Frailty in peri-operative patients in three South African Academic Hospitals

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of

Master of Medicine in the branch of Anaesthesiology

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Declaration

I, Ngozi Leopold-George, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Anaesthesiology at the University of the Witwatersrand, Johannesburg. This research report has not been submitted before for any degree or examination at this or any other University.

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Signed

On this _____day of_____2018

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I would like to thank my supervisor Dr Gladness Nethathe for her guidance, patience and unwavering belief in me. To my husband, Daudi, you were my editor-in-chief and my rock. Thank you both immensely.

Abstract

Background

Frailty is a state characterised by diminished physiological reserve that leaves one vulnerable to external stressors and delays recovery thereof. Frailty assessments are proving to be more valuable in predicting poor perioperative outcomes than other well-known peri-operative risk assessment tools. There are very few studies that have been done using validated frailty assessment tools to assess the prevalence of frailty in South Africa and none have assessed the intraoperative implications of frailty in a surgical population.

Methods

We prospectively enrolled 299 participants aged 18 to 90 years undergoing various types of elective surgery between November 2016 and March 2017 in three South African Academic Hospitals. Frailty was assessed using the nine-point Clinical Frailty Scale (CFS) and was defined as a score of five or more. The CFS score, demographic and clinical data were documented by the anaesthetists assigned to the respective elective lists. The primary outcome measure was intraoperative complications (hypotension, desaturation, need for vasopressors and blood transfusion). We additionally compared the association between participant's comorbidities and frailty as well as the association between the CFS and the American Society of Anaesthesiologists Physical Status (ASA-PS) scores.

Results

Two hundred and ninety-nine participants were included in the study. The mean age was 50.6 years (SD15.8). One hundred and fifty-six (52%) were women. Sixty-seven (22%) were classified as frail. The frail group had significantly higher incidences of hypotension (odds ratio [OR] 1.87, 95% confidence interval [CI]1.083-3.259; p=0.02), desaturation (OR 3.79, 95 % CI 1.367-10.54; p=0.01), need for vasopressors (OR 2.81, 95 % CI 1.607-4.912; p=0.00) and blood transfusion (OR 3.26, 95 % CI 1.138-9.368; p=0.02). On multivariable logistic regression analysis, adjusting for factors related to frailty such as age, gender and comorbidities, desaturation was significantly associated with frailty (Adjusted OR [AOR] 4.21, 95% CI 1.31-13.53; p=0.01). The frail were also more likely to require blood transfusion (AOR 5.36, 95%

CI 1.50-19.16; p=0.01). The frail were older and had more comorbidities. Higher ASA-PS scores were also strongly associated with frailty.

Conclusion

The prevalence of frailty was high among surgical patients. Consistent with other studies frailty was associated with older age and multiple comorbidities. The association between frailty and intraoperative complications found in this study may indicate and help inform areas of further research.

Table of contents

Awards and research outputs arising from this project

1. Abbvie scholarship in anaesthesia: Ngozi Leopold-George, 2017/2018

2. Review article: Title Frailty: What the South African Surgeon Needs to Know Authors: Ngozi Leopold-George, Gladness Dakalo Nethathe. Submitted to South African Journal of Surgery. Accepted 12/10/2018. Awaiting publication.

3. Original Article: Frailty in perioperative patients in three South African Academic Hospitals Authors: Ngozi Leopold-George, Gladness Dakalo Nethathe. Submitted to South African Medical Journal. Ref.: SAMJ13439 Accepted 20/08/2018. Awaiting publication.

4. Abstract submission: Frailty in Perioperative Patients in three South African Academic Hospitals. Authors: Ngozi Leopold-George, Gladness Dakalo Nethathe. Faculty of Health Sciences Research Day. Date of submission 25/05/2018. Accepted for poster presentation 06/09/2018

List of tables

List of figures

List of abbreviations

ADL	Activities of daily living
AIDS	Acquired immunodeficiency syndrome
ASA-PS	American Society of Anaesthesiologists physical status
CFS	Clinical Frailty Scale
CGA	Comprehensive Geriatric Assessment
COPD	Chronic obstructive pulmonary disease
DNA	Deoxyribonucleic acid
ENT	Ear, nose and throat
ERAS	Enhanced recovery after surgery
ICU	Intensive care unit
HAART	Highly active anti-retroviral therapy
HIV	Human immunodeficiency virus
LOS	Length of stay
MRI	Magnetic resonance imaging
RCRI	Revised Cardiac Risk Index
TNF	Tumor necrosis factor
TB	Tuberculosis
TUGT	Timed up and go test
US	United States (of America)
WHO	World Health Organisation
WHI-OS	Women’s Health Initiative Observational Study

Section 1: Literature review

1.1 Introduction

The ageing population is growing at a rapid rate worldwide, with an increasing impact on medical services and surgical services.[1] In 2010 two thirds of the world's population above the age of 60 lived in developing countries [2] and the World Health Organisation (WHO) reports that the number of people above the age of 60 will effectively double by 2050.[3] In the US over 40% of surgeries are being performed on elderly patients.[1] The identification and management of conditions that impact on these patients' surgical and anaesthetic risks may improve outcomes.[4,5]

1.2 Epidemiology

The first reference to frailty and old age was in 1956 by Parfentjev.[6] It was only in the 1970s where the term 'frail elderly' was adopted when the Federal Council on Aging defined it as 'persons, usually but not always, over the age of 75, who because of an accumulation of various continuing problems often require one or several supportive services in order to cope with daily life'.[7]

Frailty is the depletion of physiological and functional reserve across many organ systems leading to a diminished capacity to withstand environmental stressors such as surgery.[8] It is an independent predictor of mortality, morbidity, complications and increased length of stay perioperatively.[9] It is predicted to become one of the most problematic public health issues that will place a heavy strain on already overburdened health care systems.[10] The cost implications in caring for frail patients are estimated to be three times that of non-frail patients.[11]

Frailty although often associated with the elderly can also affect the non-elderly as recent work has revealed.[12,13] Frailty is also not synonymous with ageing as there is a robust elderly population that would not fall under the category of being frail.[9]

In South Africa there is an estimated 12,2% (6,4 million) of the population living with HIV.[14] Age-related diseases such as frailty and comorbidities have been noted to affect younger adults infected with HIV.[15] The dual epidemic of HIV and TB remains a concern. In addition, South Africa has a high burden of trauma and injury which has implications related to surgery, critical care services and disability.[16]

Worldwide, the prevalence of frailty is quoted between 4-59.1% depending on the population sampled and the model or tool used.[17,18]

A higher prevalence is reported among hospitalised, surgical populations compared to community dwelling elderly populations.[19] Patients undergoing surgery are reported to have a prevalence ranging from 4.1-56%.[20,21]

Frailty increases with age affecting an estimates of 10% of people over the age of 65 and 25-50% of people over the age of 85.[22] In a Canadian study using The Clinical Frailty Scale (CFS) the prevalence of frailty was 32.8% in critically ill adults above the age of 50 with a mean age of 67[12] and was associated with higher in-hospital mortality, major adverse events and functional dependence. In an Australian study population, the prevalence of frailty was 10% in patients in an intensive care unit (ICU). The mean age in this study was 60. Although frailty was not significantly associated with hospital mortality it was associated with increased length of stay (LOS).[23]

Of interest is that 28% of patients in three acute general surgical admission units with a mean age of 77.3 years were assessed as frail using the CFS.[24] Frailty in this study was predictive of 30 and 90-day mortality as well as increased hospital stay even though a large proportion of their frail patients did not undergo surgery.

Although frailty can affect a younger population and deemed to be a good predictor of biological age there have been few studies conducted in the under 65 age group.[12,23,25] One study compared the prevalence of frailty using Fried's phenotype criteria and the frailty index in the 18-79 age category.[26] In this study frailty was shown to increase with age and was also present in the younger age groups. It also showed a higher prevalence of frailty in all age categories when the frailty index was used compared to Fried's phenotype.

Some studies show the prevalence of frailty in HIV infected adults to be equivalent or even greater than in the elderly.[15,27] A South African study compared frailty between HIV positive and HIV negative adults.[27] The mean ages of the HIV positive and HIV negative groups were 41.1 years and 42 years respectively. There was a 19.4% prevalence of frailty in the HIV-infected adults compared to a 13.3% frailty level in the HIV-seronegative adults (p=0.01).

Little data exists with regards to the impact of frailty on the under 65-year age group on mortality, morbidity and disability.[26] Most studies using any one of the validated frailty measuring tools have been conducted in developed countries with few published studies in the developing world and fewer still in Africa.[17,22]

1.3 Pathophysiology of factors associated with frailty

1.3.1 Ageing

The pathophysiology of ageing involves complex multiple mechanisms at a molecular and cellular level. These include cellular senescence, genomic instability, stem cell exhaustion and altered intercellular communication.[22,28] Another purported mechanism is that of age-related decline of mitochondrial function and DNA copy number which results in reduction in energy production and reserves, increased free radical production and increased rates of apoptosis.[29]

Age related changes to the cardiovascular system can lead to orthostatic hypotension which can predispose to falls. A reduction in respiratory reserve can lead to atelectasis, pneumonia and increased risk for aspiration which are most problematic in the perioperative period. Neurological changes such as autonomic dysfunction and impaired autoregulation of cerebral perfusion leads to increased risk of postoperative cognitive disorders, stroke and injury. Decline in renal blood flow and increased occurrence of prostatic hypertrophy increases the risk of renal dysfunction and urinary tract infections. Reduced muscle and strength lead to falls, immobility, venous thromboembolism and pressure injury which predisposes to increased hospital length of stay and lead to disability.[30]

The loss of functional reserve with ageing impedes homeostasis, the ability of a physiological system to function well at rest and under stress. Functional reserve allows the body to compensate and adapt to environmental stressors thus restoring homeostasis. Frailty hastens the decline in functional reserve to the extent that reserves are diminished for essential homeostatic mechanisms.[22] Accumulation of health deficits also deplete functional reserves which leads to decline of organ systems. Frailty increases with the number of impaired systems rather than the number of impairments in any one particular system.[22]

When reserve capacity is diminished, there is increased vulnerability and the ability to respond and recover from stressors such as surgery, severe illness or injury may be prolonged or not occur at all.[22]

1.3.2 **Immune and Endocrine system**

The dysregulation of immune and endocrine systems have been implicated in the development of frailty.[22] Immune system changes where there is a maldistribution and dysregulation of immune cells leading to higher levels of cytokines in the body are associated with ageing.[4]

Sarcopenia and cachexia are closely related to frailty. Sarcopenia is a progressive loss of muscle mass resulting in loss of strength and/or physical performance and is considered a hallmark of frailty.[5,31] Cachexia is a catabolic syndrome associated with chronic illness.[5] Sarcopenia is distinguished from cachexia as it is a more moderate loss of muscle mass with little to no adipose tissue loss.[11] Loss of skeletal function and mass are a result of age-related hormonal changes and inflammation. Hormonal changes include decreased growth hormone, insulin-like growth factor-1, dehydroepiandrosterone, sex steroids and increased cortisol levels. Low vitamin D levels have also been suggested to be linked with frailty.[4]

Frail patients are said to be in a constant state of chronic inflammation.[1] Elevated immune biomarkers such as interleukin-6 (IL-6), TNF-alpha and C-reactive protein have been noted in frail patients.[4] Indicators of chronic inflammation such as low albumin have been used as measures of frailty.[3] Pro-inflammatory cytokines promote protein catabolism and alter metabolic processes which have an effect on skeletal muscle, appetite, immunity, cognition and contribute to the development of anaemia.[1] Immune system activation contributes to disordered coagulation leading to elevated serum markers of coagulation such as D-dimer, factor VIII and fibrinogen. Elevated neutrophil and monocyte cell counts have been demonstrated in frail elderly.[4] Frailty has also been associated with impaired response to pneumococcal and influenza vaccines.[22]

None of these biomarkers are unique to frailty as many are also found in other conditions, making pathophysiological mechanisms leading to frailty harder to elucidate.[1]

1.4 **Risks and associations**

1.4.1 **Comorbidity**

Frailty and comorbidity although related are distinct entities. Frailty can be present without comorbidity [33] but there is overlap that becomes more evident with multiple comorbidities.[22]

Frail women were more likely to have had a previous diagnosis of coronary heart disease, stroke, diabetes mellitus, hypertension, arthritis, cancer and COPD.[34] With regards to HIV, the presence of the frailty phenotype was noted to be a predictor of AIDS or death in HIV infected men despite initiation of HAART.[35] Frailty has also been linked to chronic kidney disease as well as visual and hearing impairment.[36] Polypharmacy, which is common in the geriatric population with multiple comorbidities, has also been hailed as a possible contributor to frailty secondary to side effects experienced such as postural hypotension and myopathy. It may also just be a marker of multimorbidity.[36-38]

Frailty has shown strong associations with clinical and subclinical cardiovascular disease as evidenced by electrocardiogram features of ischemia and left ventricular hypertrophy and echocardiographic changes of reduced global left ventricular function.[32] A large degree of atherosclerotic plaques also correlated with frailty. One purported mechanism is that atherosclerosis represents a state of inflammation which may lead to frailty as a result of the catabolic state and loss of muscle mass and appetite that ensues.[32] Frailty was identified as a risk factor for mortality and prolonged institutionalisation after cardiac surgery.[39] Congestive heart failure was most strongly associated with frailty as the severely frail were seven times more likely to have this condition.

Preoperative frailty was shown to have a positive correlation with postoperative delirium.[40] Depression has also been linked to frailty.[18,34] The two conditions share common symptoms such as weight loss, low physical activity and exhaustion. Depression has been associated with the stimulation of pro-inflammatory psycho-neuroimmunological mechanisms and progressive muscle and functional loss from a reduction in physical activity. The term ‘frail identity crisis’ describes the individual who surrenders to a frail status by a psychological maladaptive state.[41] Other factors

such as religion have been found to be protective against frailty presumably due to alleviation of psychological distress and social support.[18]

Being underweight and overweight are both risk factors for frailty, as evidenced by a U-shaped relationship between body mass index and frailty, showing that extremes of body fat can be associated with lower muscle mass and strength.[34] Not only is obesity a state of heightened inflammation, the obese may be micronutrient deficient and both conditions are associated with sarcopenia. ‘Sarcopenic obesity’ is used to describe the state of being overweight but contrastingly having low muscle mass.[34]

1.4.2 **Sociodemographic**

Gender

Frailty has been reported to be higher in women compared to men.[18,33] Notably one study found that elderly men were more likely to die than women at similar levels of frailty.[18] This may be attributable to gender differences in genetic and acquired risks, immune and hormonal differences as well as health reporting behaviour. Men generally have higher levels of muscle mass and testosterone.[18] Gender differences in self-reported health might prove an important factor in gender differences.[34]

Low Socioeconomic status

The Women's Health Initiative Observational Study (WHI-OS) found low family income, low level of education and being African American was strongly associated with frailty.[34] Education and race were however weak associations after adjustment for confounders and may have been indicators of social status and not race and education per se. Most studies on frailty have been conducted on Caucasian patients in developed Western countries and in these countries the prevalence has been found to be higher in Hispanic and African Americans.[17,33] More studies are needed to further validate whether the prevalence is truly higher in other racial groups or whether this is a function of low socioeconomic status.[4] Contrastingly Gu et al found strong associations between frailty and economic level and weak associations between frailty, education and occupation.[18] A high socioeconomic status may afford an individual the resources to care for and improve their health delaying the progression to frailty. Lifestyle factors that are associated with low socioeconomic status such as smoking, alcohol use, and comorbidities such as HIV may account for the increased risk of frailty in groups of low socioeconomic status.

1.4.3 **Lifestyle factors**

Cigarette smoke contains various chemicals which can cause chronic inflammation leading to muscle wasting as well as accelerate ageing. In the WHI-OS smokers were 2.9 times as likely to become frail.[34] Moderate alcohol intake was protective with moderate alcohol drinkers having up to a 31% lower risk than non-drinkers.

A systematic review by Kojima et al showed a positive association between smoking and developing or worsening frailty.[42] Smoking is additionally associated with many comorbidities such as cardiovascular and respiratory disease as well as cancer.

Lack of physical activity is a risk factor for frailty.[33] Regular exercise has been found to be protective against frailty across all age groups.[18] Individuals that were more physically active were found to have a lower risk of death.[43]

1.4.4 **Disability**

Frailty is a potential cause and consequence of physical disability, but not all disabled persons are frail.[36] Disability is difficulty or inability to complete one or more activities of daily living (ADL).[36] It can be a consequence of frailty or chronic disease secondary to changes in musculoskeletal function. Fried et al showed only 27% of those who had ADL disability were frail and of those who were frail only 6% had ADL disability.[33] ADL disability, which was defined as needing help with one or more ADLs, although low was more common in the frail (5.9%) than non-frail (0.7%) in the WHI-OS.[34]

The WHI-OS measured participants baseline level of frailty at the beginning of the study and defined it as 3 or more of Fried's frailty components. Baseline frailty was strongly associated with ADL disability at year 3 of follow-up which demonstrates that the frail are at increased risk of disability. The main distinguishing point between frailty and disability is that frailty is dynamic and can be reversible whereas disability tends to be permanent.[15] It is therefore important to identify frail patients and implement prevention strategies before they become disabled.

1.5 **Risk estimation in surgical patients**

The preoperative assessment provides a means of recognising those at risk in order to identify factors that can be optimised preoperatively.[30] It should also present an opportunity to discuss issues of harm and benefit as well an opportunity to map out the likely postoperative outcome.[44]

Older surgical patients tend to have a high comorbidity burden and are at an increased risk of poor surgical outcomes and anaesthesia-related complications and death.[4,45] The implications of these comorbidities on the perioperative course is not always apparent.[45] Age alone as a criterion for selecting persons at risk of interventions has been shown to be less than ideal across a wide spectrum compared to frailty assessments.[46]

The American Society of Anaesthesiologists Physical Status (ASA-PS) classification system has been found to predict outcomes in surgical patients but mainly younger patients and with higher predictive value in those that score 3 or more. There is also wide interrater variability when using the ASA-PS.[25] Frailty assessments have been shown to be a better indicator of overall health and physiological status as well as better predictors of postoperative complications, mortality and morbidity in the aged than other preoperative assessments such as the ASA-PS and the Revised Cardiac Risk Index (RCRI).[20,47,48] Frailty assessments are unique as they are one of the few assessments that estimate the individual's global physiologic reserve.[20] The debate remains as to which frailty assessment tool is best to use in clinical practise to predict outcomes among surgical patients. Some authors have suggested combining risk assessment tools such as the ASA-PS and frailty assessments to improve postoperative risk prediction.[5,25]

Correct assessment will identify the most vulnerable and may help facilitate discussions about realistic treatment goals, improve clinical risk prediction and inform health resource utilization practice.[49]

1.6 **Assessing frailty**

Multiple models have been used to measure frailty. The two most popularised models are the frailty phenotype [33] and frailty index or deficit accumulation model [50] which are models developed from data taken respectively from the Cardiovascular Health Study and the Canadian Study of Health and Aging. The frailty phenotype was proposed by Fried et al in 2001 who defined frailty as a syndrome based on phenotypic features which are unintentional weight loss, exhaustion, weakness (low grip strength), slow walking speed and low physical activity. Three or more out of the five features would make the diagnosis of frailty whereas one or two features would

be considered pre-frail.[33] This definition has been criticised as being non-specific and placing too much emphasis on the physical nature of frailty.[8] It also requires special equipment such as a dynamometer to measure grip strength which may not always be readily available.

The deficit accumulation model views frailty as a state of vulnerability as a result of the accumulation of an individual's health deficits. This model consists of adding the number of health deficits or impairments in an individual and dividing it by a pre-determined number of possible health deficits to create a frailty index.[51] This model places more emphasis on psychosocial aspects as well as physical disability, comorbidity and cognitive impairment.[8,52] The frailty index ranges between 0 and 1 with a deficit value above 0.25 generally accepted as frailty and higher values representing higher degrees of frailty.[53] Concerns with this model is that the number of possible health deficits may be numerous making it a cumbersome tool for the everyday clinician. It has gained popularity as a research tool.[1] Both models have been shown to be valid ways of measuring frailty and good predictors of morbidity and mortality.[33,51]

Many other scales have been derived from these two models such as The Modified Frailty Index which contains 11 deficits and was shown to be useful in predicting morbidity and mortality following surgery.[47] The Edmonton Frail Scale is a 17-point scale with nine frailty components: cognition, general health status, functional independence, social support, polypharmacy, nutrition, mood, continence and functional performance[54] but it might not be applicable in an emergency setting.[22]

The addition of laboratory markers of chronic disease such as plasma albumin concentration to increase the predictive value of preoperative frailty assessments has been suggested.[55] Fried's phenotype model was combined with biomarkers such as anaemia and low albumin as well as factors such as comorbidity, cognition and a history of falls to predict longer hospital stays and higher readmission rates in a colorectal and cardiac surgical population.[21]

Screening tools were developed and validated in order for physicians to quickly identify frailty. Some of these include the Clinical Frailty Scale, the FRAIL, the Cardiovascular Health Study Frailty Screening Measure and the Gérontopôle Frailty Screening Tool.[36]

The Clinical Frailty Scale (CFS) was developed in Dalhousie University in Canada in attempting to address the need for a screening tool that was more clinician friendly.[52] It is a 9-point scale with pictographs from 1 (very fit) to 9 (terminally ill) and a score of 5 or more is used to classify frailty. Judgement is made about the degree of frailty based on the history and clinical examination. It also grades the severity of frailty. It has been validated to predict outcomes in hospitalised patients though not extensively studied in clinical settings.[52] It was found to have good interrater reliability[12] and predictive of mortality and functional decline when used by junior medical staff with no prior training on how to use the scale.[56]

The FRAIL scale has 5 components: fatigue, resistance, ambulation (slow walking speed), illness, loss of weight with 3 or more components needed to classify frailty. It was shown to predict mortality in middle-aged African Americans.[57]

Performance based tests such as gait speed, timed up and go test (TUGT) [58] and grip strength are more objective tests of functional ability and have been proven to predict adverse health outcomes.[10] TUGT measures the time taken from sitting to rising from a chair to a standing position, walking a specified distance on a flat surface and returning and sitting on the chair.[1] Gait speed is postulated to be the single best indicator of frailty in Fried's frailty components and was the most significant predictor of mortality and morbidity in elderly patients after cardiac surgery.[59] These tests however require special equipment such as a dynamometer for grip strength whereas gait speed and TUGT are not feasible for patients that are not ambulant. Morphometric tests which utilise imaging to measure low muscle mass or sarcopenia have also been introduced as a surrogate measure of frailty.[60]

There are geriatric assessments that assess components of frailty such as the Mini-Mental State Examination, the Katz Index of Independence in Activities of Daily Living, the Mini-Cog test and the Short Physical Performance Battery.[10] Comprehensive geriatric assessment (CGA) is the established gold standard to evaluate older people which assesses medical, psychosocial, nutritional and functional ability.[22] CGA has been shown to improve outcomes in older surgical patients.[61]

Frailty screening can identify those patients that can benefit from the CGA. Current resources cannot provide CGA for all old people as it requires time and the expertise

of a multidisciplinary team such as a geriatrician, occupational therapist, physiotherapist and dietician.[11] Frailty screening will also identify patients that would not ordinarily receive a CGA based on their chronological age but whose biological age would warrant one.

There is call for a standard, reliable measurement for identification of frailty worldwide[10] however it is not known which frailty assessment or tool is most useful in a clinical surgical setting in predicting outcome as different frailty measurements may be suited for different populations.[55] The ideal perioperative frailty assessment should not only be predictive of complications and mortality but also be easy to calculate by non-geriatricians.[55]

Table I: Comparison of frailty measurements

Frailty measurement (Year)	Description	Reference	Study population and procedure	Outcomes
Frailty phenotype (2001)	3 or more of 5 components: Slow mobility Weakness Weight loss Exhaustion Low physical activity	Fried et al [33] Makary et al [20]	Prospective study of patients ≥ 65 yrs undergoing all types of elective surgery	Preoperative frailty associated with increased risk of postoperative complications and LOS OR 2.54, 95% CI 1.12-5.77
Frailty Index/ deficit accumulation (2001)	Use of 30+ variables No. of health deficits present/number of possible health deficits e.g. 10 out of 50 deficits= frailty index of 0.20	Rockwood and Mitnitski [50] Theou et al [62]	Retrospective study of people ≥ 50 yrs in the Survey of Health Ageing and Retirement in Europe (SHARE)	Frailty predicts all cause mortality at 2 and 5 years area under the receiver operating characteristic curve (AUC) = 0.77, 95% CI 0.75–0.7; AUC = 0.75, 95% CI 0.74–0.77
Clinical Frailty Scale (2005)	Score of 5 or more out of 9	Rockwood et al [52]	Prospective study of	Frailty associated with higher in hospital mortality

	Based on impairment in mobility, function and clinical judgement	Bagshaw et al[12]	critically ill adults ≥ 50 yrs	OR 1.81, 95% CI 1.09-3.01 and major adverse events OR 1.54, 95% CI 1.01-2.37
FRAIL scale (2012)	3 or more of 5 components: Fatigue Resistance Ambulation Illness Loss of weight	Morley et al [57] Kaehr et al [63]	Retrospective study of patients ≥ 65 yrs in long term care	Frailty predicts mortality at 6 months adjusted odds ratio (AOR) 3.36, 95%CI 1.26-8.98 Pre-frailty associated with risk of falls at 6 months AOR 2.62; 95% CI 1.25-5.54;
Modified Frailty Index (2012)	Frailty Index condensed to 11 variables: 1. Diabetes mellitus 2. Dependent functional status 3. Chronic obstructive pulmonary disease or pneumonia 4. Congestive heart failure 5. Myocardial infarction 6. Angina or prior coronary intervention including stent or coronary artery bypass graft	Farhat et al [47]	Retrospective study in patients ≥ 60 yrs undergoing emergency general surgery	Frailty index using mFI predicted mortality at 30 days OR 11.70

	7. Hypertension requiring medication 8. Peripheral vascular disease 9. Impaire d sensorium 10. Prior transient ischemic attack or stroke without residual deficit 11. Cerebrovascular accident with residual symptoms			
Edmonton Frailty Scale (2006)	Score of 8 or more out of 17 with 9 frailty components: cognition, general health status, functional independence, social support, polypharmacy, nutrition, social support, mood, continence and functional performance	Rolfson et al [54] Dasgupta et al [64]	Prospective study of patients ≥ 70 yrs undergoing a variety of surgical procedures	EFS > 7 associated with increased complications OR 5.02, 95% CI 1.55-16.25 and a lower chance of being discharged home (40%, p<0.02).
Robinson Index (2013)	Katz Score ≤5, Timed Up and-Go ≥15 seconds, Charlson Index ≥3, anemia<35%, Mini-Cog score ≤3, albumin<3.4g/dL and ≥1 fall within six-months	Robinson et al[21]	Prospective study of patients ≥ 65 yrs undergoing colorectal and cardiac surgery	Frailty associated with increased LOS and readmission and predicted postoperative complications in both groups (AUC > 0.7)

1.7 **Management**

Frailty is generally a progressive disease but can improve with the right treatment and intervention.[22,57] Few studies have explored the effectiveness of interventions aimed at preventing and treating frailty in surgical populations.[4,65]

The most effective way to limit the burden of disability is by preventative actions. Though the critical window during which intervention is most likely to be effective has not yet been established, considering the spectrum from prefrailty to disability it is generally accepted that the prefrailty stage is the period during which interventions may be most effective.[17]

Exercise has been shown to increase functional performance, walking speed, balance and decrease depression and fear of falling.[66] A meta-analysis was conducted to show the effects of physical exercise on elderly people aged 60 to 85 who had problems with mobility and/or physical activity and/or multimorbidity.[67] It showed that exercise can improve mobility and physical function. High intensity exercise, with strength training being an essential component, was found to be superior to low intensity exercise and both short term and long-term interventions showed positive results.

Prehabilitation is the concept of improving functional capacity before undergoing stress or surgery.[68] This is usually done with exercise training but there is a strong move to include nutrition and cognitive interventions. A study conducted on community dwelling prefrail and frail adults showed that frailty scores were reduced over a 12 month period in the nutritional (OR 2.98), cognition (OR 2.89), physical (OR 4.05) and combination (OR 5.00) intervention groups.[69] In surgical patients prehabilitation has been shown to improve perioperative functional exercise capacity as measured by a 6-minute walk test.[70] The impact of prehabilitation on perioperative outcomes however still needs further investigation.[9]

Nutritional supplementation and increased protein intake contributes towards the prevention of weight loss, increases muscle mass and improves grip strength.[71]

Anaemia and hypoalbuminemia are common in frail surgical patients and are associated with increased morbidity and mortality.[73] The management of anaemia with oral or intravenous iron supplementation is recommended to improve surgical

outcome in patients undergoing elective orthopaedic surgery.[74] Furthermore, there is also evidence that vitamin D supplementation in frail patients that are vitamin D deficient might be helpful. Daily vitamin D supplements (800-1000u/d) was beneficial in improving gait and posture. [75] Perioperative vitamin D supplementation remains controversial.[22]

Polypharmacy with medicines such as anticholinergics and sedative medications has been associated with the development of frailty.[38] This is likely due to the effects of these medications on cognition and contribution to falls. Interventions targeted at reducing polypharmacy and high-risk prescribing may be beneficial in reducing frailty. Novel approaches include pharmaceuticals that are exploring angiotensin converting enzyme inhibitors as a way of addressing the loss in muscle mass and function but more studies are needed.[76]

Enhanced recovery after surgery (ERAS) is a multimodal, multidisciplinary perioperative approach that aims to hasten recovery and improve outcomes in patients undergoing major surgery.[77] It aims to minimize the stress response to surgery and prevent organ dysfunction through components that begin preoperatively through to the postoperative period. Preoperative interventions include patient education, prehabilitation, optimisation of comorbidities and fasting guidelines. Intraoperative interventions include appropriate selection of short acting anaesthetic agents, multimodal analgesia, fluid and temperature management as well as a minimally invasive surgical approach. Postoperative interventions focus on pain management, early removal of tubes and drains, prevention of nausea and vomiting as well as early nutrition and mobilisation. It has been shown to be a cost-effective approach to reducing postoperative complications and minimizing hospital stay after major surgery.[77,78] Frail assessments used preoperatively should identify those most vulnerable that could benefit from such interventions.

1.8 **Conclusion**

The perioperative environment provides a unique opportunity to identify frail individuals. The role of the anaesthetist is that of patient advocacy and knowing the importance of early recognition of frailty as it can allow for the optimisation of anaesthetic and surgical techniques in order to reduce frailty associated

complications. This also allows for extra vigilance with regards to the perioperative care of these patients as well as the anticipation of the postoperative course of the patient.

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Section 2: Journal guidelines to authors

General article format/layout
Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, α not a for alpha, β not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

** NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:
    - Human Gene Mapping Workshop (HGMW): genetic notations and symbols
    - HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature

- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research
Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.
Do not replicate data in tables and in text .

Structured abstract
- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article
All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.
The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion
Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study

- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions
This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make ‘new rows’:

References
NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of*

*reference manager software. Endnotes must **not** be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.
    - Click Actions > Cite
    - Alongside 'url =' copy the URL between { }.
    - Provide as follows, e.g.: http://dx.doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. DOI:10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
    - Government Gazettes:
      National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.
      In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.
    - Provincial Gazettes:
      Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.
    -

- Acts:
  South Africa. National Health Act No. 61 of 2003.
- Regulations to an Act:
  South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).
- Bills:
  South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.
- Green/white papers:
  South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.
- Case law:
  Rex v Jopp and Another 1949 (4) SA 11 (N)
  Rex v Jopp and Another: Name of the parties concerned
  1949: Date of decision (or when the case was heard)
  (4): Volume number
  SA: SA Law Reports
  11: Page or section number
  (N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.
  NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

Section 3: Submissible Article

Title

Frailty in peri-operative patients in three South African academic hospitals

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Keywords

Frailty, surgery, elderly, assessments, Clinical Frailty Scale, intraoperative complications

Abstract

Background

Frailty is a state characterised by diminished physiological reserve that leaves one vulnerable to external stressors and delays recovery thereof. Frailty assessments are proving to be more valuable in predicting poor perioperative outcomes than other well-known peri-operative risk assessment tools. There are very few studies that have been done using validated frailty assessment tools to assess the prevalence of frailty in South Africa and none have assessed the intraoperative implications of frailty in a surgical population.

Methods

We prospectively enrolled 299 participants aged 18 to 90 years undergoing various types of elective surgery between November 2016 and March 2017 in three South African Academic Hospitals. Frailty was assessed using the nine-point Clinical Frailty Scale (CFS) and was defined as a score of five or more. The CFS score, demographic and clinical data were documented by the anaesthetists assigned to the respective elective lists. The primary outcome measure was intraoperative complications (hypotension, desaturation, need for vasopressors and blood transfusion). We additionally compared the association between participant's comorbidities and frailty as well as the association between the CFS and the American Society of Anaesthesiologists Physical Status (ASA-PS) scores.

Results

Two hundred and ninety-nine participants were included in the study. The mean age was 50.6 years (SD15.8). One hundred and fifty-six (52%) were women. Sixty-seven (22%) were classified as frail. The frail group had significantly higher incidences of hypotension (odds ratio [OR] 1.87, 95% confidence interval [CI]1.083-3.259; p=0.02), desaturation (OR 3.79, 95 % CI 1.367-10.54; p=0.01), need for vasopressors (OR 2.81, 95 % CI 1.607-4.912; p=0.00) and blood transfusion (OR 3.26, 95 % CI 1.138-9.368; p=0.02). On multivariable logistic regression analysis, adjusting for factors related to frailty such as age, gender and comorbidities, desaturation was

significantly associated with frailty (Adjusted OR [AOR] 4.21, 95% CI 1.31-13.53; p=0.01). The frail were also more likely to require blood transfusion (AOR 5.36, 95% CI 1.50-19.16; p=0.01). The frail were older and had more comorbidities. Higher ASA-PS scores were also strongly associated with frailty.

Conclusion

The prevalence of frailty was high among surgical patients. Consistent with other studies frailty was associated with older age and multiple comorbidities. The association between frailty and intraoperative complications found in this study may indicate and help inform areas of further research.

Introduction

The ageing population is growing at a rapid rate worldwide resulting in an increased number of ageing individuals requiring medical services and presenting for surgical procedures.[1] In 2010 two thirds of the world's population above the age of 60 lived in developing countries[2] and the World Health Organisation (WHO) reports that the number of people above the age of 60 will effectively double by 2050.[3] In the US over 40% of surgeries are being performed on elderly patients.[4] The larger number of operations being performed on elderly patients has made it necessary to identify and manage geriatric conditions that place these patients at increased surgical and anaesthetic risk.[4, 5]

Frailty is the depletion of physiological and functional reserve across many organ systems leading to a diminished capacity to withstand environmental stressors such as surgery.[6] It is an independent predictor of mortality, morbidity, complications and increased length of stay perioperatively.[7] It is predicted to become one of the most problematic public health issues that will place a heavy strain on already overburdened health care systems.[8] Frailty although often associated with advanced chronological age can also affect the non-elderly. Rockwood et al found the prevalence of frailty to be 2.0% in those younger than 30 years[9] which is similar to the findings of Kehler et al where the prevalence of frailty in Canadians between the ages of 18 and 34 was between 1.8 to 5.3%, depending on the frailty assessment used.[10]

A number of assessment methods have been used as indicators of overall health and physiological status. The American Society of Anaesthesiologists Physical Status (ASA-PS) scoring system is a scale from 1 through 6 in increasing order of risk, with an 'E' to denote emergency surgery, that is assigned to a patient by the anaesthesiologist before surgery.[11] It was originally designed to describe the overall health status of a patient, it has since been used as a risk stratification tool and found to be predictive of postoperative morbidity and mortality.[12] The Revised Cardiac Risk Index (RCRI) is a simplified version of an earlier index.[13] It has six predictive factors with one point assigned per factor and with increasing number of points corresponding to increased rates of perioperative cardiac risk.[14] Frailty assessments have been shown to be better predictors of postoperative

complications, mortality and morbidity in the aged than other preoperative assessments.[15-17]

There are many assessment models that have been used to assess frailty. The two most commonly used models are the frailty phenotype[18]and frailty index or deficit accumulation model.[19] Both models have predominantly been used for research purposes. There have been concerns about the utility of these models in a clinical setting. Screening tools such as the Clinical Frailty Scale (CFS) from Dalhousie University in Canada were subsequently developed for practical clinical use.[20] The CFS scale is a 9-point scale which utilises pictographs to depict the degrees of functional dependency. The scale ranges from 1 (very fit) to 9 (terminally ill) and a score of 5 or more suggests frailty. Most studies using any one of the validated frailty measuring tools have been conducted in developed countries on predominantly Caucasian patients with few published studies in the developing world and fewer still in Africa.[21] One study utilising data from the WHO study on global ageing and adult health found the prevalence of frailty to be 38% in South Africa and 37.9% in Ghana in adults aged 50 and above.[22] Another South African study compared frailty between HIV positive and HIV negative adults.[23] The mean ages of the HIV positive and HIV negative groups were 41.1 years and 42 years respectively. There was a 19.4% prevalence of frailty in the HIV positive adults compared to a 13.3% in the HIV negative adults.

Combining risk assessment tools such as the ASA-PS and frailty assessments to improve postoperative risk prediction might increase the probability of correct identification of those patients who are likely to suffer adverse intraoperative and postoperative adverse events and has been suggested by some authors.[5, 24] On the other hand, combinations might make these tools more complex to use and their applicability to a wider population limited and will likely require extensive validation studies before they can be put into practise. Although much has been written about the postoperative adverse outcomes and mortality related to frailty, little is known about how frailty impacts on anaesthetic complications intraoperatively and the nature of utilisation of health services such as the intensive care unit (ICU) by patients assessed as frail. Correct risk assessment will identify the most vulnerable and may help facilitate discussions about realistic treatment goals.

The aim of the study was to determine the prevalence of frailty as well as to assess the intraoperative implications of frailty in a surgical population in three academic hospitals in Johannesburg, South Africa. We additionally assessed the association between frailty and comorbid illnesses as well as the association between the ASA-PS score and the CFS score. Finally, we assessed whether participants assessed as frail were more likely to go to a high care unit or ICU facility post operatively.

Methods

Approval for the study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M160756). Participants 18 to 90 years presenting for elective surgery at the Chris Hani Baragwanath Academic Hospital, Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital between the months of November 2016 and March 2017 were included.

This was a prospective, observational and cross-sectional study that employed convenience sampling. The surgical specialities included were general, gynaecological, orthopaedic, maxillo-facial, ENT, urological, neurosurgical and vascular surgery. We excluded known pregnant patients and patients with a diagnosis of mental impairment or dementia without any access to family members for frailty information.

Frailty was defined using the Clinical Frailty Scale (CFS) which is a validated 9-point assessment from the Canadian Study on Health and Aging (Table 1). Patients were defined as frail if they scored 5 or more on the CFS. Copies of the data collection sheet and the CFS were placed in the operating theatre receiving areas at the three sites. Patients presenting for any of the included elective surgeries were identified during the preoperative assessments by the anaesthetists assigned to various elective lists. The anaesthetists included medical officers and registrars at different levels of training. After obtaining written informed consent from the patient or family member, demographic data and clinical data which included comorbidities and planned procedure were documented. An ASA-PS and CFS score was assigned on the data collecting sheet. Intraoperative complications and postoperative destination were documented.

All data was entered into a password protected Microsoft Excel spreadsheet. Patient identifiable data was removed. Data was analysed using StataCorp. 2013. *Stata*

Statistical software: Release 13. College Station, TX: StataCorp LP. Descriptive statistics were tabulated using means and percentages. Chi-square and Fishers exact tests were used to describe the association between categorical variables. Logistic regression analysis was used to assess factors associated with frailty. Univariate logistic regression analysis was performed for each of the variables. Multivariable logistic regression analysis was performed to adjust for the possible confounding variables. A p value of less than 0.05 was considered statistically significant for all analysis.

Table 1: Clinical Frailty Scale

1. Very fit	Robust, active, energetic and motivated. Commonly exercise. Fittest for their age.
2. Well	No active disease symptoms but are less fit than category 1
3. Managing well	Medical problems are well controlled but not regularly active
4. Vulnerable	Not dependent on others for daily help. Symptoms limit activities.
5. Mildly frail	More evident slowing. Need help in higher order IADLs
6. Moderately frail	Need help with all outside activities. Need help with instrumental and non-instrumental activities of daily living.
7. Severely frail	Completely dependent for personal care. Not at high risk of dying
8. Very severely frail	Completely dependent. Approaching the end of life.
9. Terminally ill	Approaching the end of life or a life expectancy <6 months in those who are not otherwise evidently frail.

Results

We collected data on 312 patients. Thirteen were excluded in the final analysis (7 did not undergo planned surgery, 6 were not filled in and/or did not document consent) leaving a total of 299 patients in the final analysis. There were 156 (52%) women and 143 (48%) men. The mean (SD) age was 50.6 (15.8) with a range of 21-90 years.

The CFS score assigned ranged from 1 (fit) to 8 (severely frail). There were 67 (22%) patients classified as frail with 39 (58%) of these being female and 28 (42%) male. There were more frail women than there were men as shown in table 2. This was not statistically significant (p=0.263).

At Chris Hani Baragwanath Academic Hospital (CHBAH) 27 out of 106 (25.4%) were frail, in Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) 28 out of 112

(25%) were frail and in Helen Joseph Hospital (HJH) 12 out of 81 (15%) were frail. Of all the patients, 222 (74%) had an ASA score of 1 or 2 whereas 75 (26%) had an ASA score of 3 or 4. Higher ASA scores were strongly associated with frailty relative to an ASA score of 1 with an ASA score of 3 being the most highly associated with frailty (OR 19.01 95% CI 6.870 - 52.614; p<0.001).

Age was significantly associated with frailty OR 1.06 (CI 1.034- 1.084) p<0.001. Frailty was also associated with a higher number of comorbidities. Older age and those with more comorbidities were also more likely to experience intraoperative complications such as hypotension and need for vasopressors (see table 3).

Before adjusting for confounding variables, frailty was significantly associated with an increased incidence of hypotension, desaturation, need for blood transfusion and need for vasopressors. We then adjusted for confounding variables (age, gender, comorbidities) which are related to frailty and intraoperative complications. After adjustment desaturation was significantly associated with frailty (AOR 4.12, 95% CI 1.202-14.139; p=0.024) as well as need for blood transfusion (AOR 5.36, 95% CI 1.50-19.16; p=0.01) as shown in table 3.

Those assessed as frail were also more likely to go to high care post operatively (OR 3.01 95% CI 1.073-8.447; p=0.036).

Table 2: Baseline characteristics of study participants

	Number (%)	Mean age in years (SD)	Gender No of women (%)
Overall	299	50.6 (15.8)	Women 156 (52) Men 143 (48)
Frail (≥5)	67 (22)	62.29 (15.45)	39 (58)
Non-frail	232 (78)	47.30 (14.32)	117 (50.4)
CFS			
1	25 (8.3)	37.16 (7.79)	10 (6.4)
2	66 (22.0)	40.27 (11.14)	29 (18.5)
3	88 (29.4)	52.39 (13.05)	50 (32.0)
4	53 (17.7)	52.43 (16.11)	28 (17.9)
5	40 (13.3)	60.67 (13.86)	25 (16.0)
6	21 (7.0)	66 (17.72)	11 (7.0)
7	6 (2.0)	60.16 (17.72)	3 (1.9)

Table 3: Effect of frailty on intraoperative complications

		Univariate logistic model to assess effect of frailty			**Multivariable logistic regression controlling for other variables on effect of frailty on complications**		
		Association between frailty and hypothermia					
Factors		OR	95% CI	p-value	AOR	95% CI	p-value
Frailty	No	1					
	Yes	2.08	0.99-4.36	0.051			
		Association between frailty and hypotension					
Factors		OR	95% CI	p-value	AOR	95% CI	p-value
Frailty	No	1					
	Yes	1.87	1.08-3.25	0.025	1.87	0.81-4.34	0.14
Age category	18-34	1					
	35-49	3.04	1.23-7.49	0.01	0.80	0.24-2.68	0.72
	50-64	4.38	1.77-10.81	0.001	1.76	0.54-5.70	0.34
	>65	8.0	3.06-20.87	0.000	1.65	0.44-6.16	0.45
Sex	Female	1					
	Male	0.81	0.509-1.300	0.394			
Comorbidities	0	1					
	1	1.94	1.08-3.50	0.02	0.77	0.31-1.90	0.57
	2	2.67	1.33-5.34	0.005	0.74	0.25-2.16	0.58
	3	1.84	0.78-4.35	0.16	0.64	0.17-2.38	0.51
	4	1.10	0.20-6.06	0.90	-	-	-

		Univariate logistic model to assess effect of frailty			Multivariable logistic regression controlling for other variables on effect of frailty on complications		
		Association between frailty and desaturation					
Factors		OR	95% CI	p-value	AOR	95% CI	p-value
Frailty	No	1					
	Yes	3.79	1.36-10.54	0.01	4.21	1.31-13.53	0.01
Age category	18-34	1					
	35-49	1.48	0.28-7.63	0.63	1.29	0.23-7.26	0.76
	50-64	1.09	0.19-6.19	0.92	1.76	0.07-3.86	0.54
	>65	1.80	0.31-10.32	0.50	1.65	0.08-4.85	0.67
Sex	Female	1					
	Male	1.87	0.66-5.31	0.24	2.71	0.85-8.63	0.09
Comorbidities	0	1					
	1	0.89	0.21-3.67	0.87	0.95	0.21-4.33	0.95
	2	2.35	0.60-9.14	0.21	2.94	0.59-14.46	0.18
	3	1.67	0.29-9.65	0.56	1.91	0.26-13.76	0.52
	4	3.91	0.37-40.72	0.25	3.85	0.27-53.91	0.31

		Univariate logistic model to assess effect of frailty			Multivariable logistic regression controlling for other variables on effect of frailty on complications		
		Association between frailty and need for blood transfusion					
Factors		OR	95% CI	p-value	AOR	95% CI	p-value
Frailty	No	1					
	Yes	3.26	1.13-9.36	0.02	5.36	1.50-19.16	0.01
Age category	18-34	1					
	35-49	1.14	0.28-4.61	0.85	0.89	0.19-3.99	0.88
	50-64	1.0	-	-	-	-	-
	>65	1.50	0.34-6.64	0.59	0.52	0.08-3.18	0.48
Sex	Female	1					
	Male	1.26	0.44-3.57	0.66	1.27	0.39-4.14	0.68
Comorbidities	0	1					
	1	1.36	0.37-5.00	0.63	1.60	0.38-6.64	0.51
	2	1.84	0.44-7.68	0.40	2.27	0.41-12.35	0.34
	3	0.81	0.08-7.53	0.85	1.06	0.09-12.11	0.96
	4	1.0	-	-	-	-	-
		Association between frailty and arrhythmia					
Factors		OR	95% CI	p-value	AOR	95% CI	p-value
Frailty	No	1					
	Yes	2.34	0.38-14.35	0.35			

		Univariate logistic model to assess effect of frailty			Multivariable logistic regression controlling for other variables on effect of frailty on complications		
		Association between frailty and need for vasopressors					
Factors		OR	95% CI	p-value	AOR	95% CI	p-value
Frailty	No	1					
	Yes	2.81	1.60-4.91	0.00	1.57	0.83-2.98	0.16
Age category	18-34	1					
	35-49	1.76	0.70-4.46	0.22	1.67	0.64-4.31	0.28
	50-64	4.18	1.69-10.33	0.002	3.24	1.24-8.47	0.01
	>65	8	3.06-20.87	0.00	6.23	2.17-17.82	0.001
Sex	Female	1					
	Male	0.79	0.48-1.28	0.34	1.03	0.60-1.79	0.89
Comorbidities	0	1					
	1	1.63	0.87-3.84	0.12	1.05	0.52-2.09	0.88
	2	3.33	1.63-3.77	0.00	1.74	0.77-3.91	0.18
	3	3.02	1.27-7.14	0.01	1.74	0.66-4.58	0.26
	4	1.38	0.25-7.61	0.71	0.41	0.06-2.58	0.34

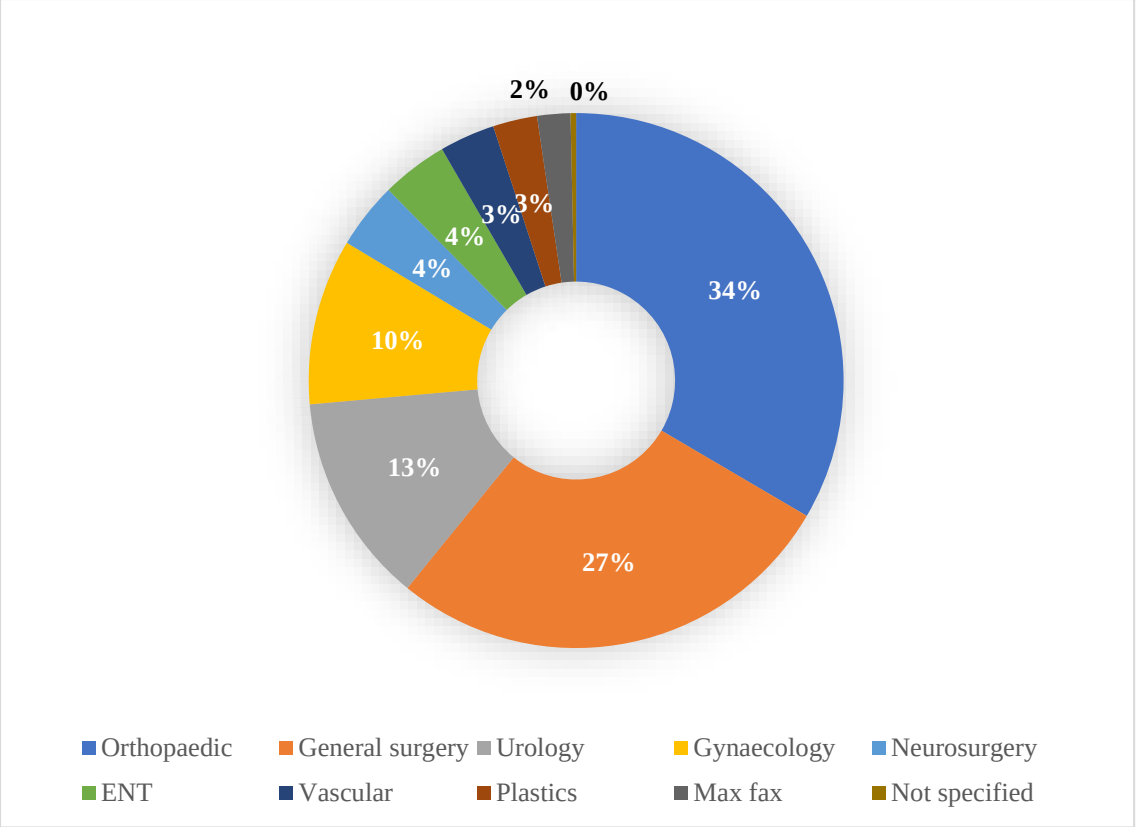

Fig. 1. Types of surgery

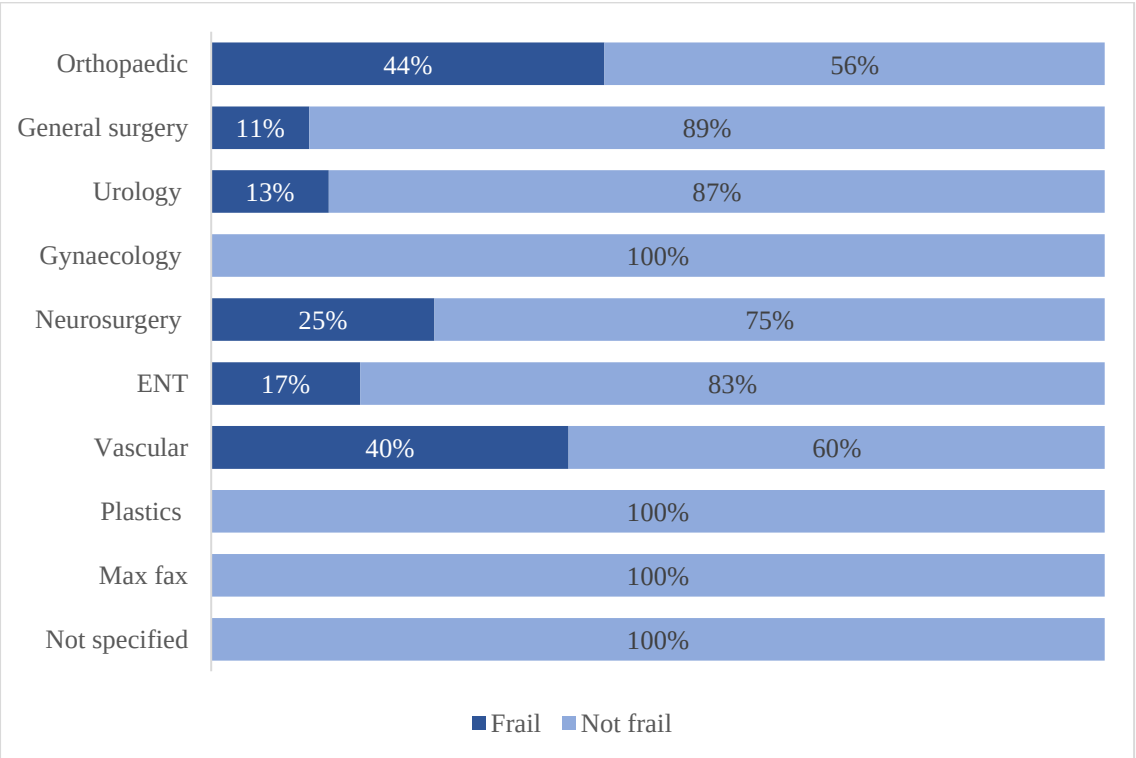

Fig. 2. Distribution of frailty across surgical disciplines

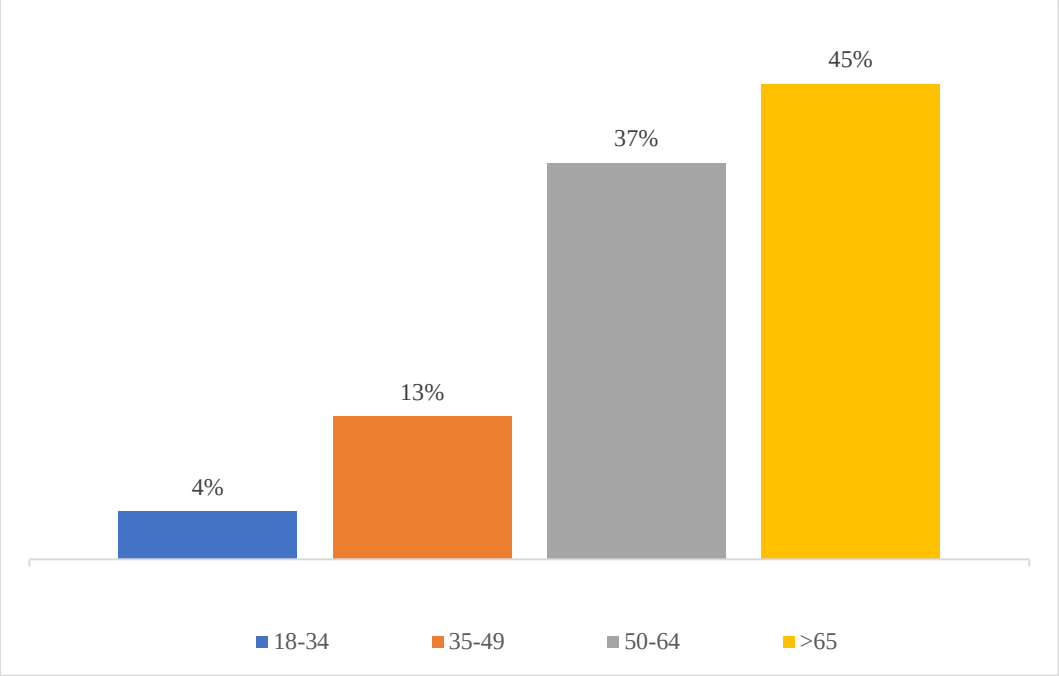

Fig. 3. Frailty within age groups

Discussion

The prevalence of frailty is said to be higher in developing countries where it ranges from 5.4% to 44% in community dwelling elderly[2] and is reported to be between 4.1% and 50.3% in patients of all ages presenting for surgical procedures depending on the assessment tool used and the population sampled.[25] This study found that 22% of patients undergoing elective surgery in three large academic hospitals in Johannesburg are frail. This percentage is lower than our estimated 30% and is also lower than the reported rates for frailty among the hospitalised elderly. Our study however was one of the few that included age groups 18 and above and on further analysis it was seen that 45% of patients above the age of 65 were frail which is on the higher end of the usual prevalence rates reported in surgical patients.

Other studies have used the CFS to predict mortality and adverse outcomes. Bagshaw et al[26] used the CFS in critically ill adults aged 50 and above and showed a frailty prevalence of 32.8%. They also showed that in-hospital mortality was higher in the frail (32% vs 16%) and major adverse events were more common (39% vs 29%). Similar to our study the frail were older and had more comorbidities which is also consistent with many other studies.[18, 27, 28] Hewitt et al[29] showed that 28% of patients aged 65 and above in three acute surgical admission units were frail

according to the CFS. The frail individuals spent longer in hospital and were more likely to die at 30 and 90 days.

This study also demonstrates the ability of the CFS to predict outcomes even when used by clinicians without prior training on how to use the scale. In a comparable study the CFS was used by junior doctors without any prior training in patients over the age of 65 admitted to an acute general medical unit.[30] In this study frailty was associated with functional decline (p=0.011) and mortality within three months (p=0.012).

There are no current studies with which we can directly compare our study as most studies have focused on postoperative outcomes.[31] The authors could not find any studies which aimed to associate frailty with intraoperative complications. Though a number of studies have shown a relationship between intraoperative complications and postoperative outcomes. The need for intraoperative blood transfusion was shown to be associated with a higher morbidity and mortality in anaemic surgical patients.[32] Intraoperative hypotension was demonstrated to be associated with myocardial injury, acute kidney injury and death.[33]

This study highlights and identifies the intraoperative environment as being an at-risk environment for adverse outcomes in the frail. This should ultimately emphasise the need for intraoperative vigilance and highlight the importance of frailty for all perioperative physicians including the anaesthetist and not just the surgeon or intensivist.

Univariate logistic regression analysis showed that frailty was associated with a higher risk of intraoperative complications such as hypotension, desaturation, need for vasopressors and blood transfusion. Frailty was only significantly associated with desaturation and need for blood transfusion after multivariable logistic regression analysis which is possibly a function of a small sample size with fewer frail patients in the sample than anticipated. Higher levels of frailty on the CFS score were more likely to receive an ASA-PS score of 3 or more which is in keeping with the findings by Robinson et al.[34] There was an association between frailty and postoperative destination with the frail being more likely to go to a high care unit but there was not a significant association between frailty and ICU admission due to sample size. The clinical significance of this is unclear.

Although the prevalence of frailty is higher among the elderly there is a noteworthy prevalence among younger age groups. This prevalence might increase with the increase of communicable and non-communicable diseases such as HIV, TB and traumatic injury.

The strength of the study is that it is the only study of its kind to be conducted in South Africa looking specifically on the effect frailty has on intraoperative complications. The study also included patients from a few of the largest hospitals in Sub-Saharan Africa. The population of patients were largely from a low socioeconomic group and is representative of the population that is seen at most South African hospitals as only a small percentage of the South African population can afford private hospital care.

Limitations

The assessment of frailty in a perioperative setting is confounded by the effects of the presenting surgical condition. To minimise the effects of acute surgical conditions only those presenting for elective procedures were included.

Data was documented by different anaesthesia providers at different levels of anaesthetic training and inter-observer reliability was not assessed. It was however important to also demonstrate the utility of the CFS as a screening tool in a real life clinical setting where it was intended for use by non-geriatricians. The CFS has shown good inter-observer reliability in a previous study.[35]

This was a single-centre study with a relatively small sample size. Future larger studies may focus on the association between frailty and postoperative complications, morbidity, length of stay and mortality in a South African surgical population.

Conclusions

The prevalence of frailty was high among surgical patients. Consistent with other studies frailty was associated with older age and multiple comorbidities. The association between frailty and intraoperative complications found in this study may indicate and help inform areas of further research.

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Section 4: Appendices

4.1 Data collection sheet

1. **Age** ____ years
2. **Gender (please select by making a cross)**

Male		Female	

3. **Comorbidity (please select by making a cross in the appropriate row):**

Comorbidity	**Indicate with a cross**
Hypertension	
Diabetes	
Ischemic heart disease	
Peripheral vascular disease	
Stroke	
Congestive cardiac failure	
Chronic kidney disease	
HIV	
Tuberculosis	
COPD	
Thyroid disease	
Cancer	
Musculoskeletal disease Please specify:	
Cognitive disorder e.g. dementia Please specify:	
Disability e.g. visual or hearing loss, amputation Please specify:	
Psychiatric disorder Please specify:	
Other Please specify:	

4. **Clinical diagnosis:**
5. **ASA classification:**
6. **Planned procedure:**
7. **Clinical Frailty Scale score (1 to 9):**
8. **Intraoperative complications (please select if any of these events occurred by making a cross in the appropriate row)**

Complication	**Indicate with a cross**
Hypothermia (core temp<36)	
Hypotension (drop in mean arterial pressure or systolic pressure > 20% from baseline or systolic BP<90mmHg)	
Desaturation (Sats<90%)	
Need for blood transfusion	
Arrhythmia	
Need for vasopressors or antiarrhythmic Please specify type:	
Other Please specify:	

9. **Where did the patient go postoperatively (please select by making a cross)**

High care	
ICU	
Ward	

Dear Sir/Madam

Hello, my name is Ngozi Leopold-George. I am a registrar in the Department of Anaesthesiology and I am currently busy with a research project for my Masters degree. I would like to invite you to participate in my research.

The aim of the study is to find out how many frail patients there are having surgery and how frailty affects them during the surgery. Frailty means how strong you are physically and the weaker patients are a medical concern as they may have more complications during the surgery. We don't know how many of the patients coming to this hospital are frail and the results of the study may be used to improve patient care in the future.

If you agree to participate in the study the doctor will fill in an assessment form based on your medical history and examination. You will remain anonymous as there will be nothing to identify you on the assessment form. It is confidential as only my supervisor and I will see the assessment and the results will not be available to any member of the public. If you decide not to participate in this study your treatment will not be affected in any way. The study has been approved by the Human Research Ethics Committee and the Post Graduate Committee of the University of the Witwatersrand as well as your hospital. If you have any questions about the study please either contact me at the number below or the secretary of the Ethics Committee Ms Zanele Ndlovu on 011 717 1234.

If you are happy to participate in the study kindly sign the consent form on the next page. Thank you for your participation.

Yours sincerely

Dr Ngozi Leopold-George

Contact number: 0847912936

Consent

I, _____ being 18 years or older,

consent to participating in a research project entitled: **"Frailty in peri-operative patients in three South African academic hospitals"**.

The purpose of the study has been explained to me and I understand the extent of my participation. I have read and understand the attached information letter.

I understand that my participation forms part of a research project, and may not provide any direct benefit to me.

I understand that my participation is voluntary, and that I am free to withdraw from the

project at any time.

_____ _____

Patient signature Date

4.2 Ethics clearance certificate

R14/49 Dr Ngozi Leopold - George

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160756

NAME: (Principal Investigator)	Dr Ngozi Leopold - George
DEPARTMENT:	Anaesthesiology Chris Hani Baragwanath Academic Hospital Charlotte Maxeke Johannesburg Academic Hospital Helen Joseph Hospital
PROJECT TITLE:	Frailty in Peri-Operative Patients in Three South African Academic Hospitals
DATE CONSIDERED:	29/07/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Gladness Nethathe
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	07/10/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in July and will therefore be due in the month of July each year.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

4.3 Approval from postgraduate committee

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

05 January 2018
Person No: 1234114
PAG

Dr N Leopold-George
196 Homestead Road
Edenburg
Rivonia
2191
South Africa

Dear Dr Leopold-George

Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Frailty in peri-operative patients in 3 South African tertiary hospitals* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

4.4 Approval from the Head of the Department of Anaesthesiology

WITS UNIVERSITY

DEPARTMENT OF ANAESTHESIOLOGY
UNIVERSITY OF THE WITWATERSRAND,
JOHANNESBURG
Tel.(011)933-9334/5 / Fax (011)933-1843

FACULTY OF HEALTH SCIENCES

15 August 2016

Ms Zanele Ndlovu
Administrative Officer
Human Research Ethics (Medical)

RE : DR NTN LEOPOLD-GEORGE STUDENT NUMBER 1234114

I herewith grant permission to Dr Ngozi Leopold-George to conduct the study titled "Frailty In Peri-Operative Patients In 3 South African Tertiary Hospitals" in the University of the Witwatersrand Department of Anaesthesiology. The proposed study entails distributing a patient frailty assessment to doctors working in anaesthesia in Charlotte Maxeke Johannesburg Academic Hospital, Chris Hani Baragwanath Academic Hospital, Helen Joseph Hospital and Rahima Moosa Mother and Child Hospital.

With Kind Regards

Yours sincerely

PROF. A.C. LUNDGREN
CHIEF SPECIALIST AND HEAD
DEPARTMENT OF ANAESTHESIA
UNIVERSITY OF THE WITWATERSRAND

4.5 Approval from the CEO of CMJAH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Mr. J. Maepa
Office of the Clinical Director
Tell: (011) 488-3365
Email:johannes.maepa@gauteng.gov.za
17 August2016

Dear Dr NTN Leopold-George

STUDY TITLE: Frailty in perioperative patients in 3 South African tertiary hospitals.

Permission to conduct the above mentioned study is provisionally approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your ethics clearance as soon as the study is approved by the Ethics committee for the CEO's to give you the final approval to conduct the study.

Supported/~~not supported~~

Dr M.I. Mofokeng
Clinical Director
DATE: 17/08/2016

Approved/~~not approved~~

Ms G. Bogoshi
Chief Executive Officer
Date: 17/8/2016

4.6 Approval from the CEO of CHBAH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 22 Aug 2016

TITLE OF PROJECT: Frailty in perioperative patients in 3 South African tertiary hospitals

UNIVERSITY: Witwatersrand

Principal Investigator: N Leopold-George

Department: Anaesthetics

Supervisor (If relevant): GD Nethathe

Permission Head Department (where research conducted): Yes

Date of start of proposed study: Aug 2016
Date of completion of data collection: Dec 2018

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Human Research Ethics Committee of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

.....
Recommended
(On behalf of the MAC)
Date: 22 August 2016

.....
Approved/Not Approved
Hospital Management
Date: 28/08/16

4.7 Approval from the CEO of HJH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Gauteng Department of Health
Helen Joseph Hospital
Enquiries: Dr. M.R. Billa
Chief Executive Officer
Tel :(011) 489-0306/1087
Fax :(011) 726-5425
E mail: Raymond.Billa@gauteng.gov.za
Date: 19 September 2016

Dr.M.R.Billa
Chief Executive Officer
Helen Joseph Hospital

Dear Dr.Billa

STUDY: Frailty in Peri-Operative Patients in 3 South African Tertiary

RESEARCHER: Dr. Ngozi Leopld

The above was discussed at the Research Committee Meeting. We recommend that permission be granted for Helen Joseph Hospital to be used as a site for the above research. However, since this is a research project involving voluntary participation.

Upon completion of the study, a copy thereof should be submitted to Helen Joseph Hospital.

Thank you

Dr. Murimisi Mukansi
CHAIRPERSON
DATE:

Approved

DR. M.R. BILLA
CHIEF EXECUTIVE OFFICER
DATE: 19.09.2016

4.8 Permission to use Clinical Frailty Scale

DALHOUSIE UNIVERSITY
Inspiring Minds

PERMISSION TO USE THE CLINICAL FRAILTY SCALE (CFS)©
as developed by Kenneth Rockwood, MD

The undersigned is granted permission to use, reproduce and distribute the CFS© in the format attached[1] for educational purposes and for non-commercially funded research and/or quality assurance projects. The CFS© must be administered free of charge to patients.

A formal Licensing Agreement is required for research funded by any commercial entity or pharma or for use in routine clinical care.

The copyright holder reserves the right to prospectively follow-up at any time to determine whether use of the CFS© meets the conditions described above.

Reselling of the CFS© or other commercial development without a license agreement is prohibited by copyright.

User Information:

Name:	NGOZI WORLD-GEORGE
Title:	DR.
Institution / Organization:	University of Witwatersrand, Johannesburg
Address:	7 York Road, Johannesburg, 2193
Telephone:	+27 84 991 2982
Email:	ngozitongeo@yahoo.com
Intended Use:	☐ Reproduce in publication (provide title of manuscript, authors and journal) ☑ Use in a study or clinical trial (provide details below) ☐ Use in routine clinical care (provide details below) ☐ Other (describe intended use below)
Describe intended use:	To assess frailty in a project: Perioperative frailty
Type of organization:	For-profit ☐ Not-for-profit ☑ Other ☐ specify Academic
Are you planning any commercial development that would incorporate the CFS?	Y ☐ N ☒
Intended period of use:	October 2016 – January 2017

By your signature below, you attest that you understand the conditions under which permission to use the CFS© is granted.

Signature: _____

Date: 09/09/16.

Completed form must be returned by post, fax or email (scan) to:

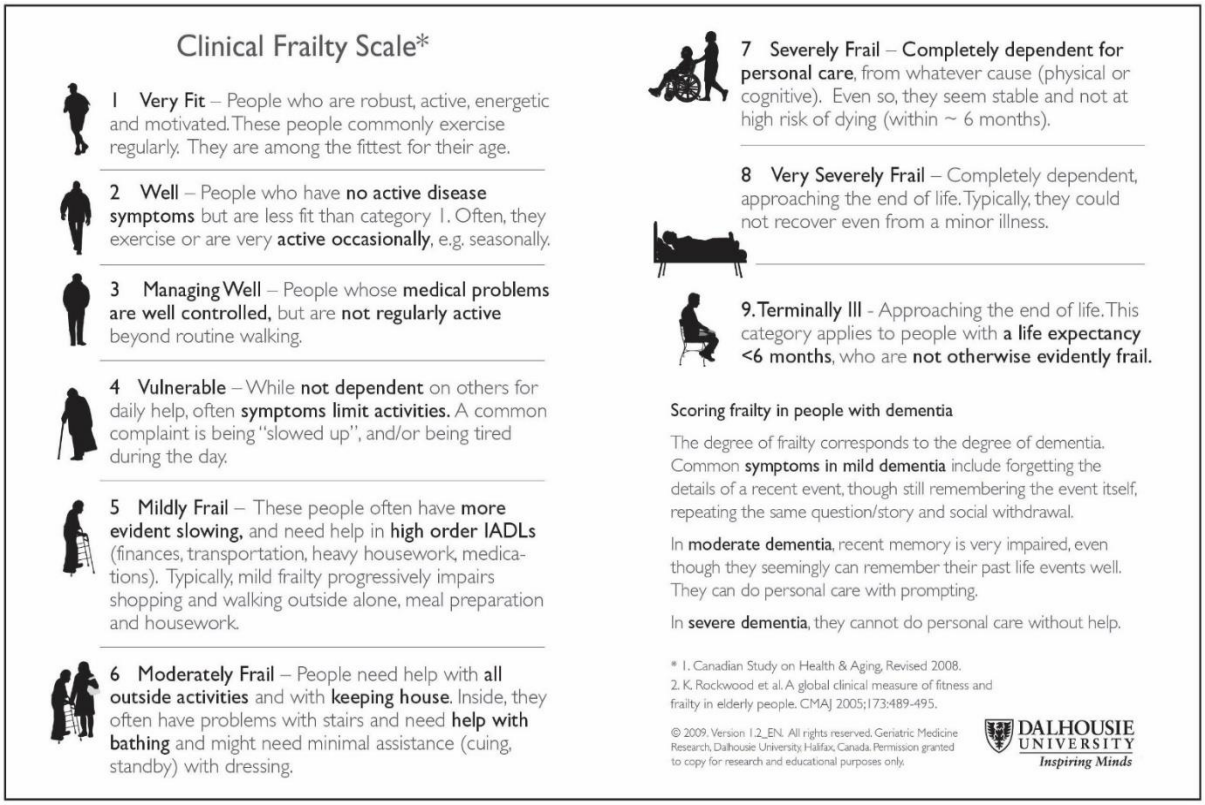
Kenneth Rockwood, MD
1421-5955 Veterans' Memorial Lane
Halifax, NS B3H 2E1 Canada
gmru@dal.ca
Fax: 902-473-1050

FOR OFFICE USE ONLY

Approved by: _____ Date: 2016/09/14
Kenneth Rockwood, MD (or delegate)

[1]A copy of the CFS will be emailed to the user upon review and approval of this request for use form. Valid only when signed by all parties.

4.9 Clinical Frailty Scale



Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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4.10 Turnitin Report

1234114:FrailtyTurnitin280518.docx

ORIGINALITY REPORT

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Section 5: Proposal

INTRODUCTION

The ageing population is growing at a rapid rate worldwide resulting in an increased number of ageing individuals. In 2010 two thirds of the world's population above the age of 60 lived in developing countries (1). In South Africa the number of individuals aged 60 years and older is projected to be approximately seven million by 2030 (2). This elderly population uses the medical services including surgery and thus the number of elderly people coming for surgical procedures has also increased.

In the US over 40% of surgeries are being performed on elderly patients (3). The larger number of operations being performed on elderly patients has made it necessary to assess and manage geriatric conditions that place these patients at increased surgical risk. Frailty is one of the conditions associated with an ageing population and estimates are that of 10% of people over the age of 65 and increases to 25-50% in people over the age of 85 (4). Frailty is not exclusive to the ageing as it has been documented in the non-elderly (5). Frailty occurs as a result of multiple physical, social and environmental factors and it is a reversible condition (1). Elderly patients undergoing surgery have been found to have a higher prevalence of frailty ranging from 25-56% (3).

There is currently no consensus on how best to define frailty with a number of definitions proposed but it is characterised by loss of physiological and functional reserves leading to a diminished capacity to withstand environmental stressors such as surgery (6).

The two most popularised definitions view frailty as either a syndrome or a state (6). Frailty was defined as a syndrome based on phenotypic features which are unintentional weight loss of more than 4.5 kg in the past year, exhaustion, weakness, slow walking speed and low physical activity (7). An alternative view, the deficit model, views frailty as a state of vulnerability that is secondary to the accumulation of an individual's health deficits which also includes cognitive and psychosocial factors which result in a frail status (8).

Age-related hormonal changes and inflammation result in a loss of skeletal mass and function also known as sarcopenia which is considered a hallmark of frailty (9). Hormonal changes include decreases in growth hormone, insulin-like growth factor-1, dehydroepiandrosterone sulphate, sex steroids and increased cortisol levels. Vitamin D deficiency has also been linked to frailty (3). Elevated biomarkers such as pro-inflammatory cytokines IL-6, TNF-alpha and C-reactive protein have been noted in frail patients (3). Indicators of chronic inflammation such as low albumin and interleukin-6 have been linked to ageing and frailty (10). Pro-inflammatory cytokines contribute to frailty by increasing protein catabolism and modifying metabolic processes which can affect skeletal muscle, appetite, immunity, cognition and contribute to anaemia (11). Immune system activation may also cause disordered coagulation leading to elevated serum markers of coagulation such as D-dimer, factor VIII and fibrinogen. Elevated neutrophil and monocyte counts have also been demonstrated in frail elderly patients (3). None of these biomarkers are unique to frailty as many of them are also found in other conditions thus making pathophysiological mechanisms leading to frailty harder to define (11).

There are many factors that play a role in the development of frailty. Frailty has been associated with congestive cardiac failure, coronary heart disease, stroke, diabetes mellitus, hypertension, arthritis, cancer and chronic obstructive pulmonary disease (12). Other risk factors include depression, poor nutrition, female sex, low socioeconomic status and lifestyle factors such as smoking and lack of exercise. Overall these factors lead to frailty which becomes a form of disability (12).

The Clinical Frailty Scale was developed as a clinician friendly tool where judgement is made about the degree of frailty based on clinical data (6). It is a 9-point scale from 1 (very fit) to 9 (terminally ill) and a score of 5 or more is used to classify frailty. It has been validated to predict outcomes in hospitalised patients (5) though not extensively studied in clinical settings.

A consensus committee recommended that all persons aged 70 years and older as well as those with significant weight loss of more than 5% over the past year due to chronic illness be screened for frailty (13). Frailty scores have been shown to be a better indicator of overall health and physiological status and better predictors of postoperative complications, mortality and morbidity than other preoperatives

assessments such as the American Society of Anaesthesiologists (ASA) physical status classification system (14,15). Chronological age does not indicate a patient's physiological capacity to withstand surgery and frailty is a better indicator of biological age (16). Correct assessment may help facilitate discussions about realistic treatment goals, improve clinical risk prediction and inform health resource utilization practice.

Many studies have recorded the prevalence of frailty but most have been in developed countries on mainly Caucasian patients with few published studies in the developing world. The prevalence of frailty appears to be higher in developing countries but these studies were done in Asia and Latin America (17). To date there have been no frailty studies using one of the validated frailty assessments conducted in Africa particularly in the context of surgical procedures and the impact of that frailty on intraoperative complications. This study is important to investigate both the prevalence of frail patients presenting for surgery as well as possible consequences of that frailty during the surgical procedure.

1. RATIONALE FOR STUDY

1.1. Research question

Do patients assessed as being frail pre-surgery have more intraoperative complications than those not assessed as frail?

1.2. Hypothesis

Frailty will be associated with more intraoperative complications than non-frail patients.

Prevalence of frailty will be higher than internationally reported due to a higher burden of diseases such as trauma, HIV and TB in South African patients.

Prevalence of frailty will be higher in a younger population than internationally reported due to a higher burden of disease affecting younger patients such as trauma, HIV and TB.

2. STUDY AIMS AND OBJECTIVES

2.1. Aim

- To determine the prevalence of frailty and intraoperative complications as an effect of this frailty in a surgical population in three academic hospitals in Johannesburg, South Africa

2.2. Primary objectives

- To determine the demographics and frailty levels of patients presenting for surgery in three academic hospitals in Johannesburg
- To determine how frailty affects the intraoperative course and physiological parameters such as heart rate, blood pressure, temperature and oxygen saturation
- To compare intraoperative complications between the frail and non-frail patients

2.3. Secondary objectives

- To compare demographics and the number of comorbidities between the frail and non-frail
- To compare the association between the frailty score and the ASA score

3. METHODS

3.1. Demarcation of study field

The study will be conducted in the Department of Anaesthesiology, affiliated to the Faculty of Health Sciences of the University of the Witwatersrand. The associated hospitals include Chris Hani Baragwanath Academic Hospital, Charlotte Maxeke Johannesburg Academic Hospital, Helen Joseph Hospital and. The Department of Anaesthesiology consists of 219 anaesthetists including medical officers, registrars and specialists.

3.2. Study design

The study will be a prospective, observational and cross-sectional study that will employ descriptive and comparative aspects.

3.3. Study population and sample

The study will be conducted on all patients 18 years and older presenting for elective surgery at the Chris Hani Baragwanath Academic Hospital, Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital (from here on referred to as the three hospitals). The research will take place over the course of two to three months after ethics approval has been obtained

Sampling procedures

Convenience sample of patients seen over a three month period at the three hospitals.

Sample size

Sample size was calculated using Statistica version 6.4 with the help of a biostatistician. Studies currently report the prevalence of frailty to be on average 25% (4,5,18). We expect a difference of 30% to the reported prevalence at a power of 80% and significance level of 0.05. The sample size thus required is 292 patients which will include frail and non-frail cases.

Selection criteria

Inclusion criteria

All inpatients 18 years and older presenting for elective surgery at the three academic hospitals will be included. The surgeries included will be general, gynaecology, orthopaedic, maxillo-facial, ENT, urology, neurosurgical and vascular.

Exclusion criteria

Patients presenting for ophthalmology and obstetric surgery.
Known pregnant patients and patients with a diagnosis of mental retardation or dementia without any access to family members for frailty information.

3.4. Data collection process and tools

Enrolment will occur after informed consent has been obtained and patients will be enrolled concurrently at the three hospitals. The anaesthetist assigned to a particular elective list will collect data on a data collection sheet (Appendix 3.1) which will include demographics and clinical data. Frailty will be defined using the Clinical Frailty Scale which is a validated 9-point assessment from the Canadian Study on Health and Aging (5) (Appendix 3.9). Patients will be defined as frail if they score 5 or more on the Clinical Frailty Scale. The anaesthetist will complete the assessment during the preoperative visits after completing a medical examination and reviewing each patient's medical records. The anaesthetic charts will also be reviewed to obtain data not recorded. There will also be a place to indicate any other events not recorded in the anaesthetic chart.
Clinical and demographic data to be collected will include (Appendix 3.1):

1. Age and gender
2. Comorbidity
3. Clinical diagnosis and ASA score
4. Planned procedure
5. Clinical Frailty Scale score
6. Intraoperative complications
7. Postoperative destination such as high care or ICU

Data analysis

Data will be captured on spreadsheets and analysed using Microsoft Excel 2011. All statistical analysis will be conducted in consultation with a biostatistician. Categorical variables will be described using frequencies and percentages. Parametric tests will be used for data that is normally distributed and will be described using the mean and standard deviation. Non-parametric tests will be used for data that is not normally distributed and will be described using the median, interquartile range and range. Chi-squared or Fisher's Exact tests will be used to compare categorical variables. Numerical data will be compared using either an unpaired t-test or a Mann-Whitney as appropriate. A p-value of <0.05 will be considered significant.

4. ETHICS

Authorisation

Approval shall be obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand prior to commencement of the study. Approval will also be sought from all three academic hospitals. The researcher will invite the patient to take part in the study. An information sheet (Appendix 3.1) will be provided for the patient and anaesthetist and written informed consent will be obtained before enrolment from all participants.

Confidentiality of Subject Records

Confidentiality of subject data will be maintained at all times. All documentation relating to the subject will be kept in a secure location. The names and identification numbers of the patients will be assigned a number on a restricted access document. The numbers will be collated to the data collected from these files on a separate data sheet. Confidentiality will be guaranteed in any resulting publication.

5. SIGNIFICANCE OF STUDY

Frailty has been shown to be a growing public health concern that negatively impacts on patients in terms of postoperative complications, mortality and morbidity. Current preoperative assessments lack prognostic ability to indicate whether a patient is physiologically fit for surgery. The frailty assessment should be integrated with other preoperative assessment scores such as the ASA score. This will increase sensitivity

in identifying those that are likely to have adverse perioperative outcome and complications in order that patients can be better counselled and optimised prior to surgery as well as lead to the better utilisation of health resources.

6. TIMING

Schedule of target dates

	2016								2017				
	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May
Protocol preparation													
Protocol submission													
Postgrad approval													
Ethics approval													
Data collection													
Data analysis													
Write up research													
Submission													

7. FUNDING

No costs will be borne by participants or by the three hospitals. The costs of photocopying will be borne by the Department of Anaesthesiology.

Budget

Item	Number	Unit Cost	Total
Printing	1600	R 1	R 1,600
Binding	3	R 200	R 600
Total			R 2,200

8. POTENTIAL LIMITATIONS

The following potential limitations, which shall be acknowledged as part of the discussion of the study's results on completion of this project, are as follows:

1. The study is contextual as it takes place in three academic hospitals that are referral centres in Johannesburg and serve a wide population. However, the majority of patients that are treated in these hospitals are Africans of low socio-economic status. The findings therefore may not be generalisable to other hospitals.
2. The researcher will be depending on other doctors to assist in collecting data therefore may have loss of data or incomplete records. Interrater reliability might be an issue as data might not be consistent between data collectors.

9. REFERENCES

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