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BRAIN NATRIURETIC PEPTIDE VERSUS THE SIMPLIFIED ACUTE PHYSIOLOGY SCORE 3 FOR PREDICTING MORTALITY IN A SOUTH AFRICAN GENERAL INTENSIVE CARE UNIT.

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ABSTRACT.

Background:
The biomarker brain natriuretic peptide (BNP) may be more useful for risk stratification in general intensive care unit (ICU) patients when compared with more complex scores, such as the Simplified Acute Physiology Score 3 (SAPS 3). This study sought to investigate the prognostic relevance of BNP levels and SAPS 3 for ICU mortality at a South African quaternary hospital.

Methods:
This was a retrospective chart review of adult patients admitted to the general ICU of the Inkosi Albert Luthuli Central Hospital in Durban, South Africa in 2018 and 2019. Patient characteristics, BNP levels, and SAPS 3 totals were collected for each patient. The study outcome was ICU mortality following admission to the ICU. The prognostic relevance of BNP levels and SAPS 3 was investigated using receiver-operator characteristic curve statistics and area under the curve (AUC).

Results:
The sample size was 376 patients (medical: 133; surgical: 243). ICU inpatient mortality was 29%. SAPS 3 demonstrated superior prognostic accuracy when compared with BNP (AUC = 0.815 vs. 0.657). However, when BNP levels were compared between patients stratified as high- and low-risk for mortality based on SAPS 3, the BNP levels were significantly higher in low-risk patients who died vs. low-risk patients who survived (median: 306.0 ng/L vs. 92.0 ng/L, $p<0.001$).

Conclusion:
Overall, SAPS 3 was superior to BNP at predicting ICU inpatient mortality. However, BNP might potentially have some prognostic utility in patients stratified as low risk according to SAPS 3.

Recommendation:
Future research, specifically larger multicentre studies, should be conducted in the African continent to validate the results of the present study.

Keywords: *Brain natriuretic peptide, Simplified Acute Physiology Score 3, Mortality, Intensive care unit*
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INTRODUCTION:

Intensive care unit (ICU) facilities are a scarce resource in South Africa. It is therefore essential to allocate this scarce resource to the most appropriate patients. More specifically, this would extend to patients who are likely to benefit from ICU admission and survive their critical illness, rather than patients in which ICU care might ultimately be futile. Validation studies of existing ICU risk stratification methods in resource-constrained African countries are scarce. The Simplified Acute Physiology Score 3 (SAPS 3) is one of the most frequently used general severity of illness scores in adult ICUs.[1] Scoring systems like SAPS 3 have been extensively studied in European and American populations, and provide a valuable foundation to predict patient outcomes, assist with quality improvement projects,

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and guide setting points of reference for comparison purposes.

Until recently, the performance of SAPS 3 had never been tested in an African ICU. A South African study found that the SAPS 3 model showed good calibration and demonstrated fair discrimination at outcome prediction, even in the context of high HIV prevalence.[2] SAPS 3 is calculated within the first hour of ICU admission and comprises 20 variables.[3] These variables are allocated a point score, which then allows for the calculation of the SAPS 3 value that is used to estimate a patient's risk of mortality. Increasing SAPS 3 totals are associated with increasing risk of mortality. The relationship between SAPS 3 totals and the respective likelihood of hospital death were previously found to be as follows: SAPS 3 total of 0-30 points predicted hospital mortality to be less than 10%, SAPS 3 total of 31-60 points predicted hospital mortality to be between 10% to 40%, SAPS 3 total of 61-90 points predicted hospital mortality to be between 40% to 85%, and a SAPS 3 total of 91 points and above predicted hospital mortality to be more than 85%.[3] The overall association between increasing SAPS 3 totals and mortality risk is supported by a prior study in South African patients admitted to an ICU at a tertiary-level facility. That study found that non-survivors had a higher SAPS 3 total when compared with survivors (mean: 62 points vs. 44 points) and that all patients with SAPS 3 totals of 92 points or higher had died.[2]

Brain natriuretic peptide, also known as B-type natriuretic peptide or BNP plays an important role in cardiovascular homeostasis.[4] It is a prohormone that is released from the myocardium in response to atrial/ventricular wall stretch, pressure overload, or myocardial ischemia/dysfunction.[4, 5] BNP has vasodilatory, diuretic and natriuretic effects. BNP measurements are widely available, and elevated BNP levels have been linked to adverse outcomes in critically ill patients. [6, 7]

Elevated levels of both BNP and N-terminal pro-BNP (NT-pro BNP), a biologically inactive fragment of BNP with a longer half-life of 1-2 hours, have been investigated as a marker of adverse outcomes in critically ill patients, particularly in the context of sepsis.[5, 8-12] This is probably because sepsis and septic shock are the leading causes of death in the ICU.[13] Pro-inflammatory cytokine over secretion, systolic and diastolic left and right ventricular dysfunction, impaired BNP clearance, renal injury, and sepsis-associated acute lung injury have been proposed mechanisms for the elevation of plasma BNP in sepsis.[12]

It's possible that given their increased sensitivity, biomarkers such as BNP might be more useful for risk stratification in general ICU patients when compared with the more complicated and time-consuming SAPS 3 model. Thus, the biomarker approach toward risk stratification could potentially improve ICU bed allocation in the resource-constrained South African public healthcare sector, by guiding the selection of patients for admission who are likely to benefit most from ICU care. This study aimed to investigate the prognostic relevance of BNP levels and SAPS 3 for ICU inpatient mortality at a South African quaternary hospital.

METHODS.

Study design.

This was a retrospective cohort study.

Study setting.

The study setting was the Inkosi Albert Luthuli Central Hospital (IALCH) adult general ICU. IALCH is a public-sector quaternary hospital, in Durban, South Africa, and provides specialist medical and surgical services to a diverse population of the Province of KwaZulu-Natal. The ICU is an intensivist-led, closed unit, which has 9 beds and admits critically ill medical and surgical adult patients from IALCH.

Study participants.

The study participants were critically ill patients admitted to the adult general ICU during 2018 and 2019. Patients with missing data were excluded.

Data collection.

Each patient's medical chart was reviewed for the relevant admission notes, doctor's progress notes, and laboratory reports. Information on demographic characteristics, admission details, BNP levels, and SAPS 3 totals were collected for each patient and entered into a Microsoft Excel spreadsheet. Plasma BNP measurements (ng/L) on admission to the ICU were performed by an accredited chemical pathology laboratory (managed by the National Health Laboratory Services), located on the hospital premises. The laboratory report is usually available within 24 hours of a blood sample being sent to the laboratory. The SAPS 3 totals on admission for each patient were established using a scoring calculator. The information used to calculate the SAPS 3 totals for individual patients was obtained by reviewing the patient's medical chart. Thus, each patient included in the final study sample would have both a BNP measurement and SAPS 3 total for comparison. The study outcome was ICU inpatient mortality following

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admission to the ICU, which was established by reviewing the discharge summary of the patient.

Data analysis.

Quantitative data analysis methods were used in this research. The characteristics of the entire study sample were summarised using descriptive statistics. Continuous variables are presented as medians with interquartile range. Categorical variables are presented as frequencies and percentages. Median BNP and SAPS 3 totals were compared between patients who survived and patients who died using the Mann-Whitney test. The overall prognostic accuracy of BNP and SAPS 3 for ICU inpatient mortality was determined using receiver-operator characteristic (ROC) curve statistics. The results of the ROC curve analyses are presented as the area under the curve (AUC). All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 27.0 (IBM Corp., USA). Where applicable, statistical significance was set at $p<0.05$.

Study bias.

Given that this study is retrospective, two main biases must be considered. Since there were only a limited number of routinely collected variables in the doctor's notes, there might have been some important confounders that were not included in this analysis because the data was not collected on these factors – Confounding bias. Furthermore, missing key variables required to compute the SAPS 3 score, missing BNP measurements, or a missing survival outcome might introduce attrition bias into the analysis.

Ethical approval.

This research was approved by the Biomedical Research Ethics Committee at the University of KwaZulu-Natal, Durban, South Africa (Protocol: BREC/00001597/2020).

RESULTS.

The derivation of the study sample is shown in Fig. 1. After excluding patients with missing data points, the final study sample consisted of 376 patients.

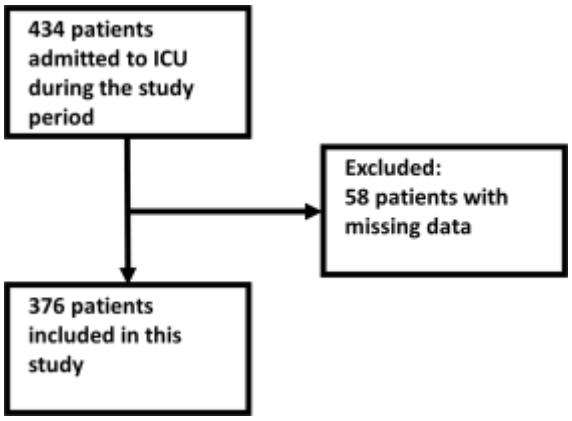

Fig. 1. Derivation of the study sample.

A brief description of the study sample is provided in Table 1. The median age was 47.0 years old. Just over half of the study sample were female (211 patients, 56.1%). Nearly two-thirds of patients were surgical patients (243 patients, 64.6%), with the majority being an emergency admission (284, 75.5%). Approximately 1 in every 5 patients was admitted from another ICU (70 patients, 18.6%). Most patients were referred from public-sector hospitals (363 patients, 96.5%). Communicable disease was the underlying indication for ICU admission in one-third of patients (136 patients, 36.2%). The median SAPS 3 total was 60 points, while the median BNP measurement was 139 ng/L. The median number of days spent in the ICU was 5.0 days. A total of 109 patients suffered ICU mortality (29.0%).

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Table 1. Description of the study sample (N=376).

Characteristic	Summary statistic
Age in years	
Median (IQR)	47.0 (42.0-61.0)
Gender	
Male, n (%)	165 (43.9)
Female, n (%)	211 (56.1)
Referring discipline	
Medical patients, n (%)	133 (35.4)
Surgical patients, n (%)	243 (64.6)
Admitted from another ICU	
Yes, n (%)	70 (18.6)
No, n (%)	306 (81.4)
Referring hospital	
Private, n (%)	13 (3.5)
Public, n (%)	363 (96.5)
Admission urgency	
Elective, n (%)	92 (24.5)
Emergency, n (%)	284 (75.5)
Indication for ICU admission	
Communicable disease, n (%)	136 (36.2)
Noncommunicable disease, n (%)	240 (63.8)
SAPS 3 total, points	
Median (IQR)	60.0 (46.0-74.0)
BNP, ng/L	
Median (IQR)	139 (36.3-533.5)
Number of days in ICU	
Median (IQR)	5.0 (2.0-10.8)
Suffered ICU mortality	
Yes, n (%)	109 (29.0)
No, n (%)	267 (71.0)

ICU non-survivors had significantly higher median BNP values of 303.0 ng/L (IQR 88.0-1122.0) when compared to 113.0 ng/L (IQR 26.0-380.0) in ICU survivors ($p<0.001$). The median SAPS 3 score in those who died was 75.0 (IQR 63.5-85.0) points versus 53.0 (IQR 41.0-67.0) in those who did not die ($p<0.001$).

Overall, the ROC curve analysis revealed that the SAPS 3 model performed better at predicting ICU inpatient mortality when compared with BNP levels (Fig. 2, AUC for SAPS 3 = 0.815 and AUC for BNP = 0.657). Using the ROC curve analysis presented in Fig. 2, the setting-specific optimal cutoff for the SAPS 3 model (the threshold for classifying the "high-risk" category for ICU inpatient mortality) was established as 70 points.

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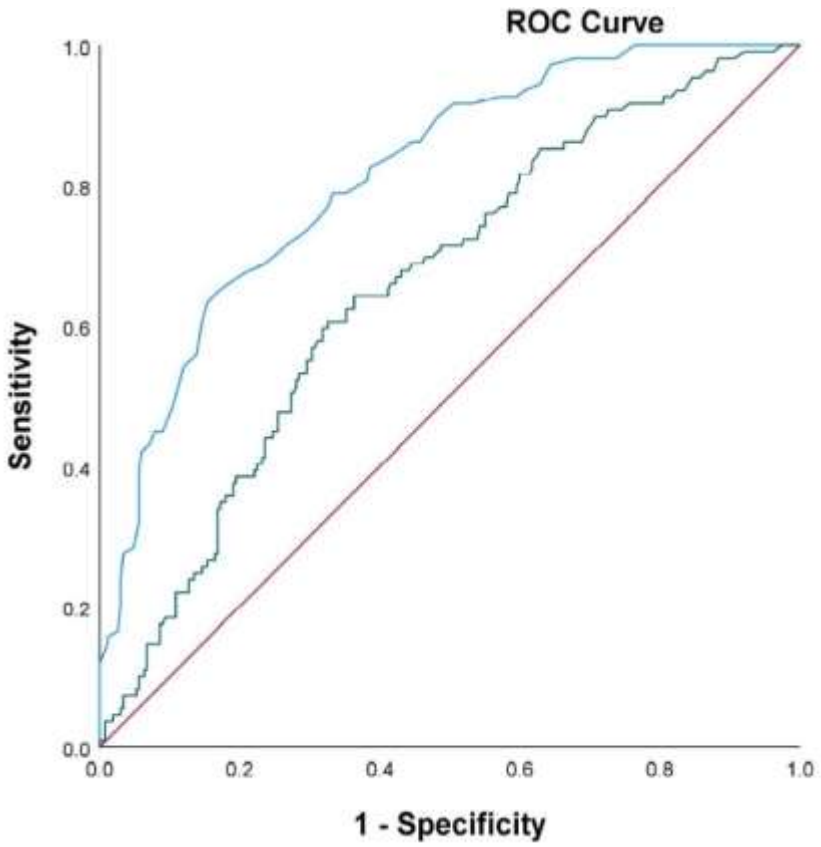

Fig. 2. Overall prognostic accuracy of SAPS 3 (Blue line) and BNP (Green line) for ICU inpatient mortality (reference line shown in red)

A summary of BNP measurements stratified by SAPS 3 risk category (>70 points, High-risk; ≤70 points, Low-risk) is shown in Table 2. Within the low-risk SAPS category, BNP levels were almost 3-times higher in patients who died when compared with patients who survived (p<0.001). Within the high-risk SAPS 3 category, BNP levels were similar in patients who died and patients who survived (p=0.723).

Table 2. Comparison of BNP levels according to SAPS 3 risk category and patient outcomes.

SAPS 3 risk category	BNP level in those who died, ng/L (IQR)	BNP level in those who survived, ng/L (IQR)	p-value
High-risk (Died=71; Survived=46)	284.0 (80.0-1228.0)	350.0 (87.5-1406.8)	0.723
Low-risk (Died=38; Survived=221)	306.0 (143.5-1090.5)	92.0 (23.0-251.0)	<0.001

DISCUSSION.

This study found significant differences in median admission BNP levels and SAPS 3 scores between ICU survivors and ICU non-survivors. The ROC AUC statistics revealed that overall, SAPS 3 performed better than BNP at predicting ICU mortality. The optimal cut-points (i.e. higher risk groups) for predicting ICU mortality in this research were >190ng/L and >70 points for BNP and SAPS 3, respectively. Median admission BNP in the lower SAPS risk category (≤70 points) was significantly higher in patients who died when compared to those who survived. Within the higher SAPS risk category (> 70 points) there was no statistical difference in median BNP between patients who died and those who survived.

Heterogeneity exists across studies regarding optimal cut-points for BNP levels, the optimal timing of the BNP

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measurement, and the post-ICU admission follow-up period. A systematic review and meta-analysis found that optimal cut-points for BNP varied across the studies ranging from 32.1 ng/L to 681.4 ng/L. It also reported variations in the optimal timing of BNP measurements, although, in most of the included studies, the BNP measurement was done on ICU admission.[5] A prospective, observational study found significantly elevated BNP in ICU non-survivors, with a median NT-proBNP level of 6776 ng/L (range: 303-35000 ng/L).[14] Another prospective study investigating the relationship between BNP and hospital mortality found that non-survivors had a median BNP level of 371.20 ng/L.[7] In a subsequent single center, a prospective observational study looking at the role of BNP in predicting ICU mortality in critically ill patients with sepsis, they observed that a BNP level >800 ng/L sampled on day 1 of ICU admission was a strong predictor of mortality at 28 days post-admission (p=0.03). Furthermore, they reported that BNP levels sampled later between day 2 and day 5 of ICU admission were similar between ICU survivors and non-survivors and therefore not predictive of outcome.[12] In this present study, the optimal cut-point for predicting ICU mortality for BNP was >190ng/L. This variation in cut-off values can be explained by the differences in the timing of sampling and methods of measurement. BNP is also a dynamic biomarker that constantly changes as the patient's disease progresses. Even though BNP is generally sampled during day 1 of the ICU admission, there is no fixed time point for the disease process.[6] Depending on when the patient is admitted to ICU, a single BNP value taken on admission or day 1 in ICU will vary across population groups and different case mixes. In this present study, the BNP level sampled on day 1 was used to be consistent with the SAPS 3 score which is also calculated in the first 24 hours. The optimal cut-off for the SAPS 3 threshold for classifying the high-risk category for ICU inpatient mortality was established as >70 points in this research. This finding correlates with the findings of a prospective multicentre, multinational cohort study where they found that at a SAPS 3 score of more than 70, the probability of death in the hospital was more than 60%.[3]These findings were supported by a similar finding in a local South African study which found that high hospital mortality was observed at a mean SAPS 3 score of 58 with non-survivors observed to have a mean SAPS 3 score of 61.58 points[2]. A prospective observational cohort study also found that ICU patients with a median SAPS 3 score of 66 and above had higher 30-day mortality [15]. Even though the SAPS 3 score has not been validated on the African continent in a multicentre prospective study, the strength of the cut-off for SAPS 3 and BNP used in this current study is that it was established from the ROC characteristic curve for this sample population.

Elevated BNP as a marker of adverse outcomes in critically ill patients has been investigated in several studies and found to be caused by multiple factors. The findings of some of these studies showed that elevated levels of both BNP and NT-pro BNP independently predicted mortality in critical care settings, [5, 7, 12, 14, 16-19] which is consistent with the findings of the current study. The majority of these studies looked specifically at the subgroup of the septic critically ill patients, with or without septic shock. In the current study, 36.2% of the patients who were admitted to the ICU had a primary diagnosis of severe infection or sepsis. BNP elevation in patients with sepsis can be significantly high, even in the absence of cardiac pathology. Normal BNP levels in sepsis can be used to exclude the need for further cardiac investigation pending other clinical indications suggestive of cardiac disease.[5] High plasma BNP levels are associated with poor outcomes in sepsis.[5, 9] There appear to be several reasons for increased BNP levels in septic patients, including sepsis-related biventricular dilatation, lipopolysaccharide stimulation, proinflammatory cytokines, impaired renal clearance, volume resuscitation, and sepsis-related acute lung injury or ARDS.[9]

A higher proportion of the current study cohort was surgical (243; 64.6%) versus medical (133; 35.4%), and 24.5% of the total admissions were post-major elective noncardiac surgery patients who were admitted for postoperative monitoring. Levels of cytokines such as tumor necrosis factor-alpha, interleukin -1β, and interleukin-6 have been shown to increase following surgery. These cytokines have negative inotropic effects,[14] which might explain a possible reduction in left ventricular function following major surgery.[14] An individual patient meta-analysis investigating the prognostic value of pre-and post-operative BNP in patients undergoing noncardiac surgery found that an elevated post-operative BNP level was the strongest predictor of death and nonfatal myocardial infarction at 30 days and ≥180 days after noncardiac surgery.[20]

The current study results show that the BNP did not add any additional prognostic value in those patients that are high risk according to the SAPS score. BNP is a useful tool for assessing fluid overload and post-dialysis fluid excess correction in hospitalized patients receiving hemodialysis.[21, 22] NT pro-BNP has a significant prognostic value in individuals with a GFR of 90 and above (odds ratio: 1.18, 95% CI: 0.80-1.76) but not in patients with a GFR less than 30mL/min/1.73m2.[23] Therefore it may be more appropriate to use higher cut-off values of BNP for risk prediction in critically ill patients with renal insufficiency.[23] The higher risk group in this study could have included patients with a low GFR and specifically a GFR less than 30mL/min/1.73m2. Even though renal insufficiency was adjusted for with the use of the SAPS 3 score which includes creatinine levels as one of its variables, GFR was not calculated or analyzed in this present study.

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Elevated BNP levels have been associated with greater severity of illness in previous studies. [12, 14, 16-18]. The increased BNP in the high-risk group may be associated with the severity of disease only and not necessarily ICU mortality. In a 2007 study where disease severity was assessed using the APACHE II score, the NT-proBNP levels were higher as the severity of the disease increased.[17] Mechanical ventilation and the use of vasopressor use were more common at higher NT-proBNP concentrations. These treatment modalities frequently used in the ICU cause an increase in BNP and NT-proBNP through their influence on intrathoracic and intra-cardiac pressures. [17, 24]
This could be another reason why even though BNP level was elevated in the high-risk SAPS 3 group in this current study, it was not predictive of ICU mortality in this group.

GENERALIZABILITY.

This research was conducted in a single-center quaternary-level hospital in the South African public healthcare sector, with a case mix that is very different from what would be seen in patient populations attending lower-level regional and tertiary-level healthcare facilities. Therefore, the findings of this study might not necessarily be completely applicable to other ICU populations in South Africa or Africa.

CONCLUSION.

In conclusion, this research from a general ICU located in a low-income country revealed that there is a significant difference in admission BNP and SAPS 3 scores in ICU survivors when compared to ICU non-survivors. However, SAPS 3 had a better overall prognostic ability when compared with BNP. Of interest, BNP levels might have some prognostic utility in patients stratified as low-risk for mortality based on SAPS 3. Future research, specifically larger multicentre studies, should be conducted in the African continent to validate the results of this present study.

STUDY LIMITATIONS.

This is a single-center quaternary level hospital that has patients referred from other centers and therefore admission to IALCH may occur at a late stage in a patient's clinical course, and because it's a single-center study, the study findings might not apply to other ICUs.
This was a retrospective study, admission to the ICU and the primary admission diagnosis including that of sepsis was at the discretion of the admitting ICU doctor and could change during the ICU course. The information in the patient's medical file also depended heavily on whether events in the ICU were properly documented by the attending clinician. BNP is part of routine laboratory testing in the IALCH general ICU, therefore clinicians were not blinded to the results. This could have influenced clinical decision-making in the ICU and therefore ICU outcomes. This study could not exclude the presence of cardiovascular disease on admission in the cohort and the role this had on elevated BNP could not be assessed. A validation study classified the risk of in-hospital mortality of critically ill patients as low- or high-risk using the SAPS 3 score on ICU admission. However, in the current study, ICU mortality (rather than inpatient mortality) was used as the primary outcome measure because extracting data for this outcome was more reliable. Follow-up of the patient post-ICU discharge in the current study was difficult as patients were often transferred to other healthcare facilities.

RECOMMENDATION.

The findings from this study should be validated in a prospective, multicentre study.

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LIST OF ABBREVIATIONS.

ICU: Intensive care unit
BNP|: Brain natriuretic peptide
NT-proBNP: N-terminal pro-brain natriuretic peptide
SAPS 3: Simplified Acute Physiology Score 3
IALCH: Inkosi Albert Luthuli Central Hospital

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This study was not funded.

CONFLICT OF INTEREST.

The authors declare that they have no conflicts of interest.

GRANT INFORMATION.

No grants were received in support of this research.

AUTHOR BIOGRAPHY.

TG was a registrar in Anaesthesiology and Critical Care based at IALCH, who was studying towards an MMed degree at the time of this research study. TK is an intensivist at Dr Pixley Ka Isaka Seme Memorial Hospital, Durban. She also holds a joint academic appointment at the University of KwaZulu-Natal, Durban. YM is an epidemiologist and public health researcher based at Stellenbosch University, Cape Town. He also holds an honorary researcher appointment at the Central University of Technology.

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