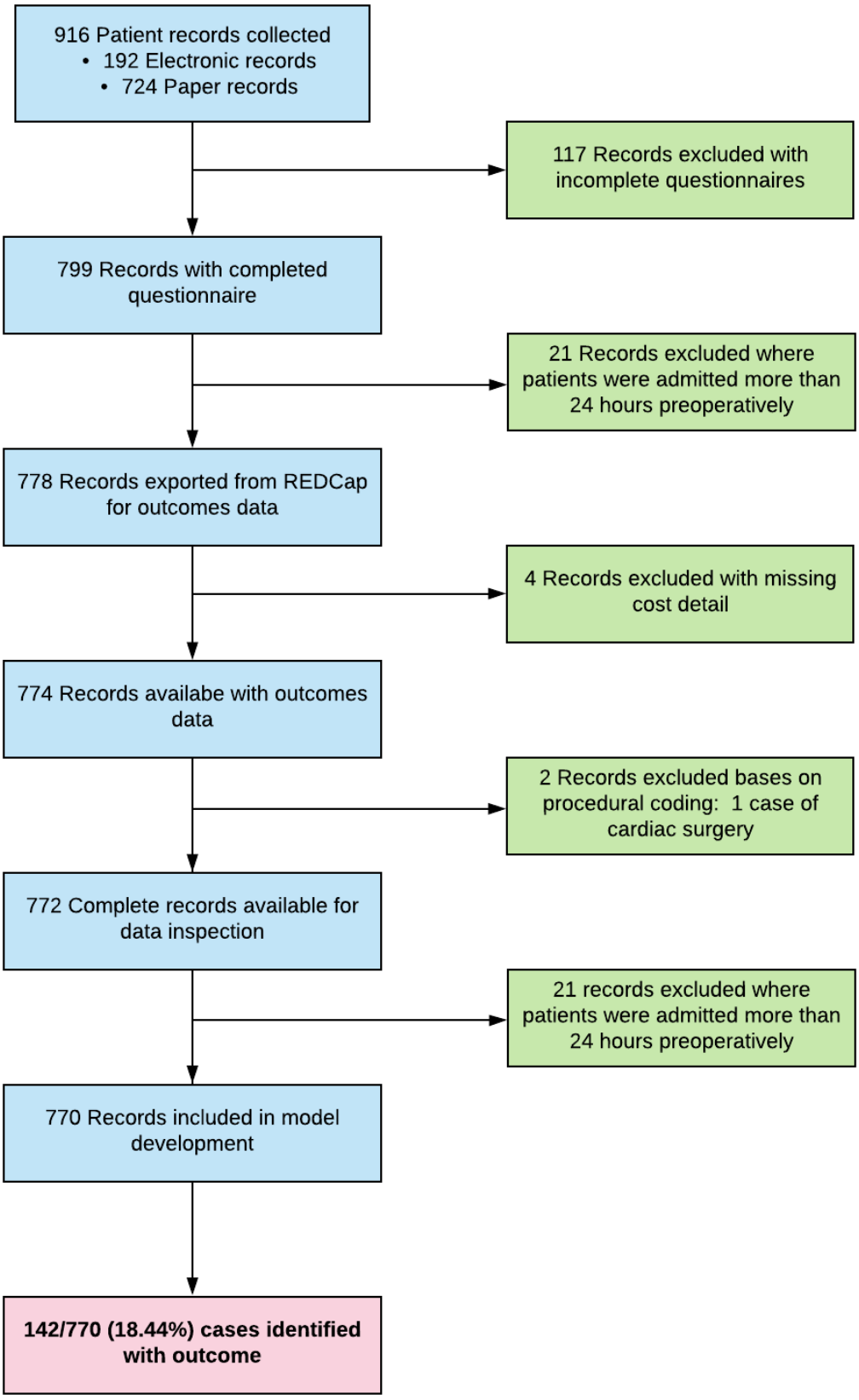

Figure 11: Diagram illustrating flow of patients through the study

The characteristics of the participants are described in Table 14.

Table 14: Characteristics of the patients in the cohort before exclusion of patients with extreme values for cost.

Characteristic (N=772)	Missing n	Frequency n (%)	Proportion (95%CI)
Age category	0		
<35yrs		136 (17.62)	0.150 (0.151-0.205)
45yrs<Category 1>=35yrs		142 (18.39)	0.184 (0.158-0.213)
55yrs<Category 2>=45yrs		152 (19.69)	0.197 (0.170-0.226)
65yrs<Category 3>=55yrs		189 (24.48)	0.245 (0.216-0.276)
Category 4>=65yrs		153 (19.82)	0.198 (0.171-0.228)
Sex	0		
Male sex		324 (41.97)	0.420 (0.385-0.455)
Female sex		448 (58.03)	0.580 (0.545-0.615)
Race	12		
Black		43 (5.66)	0.056 (0.042-0.075)
White		690 (90.79)	0.908 (0.885-0.926)
Asian		16 (2.11)	0.021 (0.013-0.034)
Mixed		11 (1.45)	0.014 (0.008-0.026)
Physical status self-assessment	0		
Healthy		392 (50.78)	0.508 (0.472-0.543)
Ongoing illness affecting daily life mildly		312 (40.41)	0.404 (0.370-0.439)
Ongoing illness affecting daily life severely		64 (8.29)	0.083 (0.065-0.104)
Ongoing illness is a constant threat to life		4 (0.52)	0.005 (0.002-0.014)
Body mass index	52		
<25		172 (23.89)	0.239 (0.209-0.271)
>=25		250 (34.72)	0.347 (0.313-0.383)
>=30		164 (22.78)	0.228 (0.198-0.259)
>=35		77 (10.69)	0.107 (0.086-0.132)
>=40		30 (4.17)	0.041 (0.029-0.059)
>=45		27 (3.75)	0.037 (0.026-0.054)
Hypertension	0	255 (33.03)	0.330 (0.298-0.364)
Diabetes	0		
Not using insulin		60 (7.77)	0.078 (0.061-0.099)
Using insulin		18 (2.33)	0.023 (0.015-0.037)
Smoking	0		
Previous smoker		147 (19.04)	0.190 (0.164-0.220)
Current smoker		151 (19.56)	0.195 (0.169-0.225)
Ischaemic heart disease	0	67 (8.68)	0.087 (0.069-0.109)
Metabolic syndrome	0	103 (13.34)	0.133 (0.111-0.159)
HIV	0	28 (3.63)	0.036 (0.025-0.052)
History of tuberculosis treatment	0	12 (1.55)	0.015 (0.009-0.027)
History of VTE	0	45 (5.83)	0.058 (0.044-0.077)
Reported current renal impairment	0	15 (1.94)	0.019 (0.012-0.032)
Previous admission to hospital for lung disease	0	61 (7.90)	0.079 (0.062-0.100)
Current cancer treatment	0	13 (1.68)	0.017 (0.010-0.029)
Obstructive sleep apnoea risk	0	86 (11.14)	0.111 (0.091-0.136)
Previous stroke	0	23 (2.98)	0.030 (0.020-0.044)
Valvular heart disease	0	37 (4.79)	0.048 (0.035-0.065)
Reported ‘weak heart’	1	38 (4.28)	0.420 (0.030-0.060)
Frail	0	22 (2.85)	0.028 (0.019-0.043)
Hypothyroidism	1	124 (16.08)	0.161 (0.136-0.188)

Characteristic (N=772)	Missing n	Frequency n (%)	Proportion (95%CI)
Previous surgery for same problem	10	34 (4.46)	0.955 (0.938-0.968)
Low dose aspirin use	2	169 (21.95)	0.219 (0.192-0.250)
Recent URTI or fever	1	129 (16.73)	0.167 (0.142-0.195)
History of difficult airway	0		
Reported recreational drug use	3	15 (1.95)	0.019 (0.012-0.032)
Anabolic steroid use	3	15 (1.95)	0.019 (0.012-0.032)
Reported herbal medication use	5	122 (15.91)	0.159 (0.135-0.187)
Previous reaction to an anaesthetic or anaesthesia-related complication	2	107 (13.90)	0.139 (0.116-0.165)
Family history			
Malignant Hyperthermia	3	1 (0.13)	0.001 (0.000-0.009)
Scoline Apnoea	4	16 (2.08)	0.021 (0.013-0.034)
Porphyria	9	11 (1.44)	0.014 (0.008-0.026)
Type of surgery	0		
Neurosurgery		17 (2.20)	0.022 (0.014-0.035)
Spinal surgery		40 (5.18)	0.051 (0.038-0.070)
Orthopaedic surgery		205 (26.55)	0.265 (0.235-0.300)
Ear, nose & throat, head & neck surgery		42 (5.44)	0.054 (0.040-0.073)
Thoracic surgery		16 (2.07)	0.021 (0.012-0.033)
Vascular surgery		48 (6.22)	0.062 (0.047-0.081)
Upper GIT surgery		243 (31.48)	0.315 (0.283-0.348)
Lower GIT surgery		53 (6.87)	0.069 (0.053-0.089)
Genitourinary surgery		68 (8.81)	0.088 (0.070-0.110)
Plastic- & breast surgery		38 (4.92)	0.049 (0.036-0.067)
Other surgery		2 (0.26)	0.002 (0.001-0.010)
Health literacy (confidence filling forms)	5		
Extremely confident		508 (66.23)	0.662 (0.628-0.695)
Quite confident		187 (24.38)	0.244 (0.215-0.275)
Somewhat confident		56 (7.30)	0.073 (0.056-0.094)
A little bit confident		12 (1.56)	0.156 (0.009-0.027)
Not at all confident		4 (0.52)	0.005 (0.002-0.014)
Inadequate information received on what to expect	6	30 (3.92)	0.039 (0.027-0.055)

The continuous outcome as described in the methods section can be summarised as follows (this summary is done after exclusion of outliers during data inspection, N=770):

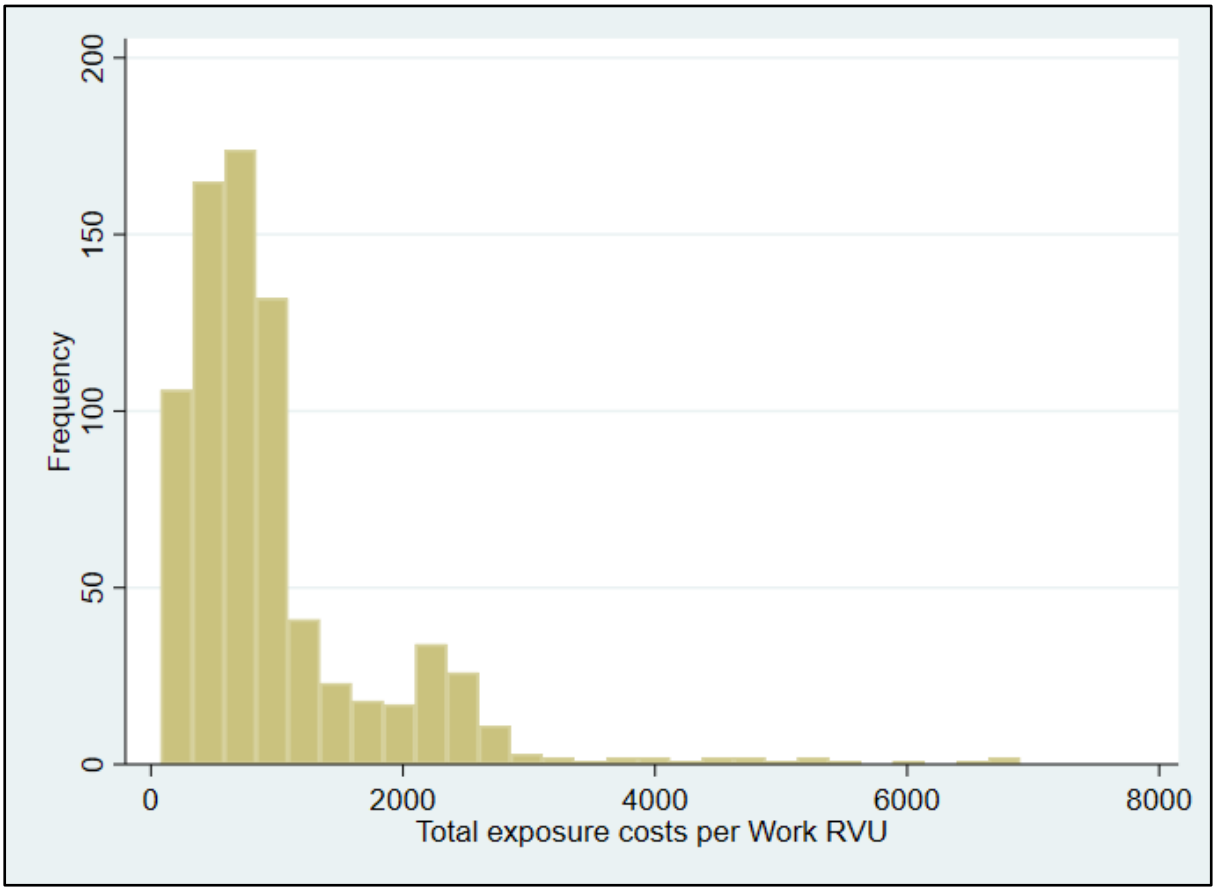

Figure 12: Histogram illustrating the frequency distribution of cost per Work RVU

Table 15: Summary of total exposure costs in Rand per Work RVU

Percentiles		Smallest	N=770
1%	138.67	77.37	Mean (SD): 1003.34 (894.62)
5%	205.34	79.85	Median: 794.10
10%	274.08	96.71	Geometric Mean (95%CI): 753.01 (714.02-794.14)
25%	499.61	100.01	
50%	794.50	Largest	
75%	1094.55	6096.43	
90%	2209.28	6576.67	
95%	2548.34	6868.08	
99%	5010.26	6896.13	

Log transformation of the continuous outcome can be summarised as follows (N=770):

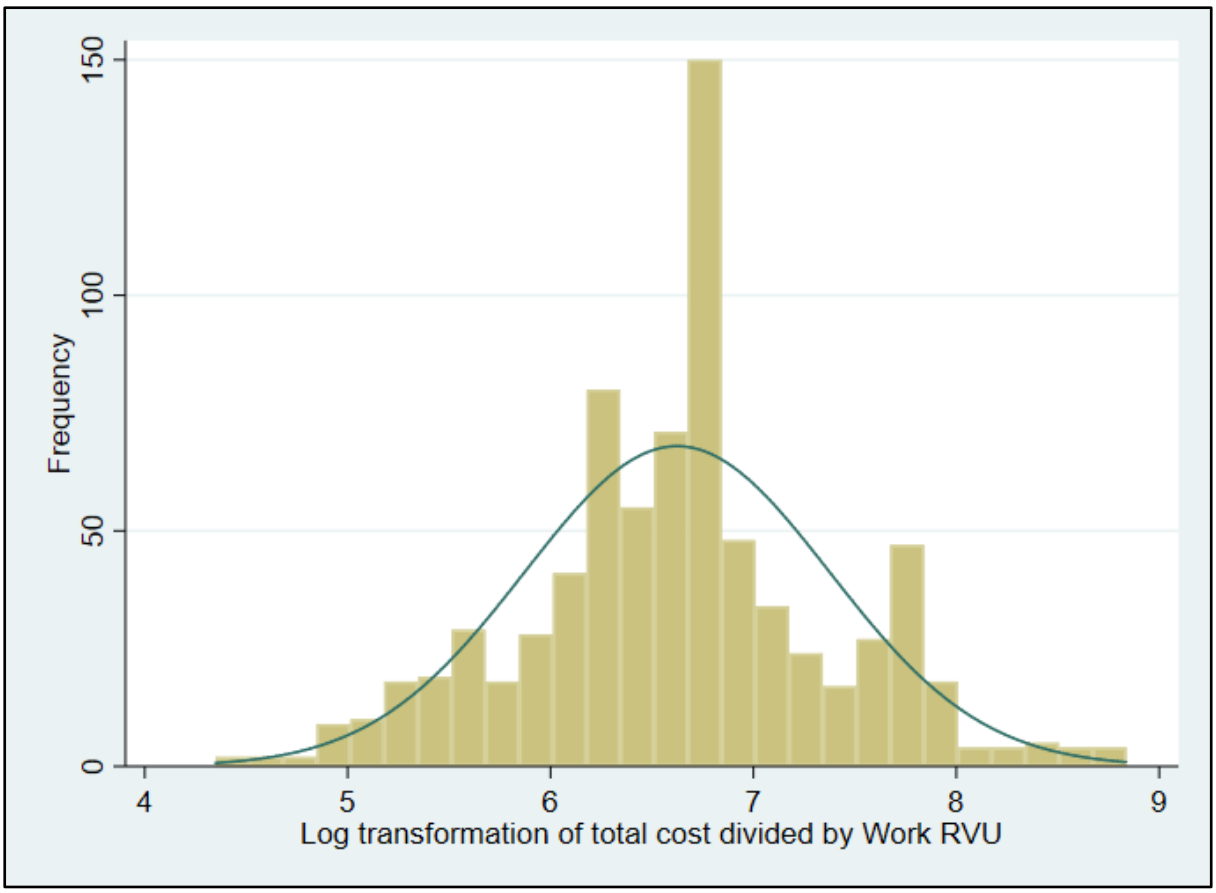

Figure 13: Histogram illustrating the frequency distribution of log transformed continuous outcome.

Table 16: Summary of transformed continuous outcome.

Percentiles		Smallest	N=770
1%	4.932	4.349	Mean (SD): 6.624 (.752)
5%	5.325	4.380	Median: 6.677
10%	5.613	4.572	Geometric Mean (95%CI): 6.581 (6.527-6.635)
25%	6.214	4.605	
50%	6.678	Largest	
75%	6.998	8.715	
90%	7.700	8.791	
95%	7.843	8.835	
99%	8.519	8.839	

Two cases were excluded as outliers. In both instances the diagnosis of a malignant skin lesion was recorded. One case was an outlier for high cost per RVU, which probably reflects chemotherapy or other cancer treatment being initiated during

hospital stay. The other case was an outlier for low cost per RVU, since the total amount of RVUs recorded was high (Table 17).

Table 17: Information on cases with extreme values excluded from derivation cohort.

Variable	Variable value excluded case 1	Variable value excluded case 2
Age in years	68	43
Physical status self-assessment	Chronic illness affecting life mildly	Healthy
Length of hospital stay in days	1	1
ICU admission	No	No
Mortality	No	No
Procedure	Excision skin lesion	Excision with free skin flap
Duration of procedure in minutes	74	40
Diagnosis according to ICD10	Malignant skin lesion	Malignant melanoma
Hospital cost in Rand (fee included)	792680.02	6955.77
Theatre cost in Rand (fee included)	6293.41	5645.06
Ward cost in Rand (fee included)	786386.61	1310.71
Work Relative Value Units	13.34	41.59
Exposure cost in Rand per RVU (exclusion variable)	27221.82	24.56
Reason for exclusion	High ward cost probably due to cancer therapy	High Work Relative Value Units in relation to cost – probably inappropriate RVUs recorded

The type of surgery variable categories were created as follows:

Upper gastro-intestinal surgery was taken as the reference category, since the cases in this category contributed to 31.56% (n=243) of the total cohort. After univariate logistic regression with high hospital cost as outcome, surgical types with similar odds ratios (clinically relevant and statistically significant) were grouped together. The number of categories were reduced from 11 to 8. The relative contribution of the procedures to the categories are expressed in pie charts (Figure 14 and 15):

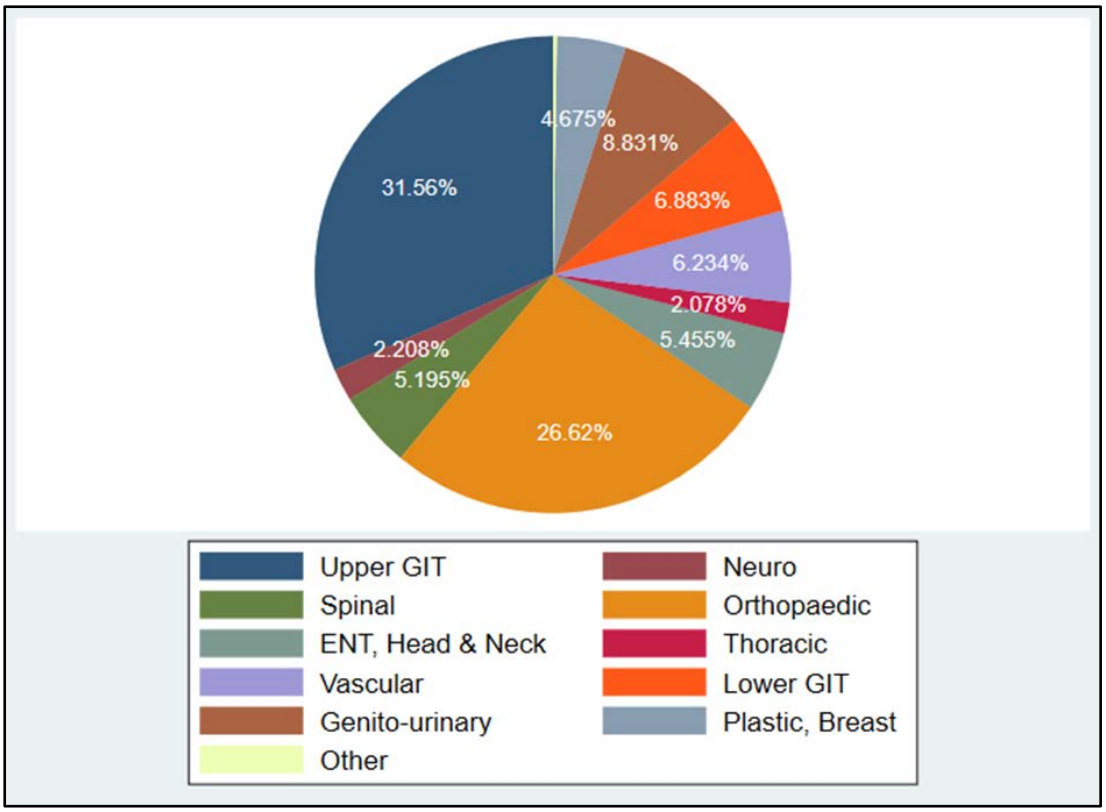

Figure 14: Categories of type of surgery with relative contribution in percentage.

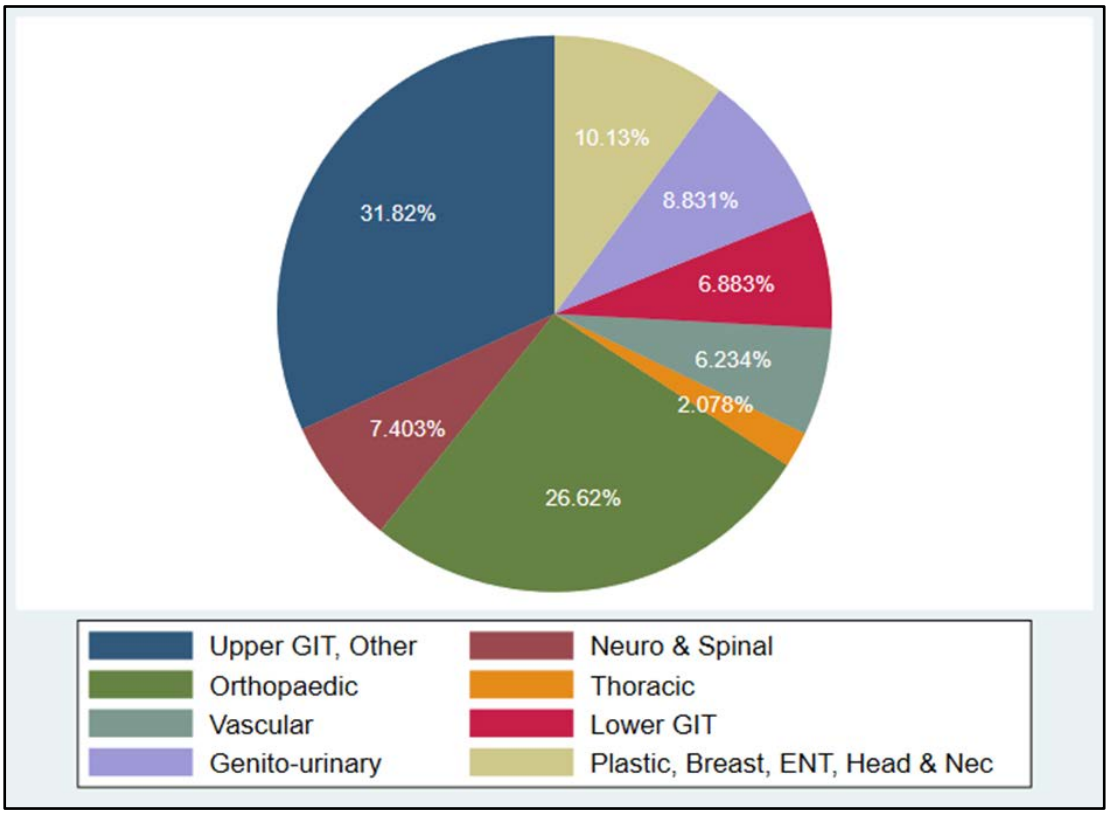

Figure 15: Reduced categories of type of surgery with relative contribution in percentage.

3.2 Model development

After univariate regression analysis, predictors were subjected to a stepwise regression selection if the p value in univariate analysis was less than 0.050. Certain predictors were developed *post hoc* (but before inclusion in stepwise regression selection) if clinically relevant – for example, a history of diagnosis or previous surgery for vascular disease was included as predictor when patients were not presenting for vascular surgery. When predictors were similar in definition, predictors were sequentially added or removed from stepwise selection and/or model specification, in order to find a predictor that improves model performance in relation to similar predictors.

The result of stepwise forward logistic regression was selection of variables in the model, but repeated exploration of the relative contributions of patient predictors with type of surgery was done. The variables included during selection are described in Table 18 - data are mean (standard deviation) or n (percentage).

Severity of surgery was not included as a predictor in the selection, because of its obvious association with increased cost, and the lack of an appropriate definition if cost was considered per Work RVU. This predictor was defined based on the duration of surgery and visual inspection of the associated procedural code description.

Table 18: Description of variables that were subjected stepwise regression selection.

Variable	All cases (n=770)	Without outcome (n=628)	With outcome (n=142)	Univariate logistic regression for outcome OR (95% Confidence Interval)	P value
Age	50 (15.28)	49 (15)	54.5 (16.15)	1.033 (1.019-1.047)	<0.001
Pack years (current or past smoker)	5.5 (12.11)	5.2 (12.09)	6.8 (12.14)	1.015 (1.003-1.027)	0.014
Activity Status Score (maximum 23.45)	21.29 (4.41)	21.63 (4.01)	19.66 (5.60)	0.918 (0.884-0.953)	<0.001
Physical status self-assessment					
Healthy	391/770 (50.78)	332/628 (52.87)	66/142 (46.48)	Reference	
Ongoing illness affecting daily life mildly	311/770 (40.39)	255/628 (40.61)	56/142 (39.44)	1.007 (0.666-1.521)	0.030
Ongoing illness affecting daily life severely or a constant threat to life	68/770 (8.83)	41/628 (6.53)	20/142 (14.08)	2.465 (1.375-4.417)	0.002
Hypertension	254/770 (32.99)	196/628 (31.21)	68/142 (47.89)	1.928 (1.312-2.833)	0.001
Low dose aspirin use	169/768 (22.01)	106/623 (17.01)	44/142 (30.99)	1.777 (1.167-2.705)	0.007
Previous surgery for the same problem	34/760 (4.47)	24/623 (3.85)	10/142 (7.04)	2.147 (1.000-4.607)	0.050
Indication for surgery affects life severely	51/770 (6.62)	31/628 (4.94)	18/142 (12.68)	2.710 (1.463-5.018)	0.002
Hypothyroidism	124 /769 (16.12)	95/628 (15.15)	28/142 (19.72)	1.664 (1.043-2.655)	0.033
Short-lived limb weakness or blindness not presenting for vascular surgery	11/766 (1.14)	6/628 (0.96)	4/142 (2.86)	4.282 (1.286-14.251)	0.018
Depression self-assessment and on treatment for chronic pain	36/763 (4.72)	120/628 (19.11)	19/140 (13.57)	4.965 (2.503-9.848)	<0.001
Frailty	22/770 (2.86)	12/628 (1.91)	4/142 (2.82)	2.394 (0.956-5.996)	0.062
Type of surgery					
Upper GIT	245/770 (31.82)	214/628 (34.08)	5/142 (3.52)	Reference	
Neuro & spinal	57/770 (7.40)	59/628 (9.39)	8/142 (5.63)	6.72 (2.050-22.032)	0.002
Orthopaedic	205/770 (26.62)	125/628 (19.9)	85/142 (59.86)	33.322 (13.169-84.314)	<0.001
Thoracic	16/770 (2.08)	13/628 (2.07)	3/142 (2.11)	6.857 (1.220-38.528)	0.029
Vascular	48/770 (6.23)	25/628 (3.95)	21/142 (14.79)	24 (8.234-69.954)	<0.001
Lower GIT	53/770 (6.88)	54/628 (8.6)	9/142 (6.34)	6.128 (1.786-20.908)	0.004
Genito-urinary	68/770 (8.83)	61/628 (9.71)	4/142 (2.82)	3.809 (1.069-13.569)	0.039
Plastic, breast, ENT, Head & Neck	78/770 (10.13)	77/628 (12.26)	7/142 (4.93)	2.594 (.679-9.912)	0.163
Alternative definitions for predictors					
Short-lived limb weakness or blindness	16/766 (2.09)	7/627 (1.12)	8/140 (5.71)	4.043 (1.477-11.064)	0.007
Chronic pain	188/763(24.64)	149/624 (23.88)	54/140 (26.57)	2.213 (1.479-3.312)	<0.001

Variable	All cases (n=770)	Without outcome (n=628)	With outcome (n=142)	Univariate logistic regression for outcome OR (95% Confidence Interval)	P value
Depression	105/768 (13.67)	80/628 (12.74)	29/140 (20.71)	1.810 (1.108-2.957)	0.018
Chronic pain AND Depression	46/770 (5.97)	28/628 (4.46)	12/142 (8.45)	2.884 (1.522-5.464)	0.001
Activity Status Score according to cause if reduced activity					
Joint, bone or back problems	75/164 (45.73)	16.97 (4.86) min 7.2 max 23.45	16.77 (7.013) min 0 max 23.45	0.994 (0.919-1.075)	0.882
Difficult breathing	27/164 (16.46)	15.15 (5.090) min 7.2 max 23.45	20.15 (3.012) min 17.95 max 23.45	1.303 (0.983-1.726)	0.065
Pain, pressure, or discomfort in chest, neck or arm	22/164 (13.41)	16.22 (3.063) min 13.45 max 23.45	15.82 (4.419) min 12.7 max 18.95	0.955 (0.579-1.575)	0.858
Pain or cramps in legs	40/164 (24.39)	14.23 (4.937) min 4.5 max 18.95	14.34 (4.278) min 6.25 max 18.95	1.005 (0.876-1.154)	0.939

3.2.1 Model specification

The full prediction model with all regression coefficients and the model intercept is presented in Table 19. (The questions defining the patient-reported predictors are listed in Table 12).

Table 19: Full clinical prediction model for binary cost outcome.

Variable	Coefficient	Standard Error	z	95% Confidence Interval	P > |z|
Intercept	-2.7489	0.6724	-4.09	-4.0668 to -1.4311	<0.001
Type of Surgery					
Upper GIT & other surgery	*Reference*				
Neuro & spinal surgery	1.6188	0.6324	2.56	0.3793 to 2.8583	0.010
Orthopaedic surgery	3.4483	0.4759	7.25	2.5156 to 4.3809	<0.001
Thoracic surgery	1.9026	0.8853	2.15	0.1674 to 3.6378	0.032
Vascular surgery	3.0476	0.5508	5.53	1.968 to 4.1272	<0.001
Lower GIT surgery	1.9084	0.6289	3.03	0.6757 to 3.1412	0.002
Genito-urinary surgery	1.3615	0.6516	2.09	0.0843 to 2.6386	0.037
Plastic, breast, ENT & Head & Neck surgery	0.9997	0.6870	1.46	-0.3469 to 2.3462	0.146
Depression and on chronic pain treatment	0.9107	0.4281	2.13	0.0717 to 1.7497	0.033
Activity status count	-0.0549	0.0241	-2.28	-0.1020 to -0.0077	0.023

The number of categories within the predictor type of surgery was sequentially reduced during repeated regression if P > 0.050. The resultant restricted model is displayed in Table 20.

Table 20: Restricted clinical prediction model for binary cost outcome.

Variable	Coefficient	Standard Error	z	95% Confidence Interval	P > |z|
Intercept	-1.7140	0.6832	-2.51	-3.0530 to -0.3750	0.012
Neuro & spinal surgery	3.0525	0.2726	11.20	2.5183 to 3.5868	<0.001
Thoracic surgery	2.5072	0.3566	7.03	1.8082 to 3.2062	<0.001
Vascular surgery	1.4875	0.4217	3.53	0.6610 to 2.3140	<0.001
Depression and on chronic pain treatment	2.2495	0.5725	3.93	1.1274 to 3.3717	<0.001
Activity status count	-0.0606	0.0306	-1.98	-0.1207 to -0.0006	0.048

3.2.2 Model performance

Restricted model performance is illustrated in Figure 16. AUC 95% confidence interval 0.8044 – 0.8762.

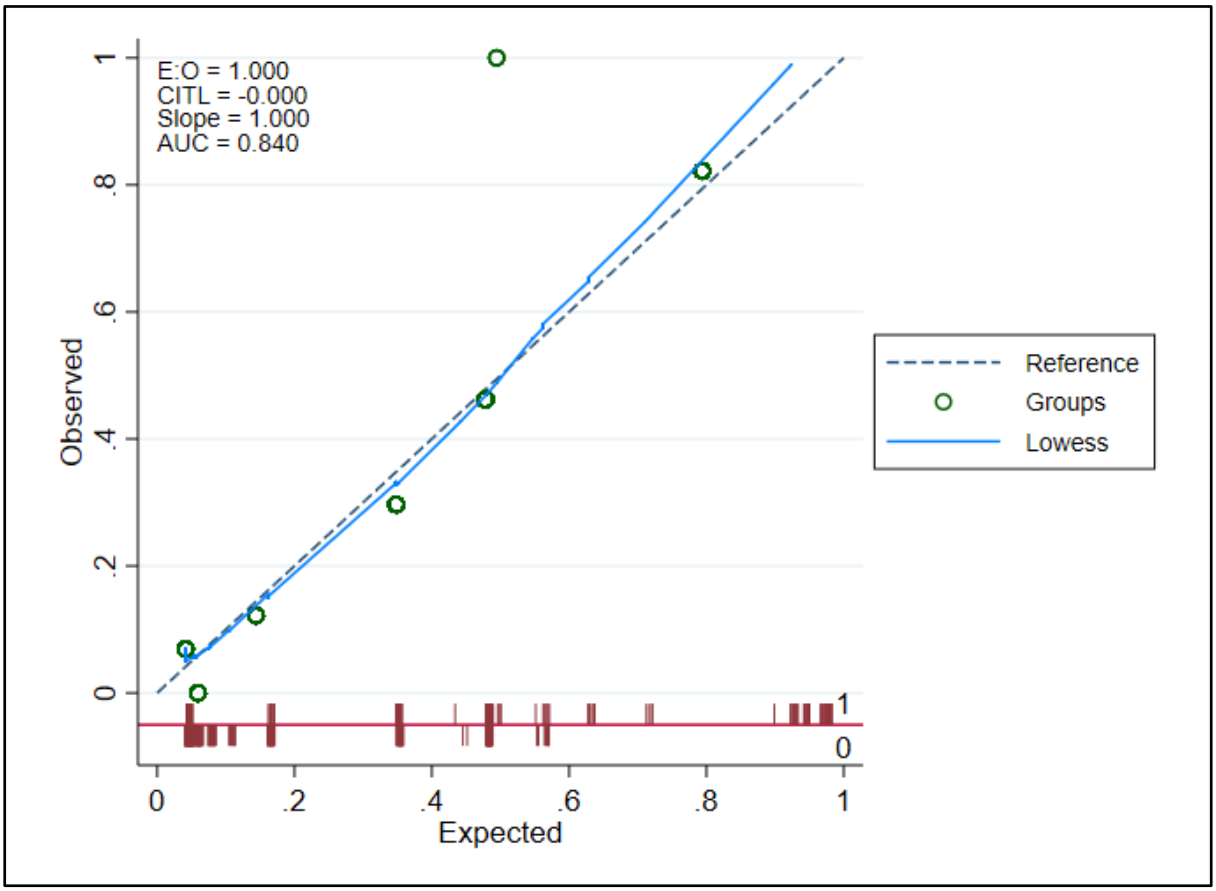

Figure 16: Calibration plot for restricted prediction model with binary cost outcome.

Since the development cohort was representative of the full range of surgical procedure types, excluding non-obstetric and non-cardiac surgery, the full model was assessed with regards to performance.

The *discrimination* of the full prediction model was assessed by calculating the area under the receiver-operating curve (AUROC), as 0.8262 (95% confidence interval: 0.7894 - 0.8630). This means that the probability that an individual with the outcomes

had a higher predicted probability of a paired individual without the outcome, was 0.82. The Hosmer-Lemeshow statistic was found to be non-significant (p=0.9667).

The *calibration* of the prediction model was assessed by plotting observed against expected outcomes, using Lowess smoothing. The validation plot is shown in Figure 17. E:O = Expected:Observed CITL=Calibration-in-the-large Slope=Slope beta AUC=Area under Receiver Operating Curve (c-statistic). Green circles indicate groups of patients with similar predicted risk.The distribution of subjects are indicated using red bars at the bottom of the plot: patients with the outcome above the x-axis, and those without the outcome below the x-axis. The visual display of agreement between observed and expected outcomes is indicated by the blue line using a smoothing technique. The agreement is good up to values of around 0.60, after which the model underestimates risk. Of note is that the agreement of observed outcome and predictions in certain groups of patients with similar predicted risk is poor – the green circles falling away from the dashed reference line of perfect agreement. However, the distribution of subjects with regard to predictions shows a wide spread in patients with and without the outcomes, illustrating the ability of the model to perform with regards to discrimination. The distribution is indicated in red at the bottom of the graph.

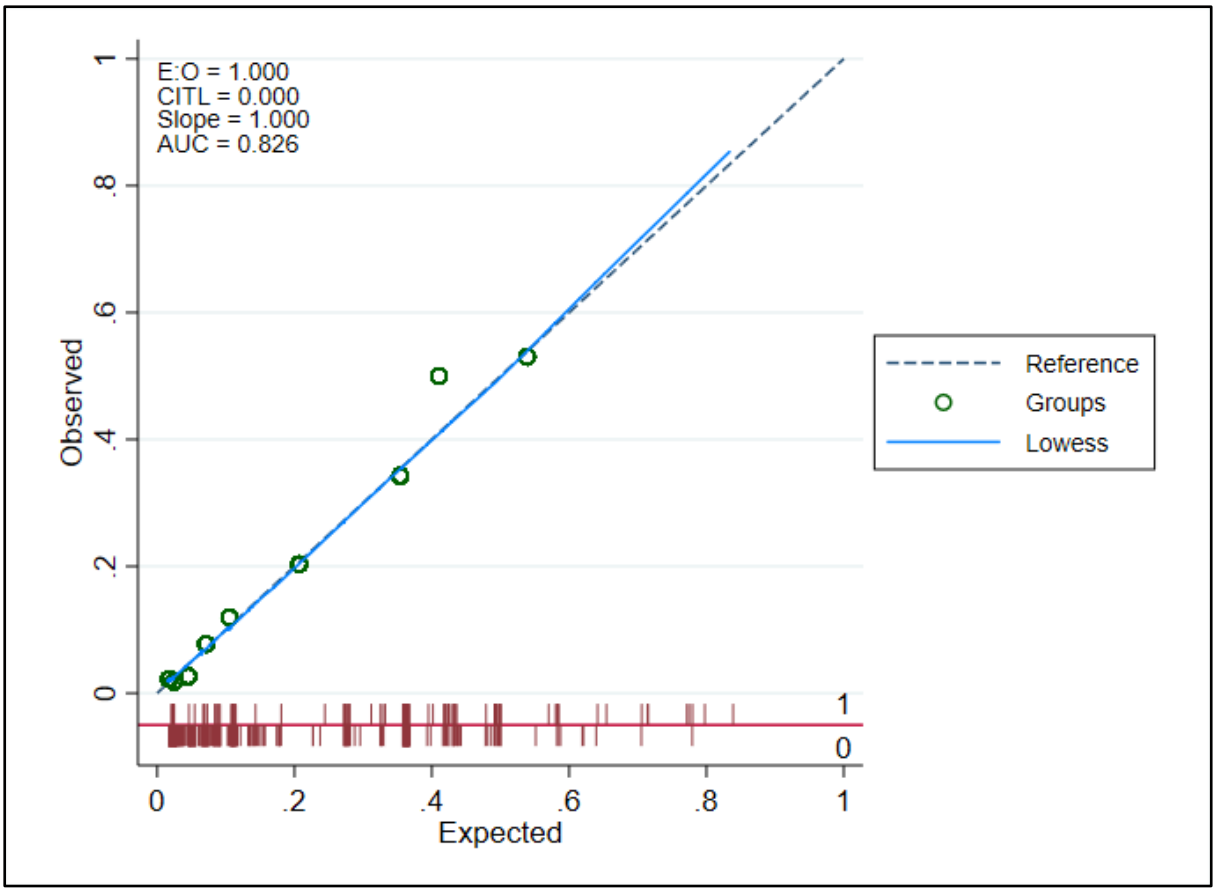

Figure 17: Calibration plot for full prediction model with binary cost outcome.

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When considering *clinical usefullness*, model performance was assessed in the following way:

Using a probability cutoff of 0.225, sensitivity and specificity were as follows:

		Actual		Total
		Positive	Negative	
Predicted	Positive	102	154	256
	Negative	26	481	507
Total		128	635	763
Sensitivity		79.69%	Specificity	75.75%
Positive predictive value		39.84%	Negative predictive value	94.87%
False negative rate		20.31%	False positive rate	24.25%

Since specificity and sensitivity “can only be used as a naïve summary indicator of usefullness”[8], net benefit was used as a summary measure. This was done using decision curve analysis, as explained previously by Vickers, Steyerberg and others.

The graph used in decision-curve analysis is shown in Figure 18. Predictions for orthopaedic surgery as a single predictor is shown as a light blue graph line. The net benefit of ‘treating’ all patients is shown in dark blue, and ‘treating’ no patients to prevent the outcome has no net benefit (red line). The prediction model probabilities is displayed as a green line.

Decision curve analysis was developed to enable the comparison of prediction models that incorporates clinical consequences important to the patient. Cost, and adjusting management to lower cost, may not be a relevant clinical outcome to use in decision-making, but the exercise does provide some insight in the relative contribution of type of surgery (e.g. orthopaedic surgery as a single predictor) compared to the prediction model incorporating patient factors, to the outcome. The graph shows that patient factors contributing to the cost risk, combined with type of surgery, predict cost better than type of surgery alone.

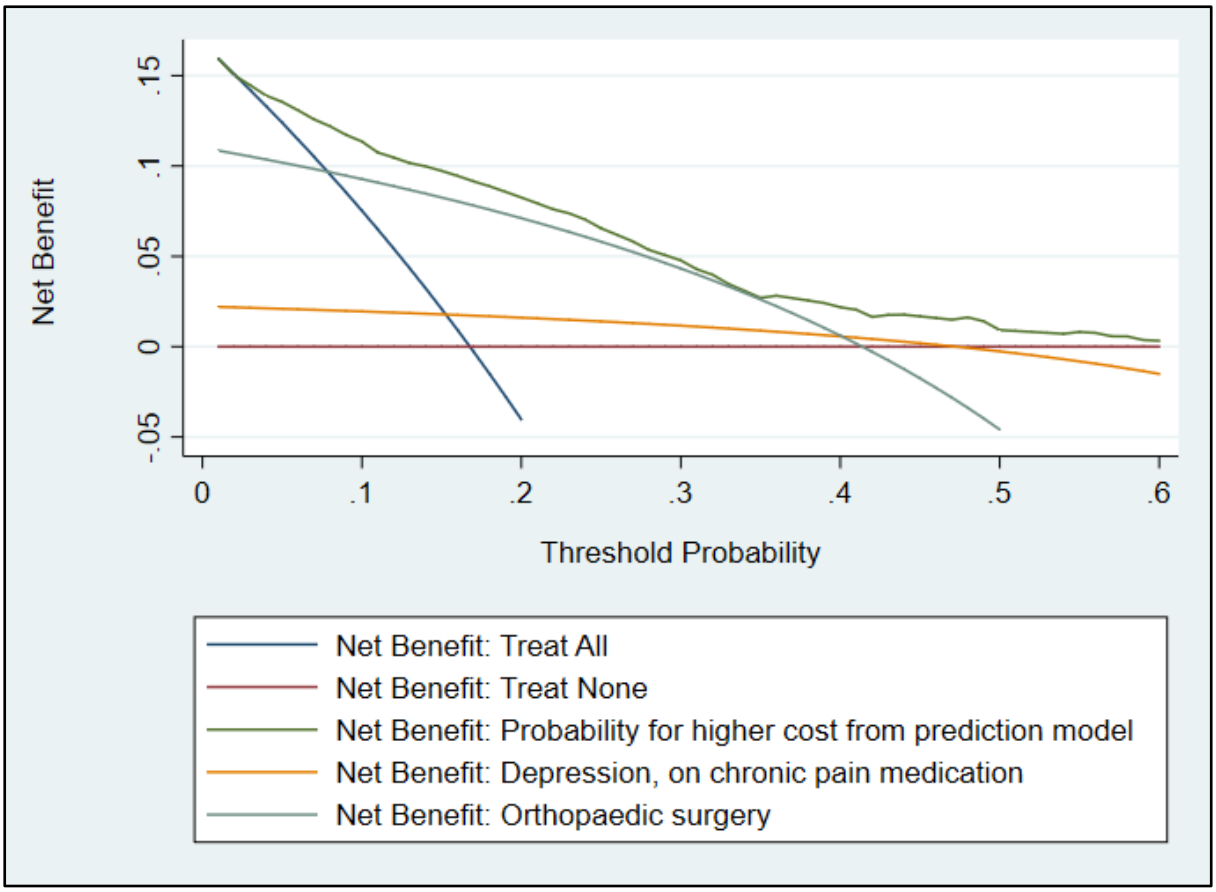

Figure 18: Graph for decision curve analysis

The full prediction model was internally validated by fitting to a bootstrap sample. The resulting AUROC was found to be 0.8566 (95% confidence interval: 0.8224 - 0.8907) and the calibration plot is shown in Figure 19.

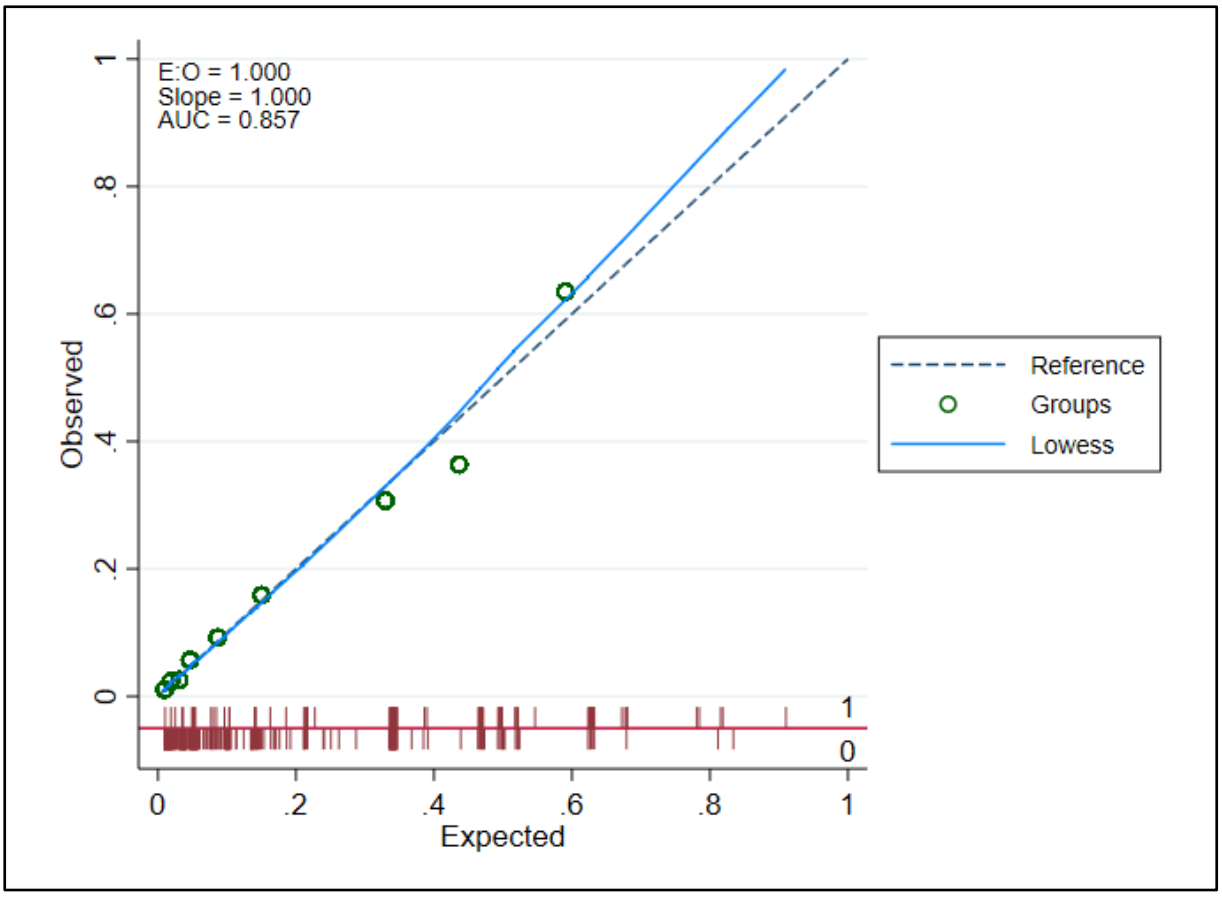

Figure 19: Validation plot for full prediction model fitted to a bootstrap sample.

The restricted model performed similar on internal validation when fitted to bootstrap samples, but a larger number of repetitions were possible – Figure 20.

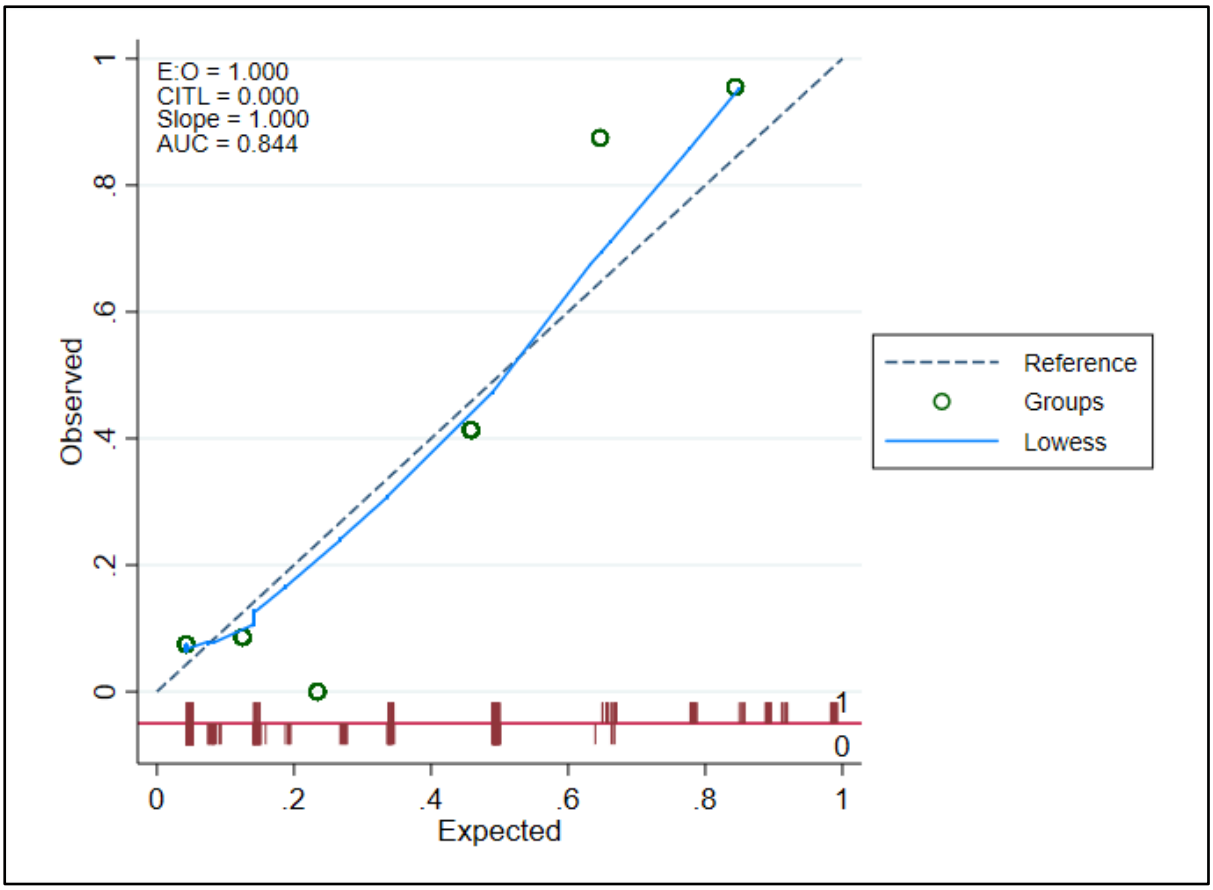

Figure 20: Validation plot for restricted prediction model fitted to a bootstrap sample.

3.3 Summary of secondary outcomes

Two patients (2/770, 0.26%) in the cohort died. No modelling for *mortality* was done.

The two cases are described in Table 21. BMI = Body mass index.

Table 21: Description of patients that died.

Age	68 years	57 years
BMI	23.9	28.4
Physical Status self-assessment	Healthy	Disease affecting life mildly
Activity Status count	23.45	23.45
Pack-years smoking	45	0
Comorbid disease	Hypertension, Depression on treatment, Ischaemic heart disease, Diagnosed with vascular disease, Previous treatment for cancer	Hypertension, Diabetes (not using insulin), Previous treatment for cancer, History of difficult airway management
Type of Surgery	Thoracic	Thoracic
Severity of surgery	Major	Major

Previous surgery for same problem	No	No
Work RVUs	192.78	135.37
Duration of surgery	262 minutes	291 minutes
Hospital LOS	28 days	66 days
ICU LOS	7 days	44 days
Further surgery during admission	Yes	Yes
Total theatre cost	R98 140.39	R113 286.04
Total ward cost	R441 771.50	R1,105 782.80
Exposure cost/RVU	R1 827.85	R4 713.58

Thirty-five (38/770, 4.94%) of patients were *admitted to ICU* postoperatively. There were no data available on the timing (immediate postoperative versus unplanned) of admission, nor the indication for admission to critical care. No data was available on the level of care (e.g. ventilation, haemodynamic support) required in critical care. Outcomes related to ICU admission were therefore merely summarized in Table 22 and related Figure 21.

Table 22: Summary of postoperative ICU admission in days.

Percentiles		Smallest	N=38
1%	1	1	Mean (SD): 4.84 (8.31)
5%	1	1	Median: 2
10%	1.5	1	Geometric Mean (95%CI): 2.75 (2.07-3.66)
25%	1.5	1.5	
50%	2	Largest	
75%	3.5	14	
90%	14	17	
95%	28	28	
99%	44	44	

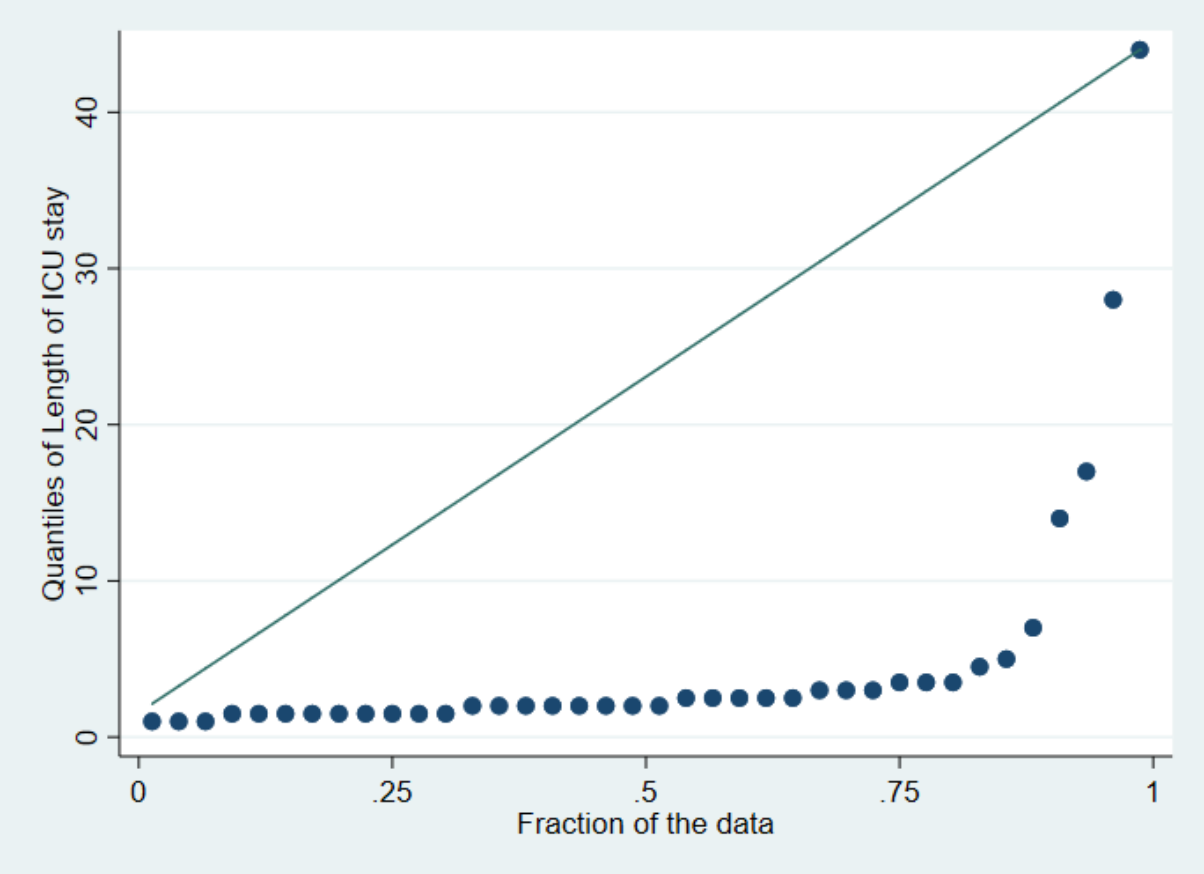

Figure 21: Quantile plot of postoperative ICU admission in days.

The endpoint of length of critical care stay was further described using means and frequency for the different categories of type of surgery, as shown in Table 23.

Table 23: ICU length of stay per type of surgery category.

Type of Surgery	Mean	Frequency
Upper GIT surgery	8.69	8
Neuro & Spinal surgery	2.25	8
Orthopaedic surgery	1.5	1
Thoracic surgery	14.62	4
Vascular surgery	2.18	14
Lower GIT surgery	3	1
Genito-urinary surgery	1	1
Plastic, Breast, ENT, Head & Neck surgery	2	1
Total	4.84	38

Hospital length of stay, including the day of surgery and preoperative stay not more than 24 hours, can be summarised as follows:

Table 24: Summary of hospital length of stay in days.

Percentiles		Smallest	N=770
1%	1	1	Mean (SD): 3.46 (4.31)
5%	1	1	Median: 2.5
10%	1	1	Geometric Mean (95%CI): 2.54 (2.42-2.68)
25%	1.5	1	
50%	2.5	Largest	
75%	4	30	
90%	6.5	42.5	
95%	8.5	47.5	
99%	21	66	

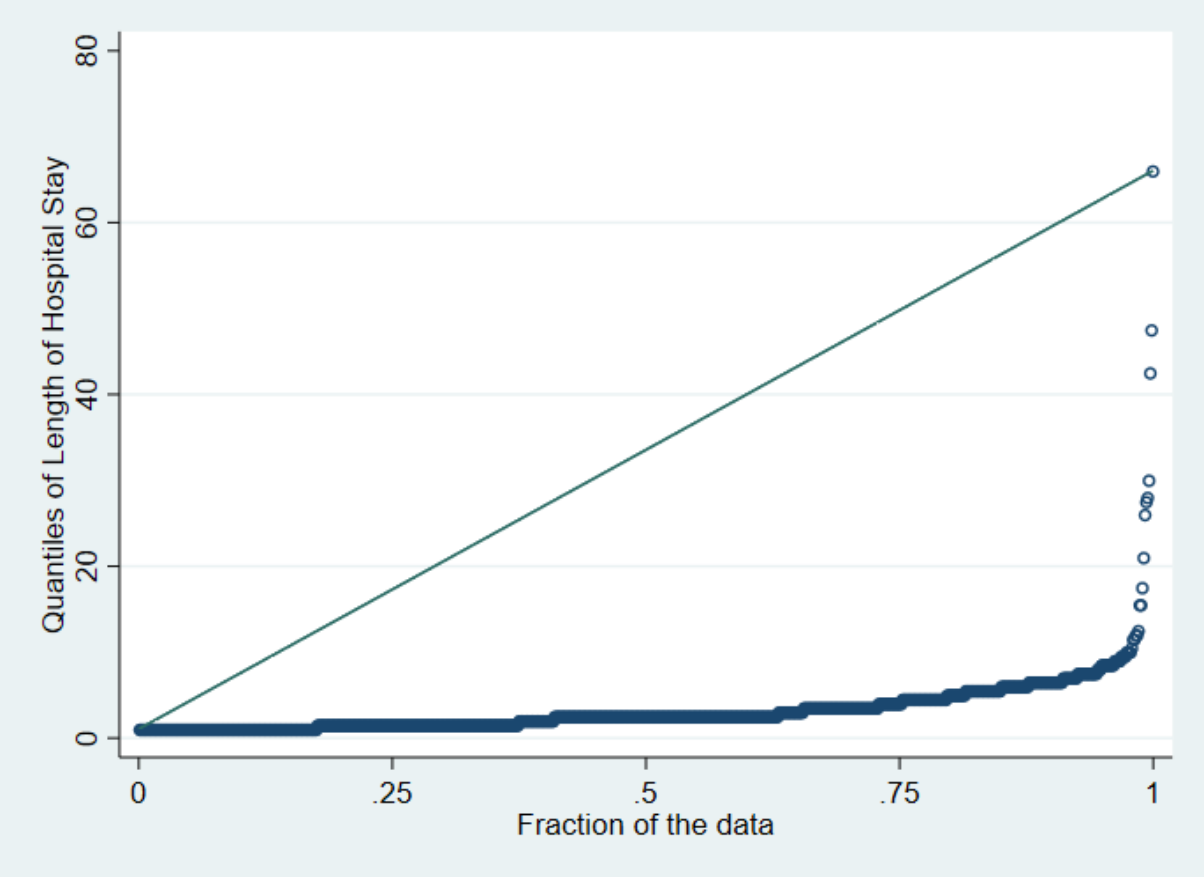

Figure 22: Quantile plot of hospital length of stay in days.

The endpoint of length of hospital stay was further described using means and frequency for the different categories of type of surgery, with subcategories for severity of surgery, as shown in Table 25.

Table 25: Hospital length of stay per type of surgery category.

Type of Surgery		Severity of Surgery			Total
		Minor	Intermediate	Major	
Upper GIT surgery	Mean	1.87	3.47	5.86	3.69
	Frequency	4	216	25	245
Neuro & Spinal surgery	Mean	1.5	2.44	5.69	5.03
	Frequency	2	9	46	57
Orthopaedic surgery	Mean	1.12	2.62	6.02	3.7
	Frequency	16	117	72	205
Thoracic surgery	Mean	.	3.78	13.78	9.41
	Frequency	0	7	9	16
Vascular surgery	Mean	1.33	1.47	4.28	2.93
	Frequency	3	20	25	48
Lower GIT surgery	Mean	1.17	2.15	5.04	2.70
	Frequency	3	39	11	53
Genito-urinary surgery	Mean	1	1.78	2.58	1.68
	Frequency	15	47	6	68
Plastic, Breast, ENT, Head & Neck surgery	Mean	1.17	1.31	6.54	2.17
	Frequency	9	56	13	78
Total	Mean	1.18	2.69	5.94	3.46
	Frequency	52	511	207	770

Predictors that were associated with length of hospital stay in univariate analysis are described in Table 26.

Table 26: Predictors associated with length of hospital stay in univariate analysis.

Variable	n/N (%) or mean (SD)	Univariate Poisson regression for outcome Coefficient (95% CI)	P value
Age	50 (15.28)	0.014 (0.012-0.017)	<0.001
Pack years (current or past smoker)	5.5 (12.11)	0.007 (0.005-0.009)	<0.001
Previous smoker	146/770 (18.96)	0.176 (0.082-0.270)	<0.001
Activity Status Score (max 23.45)	21.29 (4.41)	-0.036 (-0.044 to -0.029)	<0.001
Body Mass Index	29.8 (6.95)	0.010 (0.005-0.016)	<0.001
Physical status self-assessment			
Healthy	391/770 (50.78)	Reference	
Ongoing illness affecting daily life mildly	311/770 (40.39)	0.170 (0.088-0.251)	<0.001
Ongoing illness affecting daily life severely or a constant threat to life	68/770 (8.83)	0.483 (0.362-0.604)	<0.001
Hypertension	254/770 (32.99)	0.385 (0.308-0.462)	<0.001
Diabetes Mellitus	78/770 (10.14)	0.369 (0.259-0.478)	<0.001
Metabolic syndrome risk	103/770 (13.38)	0.167 (0.062-0.272)	0.002
Weak heart	33/769 (4.29)	0.304 (0.140-0.467)	<0.001

Variable	n/N (%) or mean (SD)	Univariate Poisson regression for outcome Coefficient (95% CI)	P value
Low dose aspirin use	169/768 (22.01)	0.112 (0.023-0.201)	0.014
Indication for surgery affects life severely	34/760 (4.47)	0.348 (0.216-0.480)	<0.001
Previous consultation for lung problem	41/770 (5.32)	0.342 (0.195-0.490)	<0.001
Previous admission for lung problem	61/770 (7.92)	0.200(0.069-0.331)	0.003
HIV	28/770 (3.64)	-0.336 (-0.574 to -0.099)	0.005
Treated for tuberculosis	12/770 (1.56)	0.374 (0.118-0.630)	0.004
Upper respiratory tract infection	117/769 (15.21)	-0.150 (-0.262 to -0.039)	0.008
Hyperthyroidism	12/769 (1.56)	0.531 (0.294-0.769)	<0.001
Short-lived limb weakness or blindness	16/766 (2.09)	0.457 (0.242-0.671)	<0.001
Stroke	23/695 (3.01)	0.222 (0.022-0.423)	0.030
Depression self-assessment and on treatment for chronic pain	36/763 (4.72)	0.199 (0.035-0.364)	0.018
Chronic pain	188/763(24.64)	0.108 (0.021-0.194)	0.014
Chronic pain AND Depression	46/770 (5.97)	0.162 (0.013-0.312)	0.033
History of renal problems	49/770 (6.36)	0.220 (0.078-0.362)	0.002
History of dialysis	12/770 (1.56)	-0.417 (-0.796 to-0.038)	0.031
Previously treated for cancer	33/770 (4.29)	0.689 (0.550-0.828)	<0.001
Metastatic cancer	10/770 (1.30)	-0.613 (-1.077 to -0.149)	0.010
History of venous thrombo-embolism	45/770 (5.84)	0.469 (0.336-0.601)	<0.001
Previous unexpected prolonged LOS	97/768 (12.63)	0.289 (0.186-0.392)	<0.001
Previous unexpected ICU admission	49/768 (6.38)	0.343 (0.209-0.478)	<0.001
History of PONV	197/768 (25.65)	-0.158 (-0.248 to -0.067)	0.001
History of difficult intubation	24/768 (3.13)	0.442 (0.263-0.620)	<0.001
Narrowing of airway, difficult breathing	57/770 (7.40)	0.237 (0.106-0.369)	<0.001
Type of surgery			
Upper GIT	245/770 (31.82)	Reference	
Neuro & spinal	57/770 (7.40)	0.310 (0.177-0.443)	<0.001
Orthopaedic	205/770 (26.62)	0.002 (-0.094-0.099)	0.964
Thoracic	16/770 (2.08)	0.935 (0.762-1.108)	<0.001
Vascular	48/770 (6.23)	-0.232 (-0.410 to -0.054)	0.010
Lower GIT	53/770 (6.88)	-0.313 (-0.490 to -0.137)	<0.001
Genito-urinary	68/770 (8.83)	-0.789 (-0.984 to -0.594)	<0.001
Plastic, breast, ENT, Head & Neck	78/770 (10.13)	-0.533 (-0.697 to -0.369)	<0.001

It was not possible to identify patient clinical risk factors for length of hospital stay during multivariate regression, therefore no modelling was performed.

3.4 Subpopulation analysis for arthroplasty

Since the cost of arthroplasty procedures is under scrutiny by medical aid funders, some attention was given to understanding the actual costs associated with this procedure. The means of costs are summarised in Table 27. CI=confidence interval. Theatre and ward costs displayed in the table include the fees the hospital charged for these services, in addition to the exposure cost (dispensary cost, etcetera). None of these costs include fees from clinicians. The means were compared using t-tests, and the confidence intervals and p value displayed in the bottom part of the table.

Table 27: Summary of cost per Work RVU for arthroplasty compared to all other procedures.

		Exposure cost per RVU		Total	Theatre cost per RVU		Total	Ward cost per RVU		Total
		Cost not high	High cost category		Cost not high	High cost category		Cost not high	High cost category	
Other procedures	Mean	676.05	2872.59	887.32	1280.50	3802.68	1523.37	533.73	1536.91	630.21
	Frequency	639	68	707	639	68	707	639	68	707
Arthroplasty	Mean	1280.06	2339.02	2305.41	1946.52	2652.37	2629.96	1352.13	1274.72	1277.18
	Frequency	2	61	63	2	61	63	2	61	63
Total	Mean	677.94	2620.28	1003.34	1282.58	3260.32	1613.91	536.28	1412.93	683.15
	Frequency	641	129	770	641	129	770	641	129	770
Significance 95% CI Total	Other	8.25-949.07		P=	1430.24-1616.51		P=	569.34-691.09		P=
	Arthroplasty	2230.91-2379.90		<0.001	2490.81-2769.10		<0.001	1150.03-1404.33		<0.001

4 Discussion

4.1 Principal findings

The study identified patients at risk for higher healthcare resource use during the perioperative stay by developing clinical prediction models.

The predictors for higher cost that were identified include type of surgery, and certain risk factors relating to physical activity, depression and chronic pain.

The calculated cost of postoperative hospital admission represents the ‘unpredictable’ cost risk and excludes clinician and hospital (bed) fees and prosthesis costs. Adjustment for surgical risk or ‘case-mix’ was done using Work Relative Value Units.

4.2 Limitations

This study has significant limitations. The first of these is that recruitment bias is highly likely since it was not possible to screen all consecutive patients for eligibility during the study period. Recruitment took place at various points: the hospital admission area, the surgeons’ consulting rooms, and preoperatively in the surgical wards.

The cohort was recruited at a single centre, and individual clinician preferences may have had a significant impact on the endpoints measured. The population may be representative of private healthcare recipients but not of the larger SA population (e.g. with regards to race and socio-economic circumstances).

Most patients chose to complete a paper questionnaire and it is therefore difficult to assess whether an electronic questionnaire could have produced more reliable data. The electronic questionnaire may not have been accessible enough, since limited funding for hardware to display the questionnaire was available.

Self-assessment data may be unreliable to use in defining predictors. Commonly used existing validated scores/indices cannot be generated with self-assessment data alone. The event rates for variables that are considered potentially important clinical predictors during preoperative assessment, such as recent ischaemic heart disease event, were low.

The opportunity to define or validate patient-reported outcomes measures for South Africa was lost by obtaining outcomes data only from the hospital. In the study setting it would have been more than possible to follow up with postoperative quality of

recovery scores, or with the standardised endpoints on patient comfort that was published (albeit not at the time of data collection).[21]

The binary outcome for cost that was used is relatively complex in its definition and there is zero evidence on its use. The *a priori* primary outcome was analysed as a secondary outcome. Outcomes data and procedural information was received from the hospital group and cannot be verified.

There is no current evidence on the validity of adjusting for surgical complexity by using Work Relative Value Units in defining a new cost outcomes variable (instead of adding it as a confounder in the dataset). Work RVU is linked to procedural codes. If all procedural codes were not captured per case, it is possible that surgical complexity is not adequately adjusted for in some cases.

R^2 when using linear regression for a continuous outcome was small when only considering patient-reported predictors, indicating that patient factors explain very little of the total variation in hospital cost. While type of surgery, when included as a predictor, improved prediction model performance significantly, the clinical relevance of doing so is doubtful. It is possible that the study would have been more relevant if results from patients undergoing a single type of surgery or a specific surgical procedure were investigated.

The cost, if any, of preoperative evaluation and optimisation was not included or considered in the study.

No updating of the prediction models were attempted subsequent to internal validation.

The prediction model that was developed could not be externally validated in different settings. It is likely that the prediction model may require significant updating when externally validated.

4.3 Interpretation

The higher cost outcome was defined from a clinical perspective, based on current understanding on how clinical factors and measures may influence cost of hospital care, e.g. cases where theatre cost was increased because of prolonged theatre time were not per se considered as having the outcome, as defined. Work RVU has been used to represent surgical complexity and is useful as a continuous variable to adjust for risk when using continuous outcome measures such as cost.

Unnecessary expenditure has to be curtailed, but healthcare providers may have to work harder to demonstrate the value of surgical intervention in patients with risk factors for high cost. Value should also be measured from a patient's perspective – using patient-reported outcome measures and capturing data at least up to the point where the intervention is shown to have improved clinical outcome, such as life expectancy compared to the population, or functional status, quality of life or disability adjusted life years.

This study then identifies possible predictors for increased cost of hospital admission that need to be further investigated. It contributes to the understanding of clinical factors, particularly patient reported measures, which have not previously received much attention from clinicians when planning perioperative care in the SA setting.

Model performance overall was satisfactory, but clinical usefulness is not of much concern with cost as outcome. False-negative predictions with a resulting lack of clinical intervention to decrease cost, are unlikely to contribute to patient harm. False-positive predictions may increase awareness on patient factors that contribute to higher cost. Ultimately the aim would be to provide appropriate care to patients that need it, and not withholding care because it will increase cost.

The study results may indicate that a patient-centred approach to perioperative planning has merit. Other studies reported similar findings, for example: pre-surgery depression and lower self-efficacy were shown to be associated with poorer quality of life, health status and personal well-being in the two years following colorectal cancer surgery.[228] It is also important to recognise or identify patients at increased risk for higher cost due to patient factors, so that such patients are not penalised when instituting cost-cutting measures for specific types of surgery.

A number of the patient predictors identified as candidate predictors for the prediction model, were related to a patient's self-assessment of activity status and quality of life. Although functional capacity assessment and exercise testing has been well-described in risk assessment for clinical outcomes, this is not commonly considered by clinicians when planning healthcare resource use in the perioperative period. The role that depression and chronic pain plays in patients' perioperative course has been investigated, but it is important to consider preoperative optimisation strategies also from a cost-effectiveness perspective. The duration that a patient has been experiencing disability in any form related to the indication for surgery, will impact on the measurement of disability adjusted life years (DALYs).

4.4 Implementation

Should it be possible to externally validate the model, it is reasonable to suggest that the model can be presented as part of a decision tree on the need for preoperative anaesthesia consultation and risk management.[8] A low positive predictive value may not be of concern in screening patients preoperatively for optimisation before surgery, provided that a clinical consultation by a specialist aware of the cost implication of additional preoperative testing follows screening.[229] A prediction model containing patient-reported predictors can be combined with alerts on patient factors important to

anaesthetists (e.g. history of postoperative delirium or confusion, difficulty in managing airway) to indicate the need for anaesthesia consultation. If implemented on an electronic platform there may be other important advantages: improved communication between patients and anaesthetists and improved preoperative assessment in the current absence of preoperative clinics or early consultation.

The questionnaire that was used was designed to be easily administered (yes/no checkboxes) on an electronic platform (REDCap[138]). Future research opportunities may be created by efforts to enable and simplify electronic data capturing by patients and clinicians, and standardising variables to be collected in registries or databases. Patient-reported predictors and outcomes measures should be analysed in conjunction with data on healthcare resource use.[21,230] There is also a need to validate well-known predictive scores/indices/calculators in the SA private healthcare population should more data become available from this sector. Information on healthcare resource use is also crucial to inform policy-makers as South Africa is moving towards universal healthcare.

A ‘best-care’ guideline,[231] taking into consideration patient-generated data before and after the procedure (e.g. patient-reported outcome measures) and providing opportunity for preoperative optimisation, must be considered in all attempts at reducing costs for specific procedures. It is important that appropriate resources are used to reduce the incidence of clinical outcomes in patients at risk.

The study population may very well be representative of the larger private healthcare population. It is however possible that this model cannot be externally validated because of the inability to replicate the defined outcome from accessible data in future. The study and the results may however assist in changing culture: it is imperative that

more research is done in the South African private healthcare sector, that clinicians understand the importance and interpretation of data on healthcare resource use, that clinicians voluntarily collect clinical data additional to that required for billing purposes, and, most importantly, that patient welfare (not economics) is central to care processes such as preoperative assessment and –optimisation, and patients take ownership of health information exchange.

4.5 Future research

The variables used in this study were included when the Perioperative Shared Health Record (PSHR), a patient-centric, interoperable, web-based platform for electronic data collection, was developed by Safe Surgery SA.

It is therefore possible, if sufficient uptake of the PSHR is realised, to externally validate and update a prediction model. I believe that the predictors identified during risk-adjustment for cost warrant further investigation, whether in an economic analysis or in other risk-adjusted outcome models.

Since the data for the development cohort of the prediction models was collected, the evidence-base for the definitions of possible patient-reported measures has increased. The definition for the following predictors should therefore be revised in the Perioperative Shared Health Record:

- The complete Duke Activity Status Index should be included.[18]
- A Frailty Score, possibly derived from ICD10 diagnostic codes,[186] or a combination of ICD10 codes and self-assessment measures, should be validated and included.
- Detailed self-assessment on mobility and quality of life, where not already represented, should be included in the preoperative questionnaire.

Patient-reported outcomes measures, particularly with regards to patient comfort,[21] have been included in the Perioperative Shared Health Record, but as the effort to standardise the definitions of patient-centred endpoints is continuing, these should be continuously updated.

Further efforts to adjust for procedure mix, to allow for a universal prediction or risk stratification tool, should be made.[50,73,232–234] This process of 'statistical learning'[235] can only happen once larger volumes of information on heterogeneous surgical procedures is collected.

The PSHR can then be used as a data collection tool and prediction model implementation tool for future research. Ideally, with funding, Safe Surgery SA can develop in time on the same lines as initiatives such as the Perioperative Quality Improvement Programme (PQIP) in the UK.

Chapter Four: Conclusion and Proposal for the Future

If I have seen further it is by standing on the shoulders of giants – Isaac Newton

I will clamber on the shoulders of giants to get my feet out of the mud – Hyla Kluyts

1 Principal findings

The clinical prediction model for mortality that was developed from the South African cohort in the African Surgical Outcomes Study performs well on temporal validation, but the predictor definitions should be changed before it can be expected to be generalizable.

The clinical prediction model for a binary outcome of cost that was developed in a single South African private hospital performs well on internal validation, but the definitions of the endpoint and predictors should be standardised (or expert consensus reached on standardisation) before external validation.

Adjustment of outcomes regarding surgical procedural risk is central to the performance of both prediction models. Severity of surgery as a procedure-related predictor for postoperative outcome requires further investigation regarding its definition.

2 Limitations

The data in ASOS were not collected for the purpose of clinical prediction model development. Variables were therefore defined to be in line with the definitions used in other international studies on surgical outcome.

The quality of the data used to develop the prediction models may be questioned, since it was captured by clinicians or patients.

The statistical analysis was done using unsophisticated simple methods, and prediction models may be improved if modern methods are used, e.g. for model estimation.

There are no data available to enable external validation of the prediction models. Predictor definitions are based on assumptions made regarding future opportunities for data collection.

3 Interpretation

It is important that prediction models are presented in such a way as to clearly reflect the purpose for which a model was developed – “to address clinical needs”.[8] External and ongoing validation, or allowing for regular adapting of the model to customise it to changes in the profile of surgical procedures done, or the health of the population sampled, is necessary in the changing environment of a developing country. Subsequent to presenting a prediction model, an impact analysis must be done before it can be adopted and implemented in daily practice.[236]

Recording risk-adjusted outcomes of interest should be as simple a process as possible. The model algorithm, or the coefficients of the predictors, may change as it is validated in different populations, but there should be limited change in the predictor inclusions and definitions of all variables.

Patients should be allowed the opportunity to report measures. This may have the benefit of not increasing the workload of the individual practitioner and at the same time improve patient engagement.

It seems reasonable to present computerised prediction models that will risk stratify patients on entering of the electronic patient data. This presentation will be more

accurate in predicting individual risk than using a risk scoring tool. Although the result of risk stratification will be immediately available during electronic data capturing, it is important that, before further validation, the information is not used to definitively categorise individual patients or advocate specific clinical pathways or interventions. Electronic data capturing also allows for input of variables not entered in the prediction model, so that models can be adapted over time to reflect changes in practice.

The endpoints of the two clinical prediction models that were developed are both relevant in the context of the South African healthcare system: 30-day in-hospital mortality after surgery, and cost of care during hospital admission for surgery. The models describing the predictors influencing estimates of these endpoints may primarily be used in ‘benchmarking’ or comparing observed versus expected outcome in different settings.

The prediction model using mortality as endpoint is most useful to identify areas for quality improvement regarding ‘procedural predictors’ such as urgent or emergent surgery, or the indication for surgery, when these are further investigated and addressed. This model should also be considered when positioning the South African healthcare system in the context of global surgery, by enabling international comparisons. It has to be implemented in all sectors of the system.

The prediction model using cost as endpoint for elective non-cardiac surgery is most useful for identifying the type of surgery that is costly, and in identifying the patient factors that can either be modified by investigating alternative interventions, or considered in planning optimal individual cost-effective care. It is unlikely that cost data for this model can be collected in the public sector, but collecting patient predictors, and patient-reported outcomes measures, is feasible. In other words, the model can

be used to estimate costs in the public sector but cannot at this stage be validated in this sector. The evidence must be generated in the private sector to inform in the public sector. Cost-effectiveness may differ between the private and the public sector due to differences in the burden of disease treatable by surgery. The ‘cost risk’ may also vary between patients, depending on patient-related factors, as demonstrated in Chapter Three. It may however be possible to, by validating and updating the prediction model described, predict the expected cost for a specific procedure. The higher the burden of disease treated by surgery in a population, the more cost-effective the surgery would be. It may be fair to assume that the burden of surgically treatable disease in the public sector is higher than in the private sector.

Where more granular information is available for model development and validation, it seems reasonable to view tools developed as ‘custom-made’ with clearly defined purpose and application, e.g. to evaluate cost-effectiveness for specific types of surgery.

4 Implications

Juran and colleagues[237] clearly elucidated the need and urgency to collect, aggregate and analyse data on surgical and anaesthesia care on a national and international level. Consideration should be given to how the implementation of a clinical prediction model can assist in strengthening the perioperative care system in South Africa. Clinicians and patients will have to be recruited as investigators based on their understanding of how risk stratification, and data feedback, can improve care both to the individual patient and the larger surgical population in the longer term. In my opinion, this is where we can best learn from initiatives such as the ACS NSQIP and the UK PQIP.

The utility of models or tools developed in this work, at this point in time, will be in clinical audit and in identifying areas for quality improvement. However, by stimulating multi-centre observational research across healthcare sectors, it may be possible to progress fairly rapidly to enhanced modelling which may be more appropriate for use in designing interventional studies, or predicting individual patient risk for other outcomes than those used to develop the models reported here. This statement is supported by the development and validation of the ASOS Risk Calculator,[14] to be used in the proposed ASOS-2 Trial, a cluster randomized study to assess the effect of increased surveillance on patients at high risk for 'failure to rescue' after surgery.[238]

The ultimate goal of applying clinical prediction models in South Africa may be to enable shared decision-making in perioperative care – this implies early preoperative individual risk stratification that allows for the team (clinical providers and the patient) to appropriately weigh the risk of surgery against the benefit of surgery, and make decisions on how to mitigate the risk. Risk stratification should ideally be done with clinical-, economic- and patient-reported measures as endpoints. Risk prediction should be accurate for individual patients, as well as procedure-specific and provider- or team-specific.

Applying prediction models in this way requires a significant volume of data, early patient-centric engagement, standardised endpoints (clinical, economic and patient-reported), and an iterative process of prediction model updating as evidence is generated and practices change.

The lack of data on perioperative care available to individual practitioners, perioperative teams, and professional clinician organisations in South Africa render this goal unattainable at the moment. However, with appropriate planning, and

strategic decision-making from national organisations representing clinicians, it may not remain so. Initiating and encouraging data collection on perioperative care may demonstrate the power of such data if the processes are ethically and legally sound. By defining the predictor variables in a perioperative dataset to align with those used in other countries may allow for international comparisons. A clinical prediction model providing a summary of the predictors that influence an outcome, if applied across sectors, is primarily of benefit to standardise predictor measurements in the fragmented system, so that data can be generated. Provider- or team performance benchmarking, if handled and reported appropriately, can have a significant impact on quality of care through ‘self-governance’. Questions such as ‘How large is the gap between quality and affordability of healthcare delivery to the different population subgroups in South Africa?’ or ‘What are the priorities to address when planning to close the gap?’ can only be answered once we have access to better and more data. By taking the lead in collecting, analysing and reporting on perioperative data, clinicians can contribute significantly to health system strengthening.

There is a want of accessible aggregated data generated in the South African private healthcare sector. Appropriate use of data from this sector, where most clinical specialists reside, has the potential to massively impact on the whole of the South African healthcare sector. Clinicians in the private sector have historically mostly been excluded from academic- and research activities, whether by choice or due to work circumstances. There have been anecdotal reports of clinicians wishing to change this. Realistically speaking though, financial incentives will contribute best to participation of clinicians in collecting data. Payment arrangements by medical funders that are made subject to submission of data on surgical events, create the opportunity for the clinical fraternity to take ownership of processes that may generate evidence on

perioperative care. It is crucial though that strict data governance rules are applied to any such processes.

It is also important that, at least in the minds of clinicians, the great social divides in the SA healthcare system are bridged. Practical proposals for implementation need to consider how clinicians in separate environments can be motivated to collect data (particularly outside of academia) and be informed on how data, both from their own and from a different environment, can inform their practice in the future.

From a practical perspective, patient-level data and related facility data for surgical procedures can be sourced from patients and clinicians. This serves as a rationale for developing South African-specific prediction models with features that will be adaptable to eventually enable a universal risk prediction model for the SA surgical population, as well as more purpose-built models.

5 Future research

The American College of Surgeons National Surgical Quality Improvement Project use prediction models of various levels of complexity for reporting to hospitals, but also developed a universal and relatively parsimonious tool to set the benchmark for ‘short-term’ outcome after surgery. In 2013 the group published a study on “Optimizing ACS NSQIP Modeling for Evaluation of Surgical Quality and Risk: Patient Risk Adjustment, Procedure Mix Adjustment, Shrinkage Adjustment, and Surgical Focus”.[50] The semi-annual reports provided to participating hospitals contained hundreds of different statistical models for various outcomes, types of surgery, specific procedures and predictors. The study provides an overview on the statistical and reporting issues common to most of these models. It is notable that the authors believe that strategies for modelling will keep evolving to enable valid, reliable and useful assessment of risk.

In contrast, the Universal ACS NSQIP calculator is used as a risk stratification tool for postoperative complications and death with more than 1500 unique procedural codes, allowing patient-specific risk estimation for almost all surgical procedures.[13] A number of clinicians in South Africa are using the Universal ACS NSQIP calculator in their practice and find the link to the web-based calculator convenient. Although models generated by NSQIP analysis are not applicable outside of the development cohorts,[10] the methodology probably most appropriately represents what needs to be done to develop, validate and implement clinical prediction models in the SA perioperative environment. Variables used in models can be defined based on evidence from South African populations, and there is enough incentive for stakeholders in the private sector to fund initiatives for procedure-specific model development.

Wu et al,[239] when advocating for the addition of patient-reported measures to electronic health records, mention the shift towards “patient-orientated comparative effectiveness research”. It is possible to ‘tether’ a patient portal to an electronic health information system to allow for capturing of patient-reported measures. Patient-reported measures, if captured appropriately and consistently, have the potential to impact significantly on the SA healthcare environment. Patients in SA are exposed either to limited options regarding access to surgery, or to providers that perform in relative isolation so that choice by comparisons are limited. Self-reporting empowers a patient in more ways than one, and there may yet be the opportunity in South Africa to practice truly patient-centred care.

In the United Kingdom, initiatives exist that aim to collect data that can be used to improve the quality of perioperative care:

1. Initiatives recruiting hospitals to continuously submit data on, amongst others, perioperative complication rates and patient-reported outcomes, and demonstrating how this data can be used to drive improvement – the Perioperative Quality Improvement Project (PQIP)[77]
2. Initiatives capturing information on a particular surgical intervention for all cases in the UK on an ongoing basis, e.g. the National Emergency Laparotomy Audit (NELA) project[240]
3. National Audit Projects collecting data from all hospitals on rare anaesthesia-related events/complications over a one year period[241]
4. Research projects to provide a 'snapshot' of clinical activity and outcomes, where data is collected by participating clinical teams over a short time period (e.g. SNAP-1).[242]

All these initiatives can be replicated in the South African setting,[243] provided that the data collection tools and data warehouses are available, and clinicians/clinical teams/hospitals are appropriately incentivised to participate.

Participation will be enhanced when data collection and submission is easy, not time-consuming and clearly of benefit to clinicians, hospitals and patients.

It is crucial to understand what is important to patients when asking for their participation in data collection. Advances in mobile technology create the opportunity to connect with patients in an easy and convenient manner.[244] Systems utilising mobile platforms can also impart health-promotion messages to registered patients. An example of such a system is MomConnect, rolled out by the South African Department of Health.[128] MomConnect has generated a national registry of pregnant patients in the SA public sector.

Future projects should use data collection tools that enable ongoing data collection to maximise on the information return generated by such projects. In other words, participating clinicians and patients should be incentivised to continuously submit data in a convenient manner after participating in a project.

The investigators participating in the African Surgical Outcomes Study were congratulated for their efforts “in the spirit of citizen science”, in an editorial on the ASOS Surgical Risk Calculator publication.[14,67] ‘Citizen science’, that is the collection and analysis of data by members of the general public as part of a collaborative project, has the potential to massively impact on the understanding of healthcare issues in the public health arena. Surgery and anaesthesia care to a population is an important public health intervention, reflected in the prevalence of diseases treatable by surgical intervention in the global burden of disease (non-communicable disease and injuries). Safe Surgery SA NPC has established platforms to allow for data collection by doctors and patients, in the spirit of ‘citizen science’. This thesis describes the development of tools to interpret and use the data to inform on and, with the hope of establishing quality improvement programmes, enhance the way in which perioperative care is provided in South Africa.

Understanding the relative position of South Africa in the global community regarding safety and quality of care can influence how individual care-givers experience their work. During the country’s history of relative isolation during the apartheid era, and subsequent ‘anecdotal’ reports of both successes and failures, little evidence has been published to motivate clinicians. When the system is underperforming, no pointers are offered regarding what to focus on to improve, and where there have been successes (‘we are doing a good job despite the circumstances’) it may have gone unrecognized.

In South Africa, it is important that surgery should be promoted with policy makers as a solution to public health problems. Researchers in the perioperative field, whether the population under investigation is being cared for in the private or the public sector, should be collaborating with public health researchers to produce evidence on the benefit of surgery in this field. The relatively artificial boundaries placed on the delivery of surgical care by the focus on primary healthcare in budgeting for healthcare expenditure, should be removed.

The biggest challenge we face as clinicians in South Africa is not generating evidence on perioperative care, but using this evidence to drive change. Moonesinghe and Pedan,[245] in a recent editorial in the British Journal of Anaesthesia, explain the concept or field of “improvement science”. The CMO framework of the field (context + mechanisms = outcome) is contrasted with the well-known OXO process (Observe, change (X), observe again) of quality improvement. Context is assessed at three levels: macro (national or international), meso (institutional) and micro (team) level. More attention is paid in the Science of Improvement to factors affecting implementation of interventions in context. The intervention for improvement’s fidelity will rely on the context in which it is implemented. Qualitative- and health economic evaluation should be part of the hypothesis development of quality improvement programmes.

It may be possible to develop research projects on improvement in the SA private sector, having qualitative and health economic measures more readily available, while keeping the resource constraints in the public sector in mind when considering implementation. Testing such programmes in the private sector and simulating results across sectors before implementing programmes, may be a rational approach in the unequal and fragmented system we deal with.

It is important to use the resources available in the SA private sector not only to provide quality surgical and anaesthesia care to this select group of patients, but to promote research that can inform and impact on the provision of healthcare to the whole population. The following proposals are preliminary ideas on how to balance the significant change that recruitment of investigators in this sector would require, against the potential benefit to clinicians, patients and the system.

5.1 Sprint National Perioperative Project (SNaPP)

Recent evidence[116] on the impact of medical treatment for cardiovascular risk in the South African population emphasises the high prevalence of hypertension, dyslipidaemia and diabetes in SA patients. The prevalence of these diseases are disproportionately high in certain subpopulations. The impact was simulated using established local and international treatment guidelines and expressed as cost saved for each DALY averted. Surgical intervention for disease may have an even bigger impact; for example, bariatric surgery as treatment for disease contributing to cardiovascular risk. It is important to generate evidence on the predictors and outcome of surgery in South Africa across all sectors, to enable simulation of cost-effectiveness of surgery to improve the lives of South Africans.

Clinical prediction models can be updated or adjusted after validating such models in different populations than where it was originally developed.[9]

The aim of the proposed research would be to collect data in the South African private sector to validate the prediction model for mortality as discussed in Chapter Two, as well as a model developed in an international cohort of patients, such as the Surgical Outcomes Risk Tool (SORT). This implies that the definitions of predictors should be similar for those required by the local and international model.

The objectives would be to adjust or update the model based on its performance regarding calibration and discrimination, so that it can be implemented in a clinically useful way across all sectors of the South African healthcare system, and allow for international comparisons.

5.2 Best Care Arthroplasty Project

Orthopaedic surgical care is costly. However, the impact that this type of surgery can have on the lives of patients may be significant enough to make it a valuable and cost-effective exercise. Arthroplasty costs in the private sector are being scrutinised for possible cost containment exercises. The benefit that the surgery and the associated perioperative care processes[231] may hold for patients are not measured during this scrutiny. Standardising processes of preoperative care and intervention, and team-driven evidence-based care during and after surgery, have the potential to impact on outcomes, patient experience and cost.[246,247]

The aim of the study would be to collect patient-reported measures during the preoperative and postoperative period, together with clinical quality measures, in order to evaluate the cost-effectiveness of arthroplasty procedures in the SA private healthcare sector. Further objectives would include the feasibility of routinely collecting patient-reported outcome measures that are useful to identify areas for quality improvement in perioperative care.

Publications related to this work

- Bishop D, Dyer RA, Maswime S, Rodseth R, Van Dyk D, **Kluyts H**, Tumukunde J et al. Maternal and neonatal outcomes following caesarean delivery in the African Surgical Outcomes Study: 7-day prospective observational cohort study. *Lancet Glob Health* 2019; 7: e513–22.
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Appendix A

Dear Patient

The Anaesthesia Network for South Africa (ANSA) is an initiative of the SA Society of Anaesthesiologists (SASA). The objective of ANSA is to gather information and to use this information to improve anaesthesia care in South Africa, both in the private and public sector. ANSA is working to achieve this objective through research-driven pilot projects. More information on ANSA can be found on www.ansa.org.za.

You may be eligible for inclusion in one of the ANSA research projects. You are eligible for the study as described on the following page if you are 18 years or older, and *not* undergoing emergency surgery, a heart operation or procedure to your heart, or a caesarian section.

Your participation in this project is voluntary. You can refuse to participate or stop at any time without giving any reason. Once the answers to the questions have been captured, you cannot recall your consent. We will not be able to trace your information. Therefore, you will also not be identified as a participant in any publication that comes from the ANSA project.

Note: The implication of answering the questions is that you consent to the inclusion of this anonymous information in the ANSA database. Thus any information derived may be used (only as combined data) by persons authorised by SASA. No patient names will be included and personal identifiers will be hidden.

The ANSA database is used to track care received and the outcomes of healthcare, and for practice/institutions to compare themselves against national averages. The data will assist in establishing what is happening in terms of patient care. The database is secure, and mechanisms are in place to ensure that there is no unauthorised access to any information stored.

Please note that answering these questions does not imply consent to anaesthesia.

Dear Patient

It is important for the doctors and nurses who will take care of you before, during and after your operation to know how healthy or sick you are before the operation. The questionnaire that follows is similar to questions asked by people that will be involved with your care. This questionnaire is part of a doctoral study in Anaesthesiology in the Department of Anaesthesiology, University of Pretoria. You are invited to participate voluntarily in this research project on "The development of a model to predict outcome after elective non-cardiac surgery using a preoperative self-assessment questionnaire in a South African private hospital population." The Research Ethics Committee of the University of Pretoria, Faculty of Health Sciences, telephone numbers 012 3541677 / 012 3541330 granted written approval for this study.

Before answering the 'screening' questions you received information on the Anaesthesia Network for South Africa (ANSA). The answers to the next questions will be stored in the ANSA database. Before you agree to fill in the questionnaire you should fully understand what is involved. If you do not understand the information or have any other questions, please contact the researcher at +27 83 680 3839, or +27 12 373 1054. You should not agree to take part unless you are completely happy about what is expected of you.

To complete the questionnaire may take about 10 - 20 minutes. This paper questionnaire will be collected in a sealed box and it will be kept in a safe place to ensure confidentiality. You may ask a family member or friend to assist you in completing the questionnaire.

The questions will help to determine your health status. You may have to answer such questions again for any of the people involved in your care. The result of the research project will be used to improve the care of all patients going for an operation in South Africa. Please answer the questions as carefully and completely as you can. Your participation in this study is voluntary. You can refuse to participate or stop at any time without giving any reason. Once you have given the questionnaire back to us, you cannot recall your consent. We will not be able to trace your information. Therefore, you will also not be identifiable in any publication that comes from this study.

Note: By completing the questionnaire you give consent that we may use your health information without using your name. Please note that completion of this questionnaire does not imply consent to surgery or anaesthesia.

Instructions: Please tick YES or NO to the questions where indicated. In some cases, should you answer YES, this leads to more questions. Please make sure that these questions are also answered. Deposit the completed questionnaire in the sealed box provided, to ensure confidentiality.

Date of form completion	2	0	Y	Y	M	M	D	D

This form is being completed by the patient				**Yes**	**No**
If not, does the patient have the mental ability to complete the form?				**Yes**	**No**
The form is being completed:					
In the doctor's rooms		At hospital administration		In the ward	

Personal Information																			
ID or Passport number																			
Date of birth	Y	Y	Y	Y	M	M	D	D	Gender		**Male**		**Female**						
Race	**Black**				**White**				**Asian**				**Mixed race**						
Please provide contact number (We will only contact you when there is data missing in your survey)																			

Information on operation				
Have you been operated for the same problem during the past month?			**Yes**	**No**
What is your weight?	kg	What is your height?	cm	

Choose ONE of the following to describe your health in general: (Check ✓)	
You consider yourself a healthy person	
You have an on-going (chronic) condition/illness that affect your daily life only mildly; that is, you can continue with your daily life as previously	
You have an on-going (chronic) condition/illness that affect your daily life severely, that is, the	

disease does not allow you to continue with you daily life as previously		
You have an on-going (chronic) condition/illness that is a constant threat to life, so severe that you must stay in bed to survive		
Is the disease(s) mentioned above the reason for having the operation (if applicable)?	**Yes**	**No**
Are you active or fit enough to:		
Get out of bed or a chair yourself?	**Yes**	**No**
Dress or bathe yourself?	**Yes**	**No**
Make your own meals?	**Yes**	**No**
Do your own shopping or sweep the floor?	**Yes**	**No**
Paint a room or mow the lawn?	**Yes**	**No**
Climb two flights of stairs without stopping?	**Yes**	**No**
Choose ONE of the following reasons for being less active (if applicable): (Check ✓)		
Joint, bone or back problems		
Difficult breathing		
Pain, pressure or discomfort in your chest, neck or arm		
Pain or cramps in your legs		
Your health:		

Do you have high blood pressure?	**Yes**	**No**	**If yes, since when?**	Year	Month
If yes, do you take medication for high blood pressure regularly?				**Yes**	**No**
Have you ever been told that you have a problem with the blood supply to your heart?				**Yes**	**No**
			If yes, when?	Year	Month
Have you ever had a heart attack?	**Yes**	**No**	**If yes, when?**	Year	Month
Have you ever received a stent in the blood supply to your heart?				**Yes**	**No**
			If yes, when?	Year	Month
Have you ever had a bypass or surgery to the blood supply to your heart?				**Yes**	**No**
			If yes, when?	Year	Month
Do you take a small daily dose of aspirin?				**Yes**	**No**
Have you ever been told that you have a weak heart?				**Yes**	**No**
			If yes, when?	Year	Month
Do you have an abnormal heart valve?				**Yes**	**No**
Have you received surgery to a heart valve?				**Yes**	**No**
Have you had rheumatic fever?				**Yes**	**No**
Have you noticed your heart beating very fast, very slow or irregularly, on a frequent basis?				**Yes**	**No**
If yes, have you felt dizzy or blacked out when this happens?				**Yes**	**No**

Have you been diagnosed with abnormal heart rate or rhythm?	**Yes**	**No**
Do you take medication for abnormal heart rate or rhythm?	**Yes**	**No**
Do you have an implanted pacemaker or defibrillator?	**Yes**	**No**
Have you had blackouts or fainting without warning?	**Yes**	**No**
Have you felt dizzy or blacked out while exercising?	**Yes**	**No**
Do you have any weakness or numbness in your arms or legs?	**Yes**	**No**
Do you wake up at night because of difficult breathing?	**Yes**	**No**
Do you get short of breath when lying flat on your back?	**Yes**	**No**
Do your ankles or legs swell?	**Yes**	**No**
Do you take a diuretic ('water tablet') every day?	**Yes**	**No**
When going up the stairs between two floors, do you have to rest in between?	**Yes**	**No**
Do you wake up coughing at night?	**Yes**	**No**
Do you have 'bad circulation' in your hands or feet?	**Yes**	**No**
Have you been diagnosed with disease of the large blood vessels such as the aorta?	**Yes**	**No**
Have you had surgery to the large blood vessels?	**Yes**	**No**
Have you ever had to see a doctor for lung problems of any kind?	**Yes**	**No**
If yes, did the lung problems affect you during the last month?	**Yes**	**No**
Have you ever been admitted to hospital for any lung problems?	**Yes**	**No**

Are you using oxygen at home?				**Yes**	**No**
Have you been smoking cigarettes in the past year?				**Yes**	**No**
Did you smoke before but stopped?				**Yes**	**No**
If yes, how many years have you been smoking/did you smoke?					
How many cigarettes per day do you smoke/did you smoke?					
Have you had a cold or 'flu' in the past 2 weeks?				**Yes**	**No**
Did you have a fever or chills in the past 2 weeks?				**Yes**	**No**
Have you tested positive for HIV?	**Yes**	**No**	If yes, when?	Year	Month
Have you ever been treated for tuberculosis?				**Yes**	**No**
Have you ever been told you have cancer?				**Yes**	**No**
Have you ever had an operation for cancer?				**Yes**	**No**
Have you ever received medication or radiation for cancer?				**Yes**	**No**
Are you currently receiving medication or radiation for cancer?				**Yes**	**No**
Have you been told that the cancer is not under control, or has spread?				**Yes**	**No**
Have you ever had any kidney problems?				**Yes**	**No**
Do you currently have kidney problems?				**Yes**	**No**
Have you ever received dialysis?				**Yes**	**No**
Are you currently receiving dialysis?				**Yes**	**No**

Have you ever had jaundice (yellow skin or eyes) as an adult?				**Yes**	**No**
Have you been told that you have a liver disease?				**Yes**	**No**
Do you have symptoms of the liver disease at the moment?				**Yes**	**No**
Do you have scarring (hardening) of the liver or liver damage?				**Yes**	**No**
Do you have high cholesterol?	**Yes**	**No**	**If yes, since when?**	Year	Month
Do you use medication for high cholesterol?	**Yes**	**No**	**If yes, since when?**	Year	Month
Are you "apple-shaped" (more fat around the waist than the hips)?				**Yes**	**No**
Do you have diabetes (high blood sugar)?	**Yes**	**No**	**If yes, since when?**	Year	Month
Do you use insulin for the diabetes?	**Yes**	**No**	**If yes, since when?**	Year	Month
Have you ever been diagnosed with an underactive thyroid gland?				**Yes**	**No**
If yes, are you taking medication?				**Yes**	**No**
Have you ever been diagnosed with an overactive thyroid gland?				**Yes**	**No**
If yes, are you taking medication?				**Yes**	**No**
Did you eat less than usual or changed your eating habits in the past two weeks?				**Yes**	**No**
Have you lost weight or decreased your dress size in the past 6 months, without dieting?				**Yes**	**No**
Are you pregnant?				**Yes**	**No**
For women: When was your last normal menstruation?	Y	Y	Y	Y	M	M	D	D

Have you had a blood clot in the deep veins or in your lung previously?	**Yes**	**No**
For women: Do you take female hormones, the pill, or do you receive any contraceptive injections?	**Yes**	**No**
Do you have a disease that causes your blood to clot abnormally fast?	**Yes**	**No**
Have you been diagnosed with inflammatory bowel disease?	**Yes**	**No**
Do you use any medication to make the blood thin?	**Yes**	**No**
Do you have a disease that prevents your blood from clotting?	**Yes**	**No**
Have you suffered from short-lived weakness in your arms or legs, or short-lived blindness?	**Yes**	**No**
Have you had a stroke?	**Yes**	**No**
Have you been feeling sad or depressed much of the time?	**Yes**	**No**
Do you take medication for depression?	**Yes**	**No**
Are you in constant pain for any reason?	**Yes**	**No**
If yes, are you taking pain medication or receiving treatment?	**Yes**	**No**
Do you get heartburn?	**Yes**	**No**
Do you have any difficulty to swallow?	**Yes**	**No**
Do you have any narrowing in your mouth, throat, or air pipe that makes your breathing difficult or noisy?	**Yes**	**No**
Have you been told that you snore?	**Yes**	**No**
Do you often feel tired, fatigued, or sleepy during daytime?	**Yes**	**No**

Has anyone seen you stop breathing while you are sleeping?				**Yes**	**No**
Has a doctor diagnosed you with sleep apnoea?	**Yes**	**No**	If yes, when?	Year	Month
How often did you have a drink with alcohol in the past year?					
Never	**Monthly or less**	**2-4 times a month**	**2-3 times a week**	**4 or more times a week**	
How many drinks did you have on a typical day when you were drinking in the past year?					
1 or 2	**3 or 4**	**5 or 6**	**7 to 9**	**10 or more**	
How often did you have 6 or more drinks on one occasion in the past year?					
Never	**Less than monthly**	**Monthly**	**Weekly**	**Daily or almost daily**	
Has any food or medicine caused you to itch, breathe difficult or develop swelling?				**Yes**	**No**
If yes, what caused the reaction?					
Do you use recreational or street drugs?				**Yes**	**No**
Do you use anabolic steroids or testosterone?				**Yes**	**No**
Do you use herbal medication or natural remedies?				**Yes**	**No**
Previous operations					
Have you had an abnormal reaction to an anaesthetic?				**Yes**	**No**
Are you aware of any difficulty to place a tube into your windpipe to help you with breathing during a previous operation?				**Yes**	**No**

Have you ever had nausea and/or vomiting after surgery?	**Yes**	**No**
Have you ever had prolonged confusion after surgery?	**Yes**	**No**
Did you have an unexpected blood transfusion after surgery?	**Yes**	**No**
Were you ever admitted to ICU unexpectedly after surgery?	**Yes**	**No**
Were you ever in hospital for longer than expected after an operation?	**Yes**	**No**
Do you have a family history of any of the following: **(Please note that should a term be completely strange to you, it is highly unlikely that you have a family member that was diagnosed with the problem)**		
Someone died because of anaesthesia-related problems	**Yes**	**No**
Someone stayed in hospital for longer because of anaesthesia-related problems	**Yes**	**No**
Malignant Hyperthermia (an inherited disease triggered by anaesthesia)	**Yes**	**No**
Scoline Apnoea (an inherited problem triggered by a muscle relaxant)	**Yes**	**No**
Porphyria (an inherited disease that may be triggered by some medication)	**Yes**	**No**
Final questions:		
How confident are you in filling out medical forms by yourself?		

Extremely confident	**Quite confident**	**Somewhat confident**	**A little bit confident**	**Not at all confident**

Are you satisfied with the information you have received about what to do, and what to expect before, during and after the operation, and after discharge?	**Yes**	**No**	**Unsure**

Appendix B

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567, Approved dd 22 May 2002 and Expires 20 Oct 2016.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 22/04/2017.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

27/11/2014

Approval Certificate
New Application

Ethics Reference No.: 489/2014

Title: Development of a model to predict outcome after elective noncardiac surgery using a preoperative self-assessment questionnaire in a South African private hospital

Dear Dr Hyla-Louise Kluyts

The **New Application** as supported by documents specified in your cover letter for your research received on the 23/10/2014, was approved by the Faculty of Health Sciences Research Ethics Committee on the 26/11/2014.

Please note the following about your ethics approval:
- Ethics Approval is valid for 1 year.
- Please remember to use your protocol number (**489/2014**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:
- The ethics approval is conditional on the receipt of 6 monthly written Progress Reports, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

*** Kindly collect your original signed approval certificate from our offices, Faculty of Health Sciences, Research Ethics Committee, H W Snyman South Building, Room 2.33 / 2.34.*

Dr R Sommers; MBChB; MMed (Int); MPharMed.
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

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✉ Private Bag X323, Arcadia, 0007 - 31 Bophelo Road, HW Snyman South Building, Level 2, Room 2.33, Gezina, Pretoria

Appendix C

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

03 November 2015

Prof B Biccard
Department of Anaesthetics
School of Clinical Medicine
biccardb@ukzn.ac.za

Dear Prof Biccard

Protocol: African surgical outcomes study (ASOS).
Degree: Non-degree
BREC reference number: BE306/15

EXPEDITED APPLICATION

The Biomedical Research Ethics Committee has considered and noted your application received on 07 July 2015.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 06 October 2015 to queries raised on 21 August 2015 have been noted and approved by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval.**

This approval is valid for one year from **03 November 2015.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **08 December 2015.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
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Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

Appendix D

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
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UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

26/11/2015

Approval Certificate
New Application

Ethics Reference No.: 539/2015

Title: African Surgical Outcomes Study (ASOS): An African, multi-centre seven day evaluation of patient care and clinical outcomes for patients undergoing surgery

Dear Dr Hyla-Louise Kluyts

The **New Application** as supported by documents specified in your cover letter dated 26/10/2015 for your research received on the 2/11/2015, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 25/11/2015.

Please note the following about your ethics approval:
- Ethics Approval is valid for 1 year
- Please remember to use your protocol number (**539/2015**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:
- The ethics approval is conditional on the receipt of 6 monthly written Progress Reports, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

*** Kindly collect your original signed approval certificate from our offices, Faculty of Health Sciences, Research Ethics Committee, H W Snyman South Building, Room 2.33 / 2.34.*

Dr R Sommers; MBChB; MMed (Int); MPharMed.
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2015 (Department of Health).

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