CRITICALLY ILL OBSTETRIC AND GYNAECOLOGY PATIENTS: THE DEVELOPMENT AND VALIDATION OF AN OUTCOME PREDICTION MODEL

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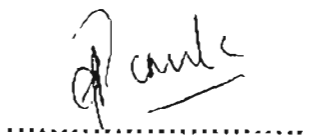
Submitted in partial fulfilment of the requirements for the degree of Doctor of Medicine in the Medical Research Council / University of KwaZulu-Natal, Pregnancy Hypertension Research Unit

[2006]

Declaration

This doctoral thesis is my own unaided work and has been performed by myself. This work has not been submitted previously to this or any other university.



Fathima Paruk

DEDICATION

This work is dedicated to the patients comprising the dataset. Their inclusion made this study possible.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS THESIS

Published Abstracts

1. Paruk F, Bhagwanjee S, Becker P, Muckart DJJ, Moodley J. Critically ill obstetric and gynecology patients : a prospective audit of 260 cases. *World Fed J Crit Care* 2005 ;22 (Suppl1) : 53 [Abstract 113].
2. Paruk F, Bhagwanjee S, Becker P, Muckart DJJ, Moodley J. Outcome prediction in critically ill obstetric and gynecology patients. *World Fed J Crit Care* 2005 ; 22 (Suppl1) : 53 [Abstract 23].

Free Papers

1. Outcome Prediction in Critically Ill Obstetric and Gynaecology Patients. Thirteenth World congress of Anaesthesiologists, Paris, 2004.
2. Critically ill Obstetric and Gynaecology Patients: the Development and Validation of an Outcome Prediction Model. National Critical Care Congress, Durban, 2004. (Received, best free paper award).

Posters

1. Faculty Research Day, 2006. (Received, best poster award).
2. Buenos Aires

Invited Lectures

1. Outcome prediction in critically ill obstetric patients. Critical Care refresher Course, Johannesburg, 2006.

2. The critically ill obstetric patient. COPICON, National Critical Care Congress, Sun City, 2005.

3. Critical Care Obstetrics. South African Society of Obstetricians and Gynaecologists National Congress, 2003, Durban, 2003.

4. Management of Mild to Moderate Hypertension in Pregnancy. South African Society of Obstetricians and Gynaecologists National Congress, 2003, Durban, 2003.

5. Management of Preclampsia-eclampsia. Critical Care Refresher Course, Durban, 2002.

6. Pathophysiology and management of severe preeclampsia-eclampsia. COPICON, National Critical Care Congress, Sun City, 2002.

ACKNOWLEDGEMENTS

I am indebted to the following persons and institution:

Professor Jack Moodley (Director, MRC Pregnancy Hypertension Research Unit, University of KwaZulu-Natal, Durban) for his dedicated teaching and supervision pertaining to research related issues.

Professor Satish Bhagwanjee (Head, Department of Anaesthesia and Director of Cardiothoracic Intensive care, University of Witwatersrand, Johannesburg) for his invaluable guidance as well as allowing me the opportunity to pursue my interest in research and critical care.

Professor David JJ Muckart (Director, Surgical Intensive Care Unit, Department of Surgery, University of KwaZulu-Natal) for his expert opinion in this field of critical care.

Professor Piet Becker (Biostatistics Unit, Medical Research Council of South Africa, Pretoria) for performing statistical analysis on the data.

Mrs Vanessa Tombe (MRC Pregnancy Hypertension Research Unit, University of KwaZulu-Natal, Durban) for advice and assistance pertaining to the layout of the thesis.

The Medical Research Council of South Africa for awarding me a research fellowship in order to conduct this study.

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ETHICS

This doctoral thesis has been approved by the Ethics Committee of the Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa. (Research Ethics Committee reference number: H144/00)

ABSTRACT

Introduction: Outcome prediction tools have the potential to provide significant adjunctive information for intensivists. Critically ill obstetric and gynaecology patients constitute a unique subset of the general ICU (intensive care unit) population yet, there exists no outcome prediction model developed specifically for these patients.

Objectives: To evaluate the APACHE II score, prospectively develop and validate an outcome prediction model, evaluate organ failure (Organ Failure score and SOFA score) and review the SIRS (Systemic Inflammatory Response Syndrome) response in a cohort of critically ill obstetric and gynaecology patients.

Design: A prospective study conducted over a 2 year period in the Surgical ICU at King Edward VIII Hospital, Durban. Institutional ethics approval was obtained. Patients were allocated to one of the following categories:

Obstetric hypertensive group (Group I), Obstetric non-hypertensive group (Group II) and Gynaecology group (Group III). Group III was further subdivided into a pregnant (Group IIIa) and a non-pregnant group (Group IIIb). Data captured included demographic details, clinical assessment, investigations, treatment, variables required for calculating the APACHE II score, organ failure (OF) assessment, SIRS criteria and patient outcome. The APACHE II system, organ failure assessment and SIRS was evaluated in the entire patient subset. For the purpose of the outcome prediction model, the subset was divided into 2 groups: a *development* group and a *validation* group. STATA 7 software was utilised for data analysis.

Results: The dataset comprised 260 inpatients. Obstetrics and gynaecology cases represented 18.5 % of the total ICU population (n=1408). The majority of the patients were young (mean age 27 ± 10.5years). The mean ICU stay was 5.5 ± 7.9 days. The observed mortality for Groups I, II, III, IIIa and IIIb was 23.4%, 43.2%, 42.9%, 33.3% and 55.5% respectively. The mean APACHE II score was significantly higher in nonsurvivors compared to survivors for all patient subgroups ($p< 0.0001$). However the APACHE II system performed variably in each of the 3 groups. The area under the curve for the ROC curves in each of the 3 main subgroups varied from 0.81 to 0.94 for APACHE II. Groups IIIa and IIIb were too small to permit ROC curve analysis. Age, mean arterial pressure, respiratory rate, temperature, the Glasgow Coma Scale score and pH were identified as significant outcome predictors. Using these parameters an obstetric and gynaecology outcome prediction (OGOP) model was developed for Groups I, II and III. The area under the curve for the ROC curves in each of the subgroups was >0.9 for the OGOP Model. A predictive equation could not be developed for Groups IIIa and IIIb (due to a small number of admissions in these two groups.) Duration and the number of organ failures, correlated with outcome. The duration and number of organ failures associated with mortality differed for each group. Three OF exceeding 72 hours, 3 OF exceeding 48 hours and 3 OF equal to 48 hours were invariably fatal in Groups I, II and III/IIIa/IIIb respectively. SOFA scores were significantly higher in nonsurvivors compared to survivors ($p<0.0001$). A day one SOFA score equal to 18 (Group I), 15 (GroupII) and 13 (Group III, IIIa, IIIb) was also invariably fatal. A SIRS response was noted in 94.2% of the patient cohort (245/260). The SIRS response varied in the

subgroups. Sterile shock and septic shock were associated with a high mortality rate. Groups IIIa and IIIb differed with respect to the mean age, duration of hospital and ICU stay and mortality rate. Although these subsets were numerically restricted (24 and 18 admissions respectively), the results suggest that the two subsets are distinctly different in nature.

Comment: The OGOP model is easier to calculate and it is superior to the APACHE II System. It needs to be validated in other local and international units. Organ failure assessment as well as the SIRS response provides useful supplementary outcome information. Although current outcome prediction tools are not designed for individual application, continued research and refinement of the available tools, as well as the exploration of novel methods, may one day result in "near-perfect" prediction estimates and further broaden the scope of their utility.

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LIST OF ABBREVIATIONS

APACHE	Acute Physiology and Chronic Health Evaluation
COAG	Coagulation
CNS	Central nervous system
CVS	Cardiovascular system
G	Group
GCS	Glasgow Coma Scale
HAEM	Haematological
ICU	Intensive care unit
MAP	Mean arterial pressure
MODS	Multiple Organ Dysfunction Syndrome
NS	Non Survivors
OF	Organ failure
OFS	Organ Failure Score
OGOP	Obstetric and Gynaecology Outcome Prediction Model
RR	Respiratory rate
ROC	Receiver operating curve
S	Survivors
SAPS	Simplified Acute Physiology Score
SD	Standard deviation
SIRS	Systemic Inflammatory Response
SMR	Standardised Mortality Ratio

CHAPTER ONE: INTRODUCTION

1.1 PREAMBLE

Intensive care medicine constitutes a relatively new discipline within the realms of the medical field. The concept of intensive care was envisaged as far back as the Florence Nightingale era, but was however only formalised as a discipline in the late 1970's.

The need for intensive care evolved from the recognition that patients with life threatening disease or injury were potentially salvageable if they were grouped into specific sectors in a health care facility. Florence Nightingale's writings highlighted the advantages of establishing a distinctly separate area for the recovery of postoperative patients. The Scandinavian Polio epidemic in 1952 saw the use of simple ventilators to improve patient survival[1]. This initiated the birth and organisation of intensive care units. In 1970 The Society of Critical Care Medicine was formed following a meeting (in Los Angeles, California) of 29 physicians with a special interest in critically ill patients.

In 1986 the American Board of Specialties approved certification of special competence in critical care for 4 primary specialties-anaesthesiology, internal medicine, paediatrics and surgery. The global growth of the discipline of intensive care medicine has ever since progressed at a phenomenal pace. The numerous societies, journals and the vast amount of literature associated with the discipline bear testimony to this.

Intensive care medicine in the context of obstetrics and gynaecology constitutes a discipline very much in its infancy. There is a distinct paucity of literature in this field. The available data is largely retrospective and is in most cases confined to numerically restricted databases. The stark reality is that intensive care unit utilisation by obstetric and gynaecology patients, although largely variable (0.17%-28%), is nevertheless in many situations substantial[2,10]. Specifically in terms of obstetric patients, one should actually assess intensive care units' (ICU) utilisation in the context of the number of deliveries performed in the obstetric population. This is important as a high ICU utilisation rate may lead to the establishment of Obstetric ICUs, as has been done in South Africa and in Texas[11,12] . In general the reported rates of ICU utilisation range from 0.9-13.4/1000 deliveries[13,8,9,11,14-26]. The wide variation in reported mortality rates (0-60%) among critically ill obstetric (and in some cases gynaecology patients) suggests that different units may in fact be managing illnesses of variable severity[15,3-25,27-33,26]. This may be attributed to factors such as: -

- Inconsistent admission criteria- there are no standardised guidelines for obstetric and gynaecology critical care
- Quality of pre ICU care – this is particularly relevant to obstetric patients, where appropriate antenatal care provision has the potential of a positive impact on patient's outcome
- Inherent characteristics of specific patient populations-certain populations may be more prone to a specific disease/disorder

In an era dominated by evidence-based medicine, there remain many unanswered questions in the field of critical care obstetrics and gynaecology. This renders the ground for research in this field extremely fertile.

The issue of outcome prediction is of paramount import in the scenario of intensive care medicine. The implications of accurate outcome prediction include:

- Appropriately informed counselling (of patients and their families)
- Selection of, and the provision of relevant preventative and therapeutic strategies
- A reduction in treatment prolongation in futile circumstances (preventing undue prolongation of anxiety)
- Appropriate patient recruitment in therapeutic trials
- Comparison of intensive care unit management and performance (quality assessment), as well as
- Appropriate resource utilisation, if triage principles are established.

Outcome prediction may vary from being purely subjective to objective determination. Objective outcome prediction has been addressed by various methods in *general* intensive care medicine or in specific subsets of ICU populations[34-50]. Critically ill obstetric and gynaecology subjects represent a specific and substantial subset of the intensive care unit patient population.

The obstetric subset of patients in particular, is unique by virtue of the following inherent characteristics:

- They are generally younger than their nonobstetric ICU counterparts
- Multiple physiological variations result, as an adaptive response to the pregnancy state
- The occurrence of pregnancy specific disorders such as pre eclampsia
- The presence of an additional patient- the fetus.

The presence of these peculiar characteristics suggests that conventional objective outcome scoring systems may not be applicable to this patient population. It is thus not surprising to note that the few (retrospective and largely numerically restricted) studies that have focussed on this issue have produced variable results[3,5-7,10-15,19,22,25,27,28,29,32,50-54]. It is difficult to comment on results elicited from retrospective trials, by virtue of their acknowledged limitations. The wide variation in results further substantiates the lack of knowledge on outcome prediction in these patients. The disparate results also suggest that perhaps, subsets of critically ill obstetrics and gynaecology patients (hypertensive obstetric patients, non hypertensive obstetric patients and gynaecology patients) behave differently and may therefore each require their individual outcome prediction model. To date there exists no literature on the development and validation of an outcome prediction score unique to critically ill obstetrics and gynaecology patients.

1.2 OUTCOME PREDICTION

Outcome prediction may be either subjective or objective.

The subjective prediction of outcome, albeit characterised by certain distinct drawbacks, has (and still does) play an important role in outcome prediction. The art of subjective outcome prediction is not entirely accurate as human judgement is prone to error [55,56].

This error in judgment may be attributed to the following [56-58]:

- The inherent tendency of the human mind towards systematic error
- The human mind has a limited capacity for rational thought
- The tendency to "block out" information that is considered insignificant. This helps the mind avoid considering new possibilities. Thus important facts may be disregarded. The "thinking process" may eventuate into biased decisions.
- The human mind tends to recall familiar and extraordinary circumstances. Thus outcome prediction will probably be more accurate in situations of greater experience/familiarity (with the disease or injury) or if one has been previously exposed to an unusual case.
- The influence of extraneous factors, which will bear positive or negative repercussions on, decision-making. A classic example is the issue of maintaining fiscal discipline in a resource-restricted environment.

It is somewhat reassuring to note that the art of subjective outcome prediction compares favourably with objective outcome prediction methods in terms of discrimination (the ability to correctly predict individual patient death or

survival) [59-62]. However, the comparison is less favourable in terms of calibration (the ability to correctly predict outcome for an entire range of risk) and reproducibility[61].

The drawback of placing sole reliance on subjective outcome prediction includes:

- Decision making may be potentially biased
- A poor reproducibility of decision making
- A lack of accuracy with respect to some decisions
- A potential for negative impact on patient outcome- the patient may be denied intensive care, appropriate life saving therapeutic strategies or inclusion in a research trial.

The ultimate aim in objective outcome prediction is to eliminate the variability that accompanies subjective decision making. In the context of general intensive care medicine there exist various outcome prediction models[34-40,42]. These models may either focus on a single point in time during the patients ICU stay, or alternatively, they may serially evaluate the patient over a period of time in order to predict outcome[34-38,46,47]. The databases have included general intensive care unit populations or have focused on specific subsets of intensive care unit populations. The rationale for focusing on specific subsets is based on the fact that certain patient populations behave differently and thus the weighting of a general score system may be inapplicable to them. An example of this is the development of the King Edward System for critically injured patients without head trauma[48].

The prerequisites of an ideal objective outcome prediction model include the following[63-66].

- It has a limited number of predictor variables
- The predictor variables are independently associated with outcome
- The model be applicable to all working environments
- The model be validated by independent researchers
- The model should not be restricted to specific diseases or injuries
- The model should predict death and potential morbidity, or quality of life assessment in individual patients

The stark reality is that no such model has been developed as yet.

It should also be pointed out that even if the ultimate outcome tool were to be available, it is of paramount import, that other "confounding variables" such as management protocols (nursing and medical) and standards of care be standardised to ensure that the tool is used correctly. Erroneous use or interpretation of the outcome prediction tool may well occur in the following situation:

- Unit A and B are compared and found to have a standardised mortality ratio (SMR = observed mortality : predicted mortality) of 0.7 and 1.1 respectively. It would appear that the Unit B is performing poorly, and management authorities could take the unit staff to task. However it may well be that Unit B is understaffed, has inadequate equipment and or no unit director, all of which, may impact on the SMR. Therefore one needs to be cognisant of these extraneous factors that may impact on the tool's interpretation and utilisation,

1.3 ETHICAL CONSIDERATIONS IN OUTCOME PREDICTION

Medical ethics is characterised by a framework of values that influence the behaviour of health care providers. These values may be summarised as follows:-

- Beneficence – to act in the interest of the patient by treating illness/injury, relieving pain and sustaining life.
- Non-maleficence – to refrain from harm
- Autonomy – to respect the rights' of the patient
- Social justice - the fair allocation of resources with respect to medical need and to patients who would benefit the most there from.

Important issues in critical care ethics relate to demand exceeding supply expand[67]. Intensive care provision is expensive. ICUs generally receive a third of the hospital budget albeit for a small number of patients. With limited resources only a finite number of patients can be provided with intensive care. As a result not all eligible candidates for intensive care will be able to receive it, and this is a global problem. Cost containment strategies therefore need to be considered and practiced by all intensivists. This presents health care providers with a dilemma with respect to decision making regarding:-

- Whom to admit
- Whom to deny admission
- Whom to fully treat
- Whom to deny or withdraw treatment

Modern medicine leans towards a utilitarian social approach, in an attempt to benefit the entire population. However this may necessitate the denial of life supporting therapy in a few patients who are considered to be unlikely to benefit from such therapy. In such situations a highly predictive outcome prediction model has the power to play an important *adjunctive* role in medical decision making by adding more information to the *subjective but scientifically informed* opinion of the intensivist. Therefore it would aid in substantiating the physician's opinion. It certainly cannot play the main role as, outcome prediction tools perform better for groups of patients than for individual patients. To date there exists no tool that is a hundred percent accurate (and there probably will never be one) in predicting outcome at a group level. To utilise such tools for as the only decision making determinant at an individual level would therefore be inappropriate and unethical.

1.4 DEVELOPMENT OF OUTCOME PREDICTION MODELS

The development of an outcome prediction model necessitates adherence to a structured "protocol". The salient elements thereof include the following:-

1. Selection of a patient population
2. Selection of outcome variable(s)
3. Constructing a hypothesis
4. Selection of outcome predictor(s)
5. Collection and analysis of data with reference to outcome(s) and predictor(s)
6. Statistical development of the prediction model

7. Validation of the prediction model and assessment of the model's accuracy (calibration and discrimination)
8. Ongoing audit of the prediction model with respect to its efficiency, effectiveness as well as utility.

Selection of patient population

Although the ideal prediction model ought to predict outcome in all populations, the truth is that even general outcome prediction models exclude certain patient subsets – the APACHE III and the Mortality Prediction Model excluded patients admitted with suspected myocardial infarction as well as subjects with burn injury. Patient population selection is important, as outcome prediction models are only applicable when utilised in a patient population that is similar to the reference population forming the database during the development of the prediction model.

Selection of outcome variable

Outcomes of interest include mortality (a binary outcome), morbidity, cost efficiency, as well as long term quality of life assessment. Mortality is by far the simplest outcome variable to assess. The other outcomes (such as cost effectiveness of care and quality of life after discharge from ICU) are more complex to quantify, as they generally cannot be expressed by binary end points. Further, they are time consuming to evaluate in view of these outcomes being complex to quantify appropriately. In terms of mortality, hospital mortality or intensive care unit mortality intensive care units are utilised. The former is used more commonly than intensive care unit mortality.

The rationale for using intensive care unit mortality is that it is believed to be more reflective of management and the quality of care in the intensive care unit. This controls for extraneous adverse events that occur once the patient is discharged from the ICU.

Constructing a hypothesis

This involves the consideration of all factors that may be associated with the predefined outcome and developing a hypothesis therefrom. It is not mandatory to have a hypothesis when developing an outcome prediction model as these factors will be considered when one is selecting predictor variables.

Selection of predictor variable(s)

One needs to identify relevant historical, clinical, laboratory and epidemiological observations as potential predictor variables. This may be achieved by one of two methods- subjectively or objectively. The former method entails the identification of a list of independent predictor variables by an expert team. In addition the team assigns (by consensus) a weight to each predictor variable in accordance with their perceived degree of abnormality[66]. This method is inexpensive and not time consuming. Its main advantage is that it does not require a separate cohort to generate predictor variables. Thus a single database will suffice – merely to validate the prediction model. This method was utilised in identifying the independent predictor variables for the Acute Physiology and Chronic Health Evaluation models (APACHE I, APACHEII) and the Simplified Acute Physiological Score (SAPS I)[34,35,37]. The

main disadvantage of this method is that the predictors are sometimes found to bear no correlation with the desired outcome as it is a subjective process. This necessitates statistical reweighting in order to achieve calibration.

The objective identification of predictor variables requires a large patient database with multiple potential predictor variables. Statistical tests isolate variables that are individually associated with outcome. A separate cohort of patients is required to validate findings. A disadvantage of this method is the need for two large databases (development and validation group). It is also time consuming, and there is a suggestion that the database (and therefore the predictor variable) may become obsolete prior to the models implementation, if there have been significant changes in therapeutic strategies. It must also be recognised that the predictor variables are opinion guided and thus there is some element of subjectivity within this objective method. This method was utilised for the development of the APACHE III, SAPS II and MPM II (Mortality Prediction Model) systems[36,38,39].

Data collection and analysis

Data collection may be performed retrospectively or prospectively. Retrospective data collection is characterised by various limitations including the possible disregard of important information (due to poor record keeping). Prospective data collection has the power to eliminate such errors. In addition it allows ongoing review (and amendment) of the data collection method. With reference to data analysis the ideal method remains to be identified. The rapid

growth in medical informatics should result in the development and identification of simple yet efficient data analysis programmes.

Statistical development of the prediction model

Model development is achieved by performing a series of tests in a stepwise manner. In the initial stages univariate statistical tests are applied to screen the potential outcome predictor variables for their predictive power. This entails the utilisation of chi square tests (for discrete variables) and Student t tests (for continuous variables). As some outcome predictor variables may only be associated with the outcome indirectly (due to confounding factors), a very liberal significance level - p value of 0.25- is utilised (as opposed to the conventional value of 0.05)[66]. The identification of the significant outcome predictor variables now allows for application of statistical techniques to obtain an association with the outcome (mortality). Multiple regression analysis is the commonly utilised technique to achieve this.

The following is assumed when utilising multiple regression analysis: -

- The dependent variable is continuous
- There is a linear relationship between the dependent variable and the independent variable- in this case mortality and the outcome predictor variable

In some situations the independent variable is not linearly related to the dependent variable, and a sigmoid curve is obtained. This is the case with mortality, which has binary endpoints. The S shaped curve may be converted to a linear one by applying the technique of logistic transformation, which is

referred to as multiple logistic regression analysis if it involves multiple variables. The logistic transformation is statistically expressed as follows:-

$$P = e^{y} / (1 + e^{y})$$

Where: -

- P represents the probability of the outcome,
- e is the base of the Naperian logarithm and
- y is the linear sum of the important predictor variables (multivariate equation).

The logistic approach renders a robust model, which provides a less biased performance with small sample sizes. In addition, it generates direct estimates with respect to outcome probability.

Validation of the prediction model and assessment of model accuracy (calibration and discrimination)

Validation is a complex issue. It requires the developers of the newly determined prediction model, to apply it to a sample population and thus test its accuracy. The sample population may comprise one of the following:

- The original population in whom the model was determined (Resampling)
- The original cohort used to devise the model is now divided into 2 groups- a development and validation set of patients (Split-sampling)

- A population that was not utilised during the development phase of the prediction model.

The last is most labour intensive and time consuming. However it is the best method. Ideally the model should also be validated by a separate group of researchers. The accuracy of the model is determined by judging discrimination (the model's ability to predict outcome in an individual patient) and calibration (the model's ability to predict outcome across an entire range of risk). Discrimination can be assessed by 2 X 2 tables or by developing receiver operating characteristic (ROC) curves. The former method yields sensitivity, specificity and predictive values. ROC curves are obtained by plotting the true positive ratio (sensitivity), against the false positive ratio (1-specificity) where:

TP RATIO = TRUE POSITIVES/(TRUE POSITIVES + FALSE NEGATIVES)

and

FP RATIO = FALSE POSITIVES/(TRUE NEGATIVES + FALSE POSITIVES)

A broad assessment of discrimination potential is obtained with this method. Any one point on the ROC curve provides information on sensitivity/specificity for a given outcome. The area under the curve provides information pertaining

to the model's accuracy- as the area under the ROC curve approaches 1 it approaches "perfection". A hypothetical value of 0.55 translates as follows:-

- A randomly selected actual nonsurvivor will have a more severe score than a randomly selected actual survivor in 55% of the time. It does not imply that a prediction of nonsurvival occurs with a probability of 55%. It also does not imply that that a prediction of death is associated with an observed nonsurvival 55% of the time.

None of the available prediction models report high sensitivities. The correct classification rates (calculated as: [True positives + True negatives] divided by the total cohort) are however acceptable.

Calibration correlates predicted outcome with observed outcome for the entire range of risk. Whilst discrimination is best presented as a percentage, calibration is best expressed graphically –observed outcome (Y axis) versus expected outcome (X axis).

It is important to recognise that the following factors also impact on the accuracy of outcome prediction models:

Lead time bias

The treatment provided pre-ICU admission may "correct" the abnormalities of some of the outcome predictor variables. Haemodialysis for example may markedly lower serum creatinine and urea values and may also result in normal urine output. Thus the creatinine, urea or urine output will be perceived

as "normal". If these are important outcome predictor variables, mortality will therefore be under predicted.

Selection bias

If the prediction model affords a weight to specific admission diagnoses, an erroneous diagnosis has the potential to under predict or over predict the mortality risk.

Detection bias

If there is incomplete data collection, the value (and contribution) of significant predictor variables will be missed and thus lead to incorrect mortality prediction.

Time frame for data capture

Most models utilise the most deranged result during the first 24 hours of ICU stay as a measure of the relevant outcome predictor variable. This timeframe is chosen as it is felt that this represents the period when the subject will be at his/her worst in terms of physiological abnormalities. The reality is that this is not the norm in all cases. Thus the suggestion that sequential daily assessment may be more accurate.

Institutional bias

Admission criteria and management protocols vary between different units, hence the potential for variable outcome prediction depending on the institution.

1.5 OUTCOME PREDICTION TOOLS

1.5.1 GENERAL OUTCOME PREDICTION MODELS

A few of the general objective outcome prediction models have been retrospectively assessed in critically ill obstetric patients[3-5,7-9,13,14,17,20,24,25,27-29,32,50-52,86]. Only 2 other small and retrospective study has addressed the same issue in gynaecology patients[2,32]. None of these studies have, as yet developed and validated an outcome prediction model specific to critically ill obstetrics and gynaecology patients. The objective outcome models or severity of illness assessment methods that have been evaluated include the following:

1.5.1.1 THE APACHE SYSTEM

The APACHE system was first introduced in 1981[34]. It was however, complex and required multihospital validation. It was subsequently followed by APACHE II and APACHE III[35,36]. APACHE II (Appendix I) evolved from the original system and is composed of the following which are assessed during the first 24 hours of ICU care:

- Points for 12 physiological variables (acute illness)
- Points for increasing age
- Points for chronic ill health

In order to develop a predictive equation, diagnostic categories (42 in total) were identified and weighted.

The logit for APACHE II is as follows

x = -3.517 + 0.146 (APACHE II SCORE) + 0.603 (y) + DIAGNOSTIC CATEGORY WEIGHT

Where, y=1(for a post surgical case) or y= 0 (for a non post surgical case)

The risk (R) of death is calculated by placing the logit (x) into the probability equation

$$R = e^x / (1 + e^x)$$

Adding individual risks of each subject with the predefined diagnosis and calculating the mean value peculiar to the subset of patients determine risk of mortality specific to a predefined diagnostic category. Summating individual risks of all the subjects and calculating the mean value elicits the risk for the entire cohort.

The model when developed displayed the following:-

~ 47% sensitivity

~ 95% specificity

~ 70 % positive predictive value (PPV)

~ 88% negative predictive value (NPV)

~ 86% correct classification rate

~ Area under the ROC curve of 0.86

~ An error rate of 15%

The low sensitivity is a cause for concern. The model appears to perform better in excluding the risk of mortality (high specificity) compared to detecting the risk of mortality (low sensitivity).

Limitations of the model include the following:-

- Prediction model is based on 1979-1982 data
- Error rate of 15%
- Reports of its lack of applicability in some units
- Many diagnostic categories were represented by small a number of patients (although the entire data base comprised 5815 subjects)
- Lack of applicability to specific subsets of patients
- Obstetric or gynaecology were not regarded as specific diagnostic categories
- The physiological changes of pregnancy are thus not accounted for in the weighting of predictor variables
- Important physiological variables (in the context of pregnancy specific disorders) such as coagulation abnormalities, liver function and urine output are not considered in the model

The APACHE III system was subsequently developed by incorporating further predictor variables and readjustment to the weighting of some of the predictors (from the APACHE II system)[36]. APACHE III yields a raw score as well as an outcome predictive equation. Although the developers purport that it is an improvement on the previous systems, APACHE III is not utilised as

commonly as the APACHE II system. This is largely attributed to the following factors:-

- A complex methodology is required to calculate the score
- Some of the predictor variables are not routinely evaluated in all ICUs
- Cost - the logistic regression equations are not public information, but need to be commercially acquired from APACHE Medical Systems.

1.5.1.2 SIMPLIFIED ACUTE PHYSIOLOGICAL SCORE (SAPS)

The SAPS I and SAPS II systems were developed as simplified models[37,38]. The SAPS II system incorporates physiological variables and chronic disease variables. The system has been used to determine prognosis in patient groups as well as to compare ICU performance between different units. It is recommended that it should not be utilised to assess individual patient prognosis[68].

1.5.1.3 MORTALITY PREDICTION MODEL (MPM)

The MPM I and MPM II models are used to determine *hospital mortality* risk. MPM II assesses hospital mortality risk at ICU admission and at hours 24, 48 and 72 post ICU admission[39]. The model is highly objective. However the majority of the variables are noncontinous and therefore misclassification can lead to erroneous results. The models use includes assessment of clinical performance (in patient groups), calculation of cost effectiveness of care and determination of hospital mortality risk in select individual patients[68-70].

1.5.1.4 THERAPEUTIC INTERVENTION SCORING SYSTEM (TISS)

TISS was introduced in 1974 as a method to stratify critically ill patients[71]. Variable points (ranging from 1 to 4) are awarded in the presence of predefined occurrences, investigation results or therapeutic interventions. A score is calculated on a daily basis and the severity of illness is accordingly stratified. The score's utility lies mainly in determining nurse: patient ratios for the ICU patient (following assessment of disease/injury severity).

1.5.2 ORGAN FAILURE

Individual organ function may constitute a spectrum of probabilities that may vary between normality, dysfunction and total failure. Organ failure in critically ill patients is known to be associated with an increase in mortality risk[43]. It is also known that the presence of 3 or more organ failures for a duration of ≥ 72 hours is usually associated with a fatal outcome[43,45-47,72-77]. Organ dysfunction therefore has the potential to be utilised as an outcome prediction tool. Although the organ dysfunction scores may correlate with mortality, they are also utilised to monitor response to therapy. Organ dysfunction or failure has been classified by various methods[43,46,47,78,79]. As organ dysfunction/failure is classified independently of the initial injury or disease, the models may be applied across the entire spectrum of critically ill patients. Organ System Failure, Multiple Organ Dysfunction Score, Sequential Organ Failure Assessment and the Logistic Organ Dysfunction Score have been utilised to assess organ dysfunction [43,46,47,79]. Organ System Failure and the SOFA Scores are easier to calculate than the Multiple Organ Dysfunction Score and the Logistic Organ Dysfunction Score

1.5.2.1 ORGAN SYSTEM FAILURE (OSF)

Knaus et al described Organ System Failure in 1985[43]. Cardiovascular, respiratory, renal, haematological and neurological failures are defined on the basis of clinical, physiological or investigative data (Appendix II). An Organ Failure Score is obtained by summating the number of organ failures. Knaus et al demonstrated in a cohort of 5677 patients of which 2719 developed OSF, that the number and duration of OSF was linked to patient outcome.

1.5.2.2 THE SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE

Vincent et al designed the SOFA Score in 1994[79]. It was initially referred to as the Sepsis Related Organ Failure score. However the terminology was subsequently changed to Sequential Organ Failure Assessment score as the score is not specific for sepsis[80]. The score is based on the premise that organ dysfunction/failure is a process that evolves (over a period of time) from normal function to variable degrees of dysfunction, or ultimately, complete failure. The SOFA Score (Appendix III) is a simple score that assesses the function of 6 organ systems. Each organ system (cardiac, coagulation, respiratory, liver, neurological and renal) is awarded a point (ranging from 0 to 4) on a daily basis. Thus the SOFA Score for an individual patient may range from 0-24 on each day in ICU. The score was primarily designed to describe morbidity. However the score has demonstrated a good correlation with survival. The score may be analysed in various ways. The sequential daily score for each individual patient may be used to assess severity of illness on a daily basis, In addition the cumulative score for each organ system (of a

patient population), may be used to assess illness severity and establish a relationship with survival. The score has not been assessed in critically ill obstetric and gynaecology patients.

The advantages of utilising the SOFA score include the following:

- It allows for the recognition of variable degrees of organ dysfunction, unlike other organ failure systems (which classify the presence of organ failure as an "all or none" phenomenon)
- Complex investigations are not required to ascertain organ dysfunction. The MODS score for example requires the calculation of pressure adjusted heart rate which is a complex task[47].
- It is simple to calculate.
- It includes the assessment of liver function, which is of particular relevance to hypertensive disorders of pregnancy – liver dysfunction is not included in all the organ failure scoring systems.

The disadvantages of the SOFA score include the following:

- The definition for organ function varies compared to other organ dysfunction grading systems.
- It requires liver function tests to be performed (which may not be routinely done in all ICUs.)

1.5.3. THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)

The progressive pathophysiological derangement, which precedes the occurrence of the multiorgan dysfunction syndrome, is collectively referred to as SIRS. In essence it represents a clinical response to either an infective (septic) or a noninfective aetiology. The American College of Chest Physicians and the Society of Critical Care Medicine has therefore defined this clinical entity that is associated with the development of MODS, as SIRS (Appendix IV)[44,81]. The main categories identified include:

- Sepsis- a predefined clinical response to an infective aetiology
- Severe sepsis- the predefined response is associated with either organ dysfunction, hypoperfusion or hypotension (which responds to intravascular volume correction)
- Septic shock- the predefined clinical response is associated with hypotension despite appropriate intravascular volume correction and there are perfusion abnormalities.
- SIRS has been addressed in various ICU cohorts[72,81-85]. It may stratify severity of illness and aid in outcome prediction[44]. The drawbacks of the above definition[44,81] includes the following:-
- The absence of noninfective equivalents of severe sepsis and septic shock
- The timeframe for assessment of the predefined clinical response is not specified – should this be done within the first 24 hours of intensive care stay or when the patient is at his/her most physiologically deranged form (which may be at any point in time of the patient's ICU stay)?
- Organ dysfunction criteria are not specified and therefore depend on the interpretive ability of the attending physician.

It has been suggested that the following additional categories be added in order to include the "noninfective" equivalents of sepsis, severe sepsis and septic shock [49]: -

- Severe SIRS and
- Sterile shock

1.6 PREDICTION MODELS IN THE CONTEXT OF OBSTETRICS AND GYNAECOLOGY

Although there is no literature concerning the prospective development of an outcome prediction model peculiar to obstetric and gynaecology patients, various general models have been "tested" in select critically ill obstetric and gynaecology populations[2-5,7-9,13,14,17,20,24,25,27-29,32,50-52,86,87]. The findings thereof are highlighted below.

1.6.1 OBSTETRIC PATIENTS

As discussed previously, the major focus has been on obstetric patients. It should however be pointed out that:

- Many trials have included abnormal pregnancy states (abortions and ectopic pregnancies) as part of their obstetric cohorts.
- Most trials are numerically restricted in terms of their population sample size
- Many of the trials have a long time span (up to 10 years) for data collection. This constitutes a long time, and therefore therapeutic advances

may have biased the results of the applicability of the outcome prediction model.

- Trials with larger patient cohorts have emanated from multicentre studies. Whilst this is perfectly acceptable, one must be cognisant of the potential limitations of adopting such a strategy in critically ill obstetrics and gynaecology patients. The absence of standardised guidelines (with respect to admission criteria as well as management protocols),has the power to introduce heterogeneity and therefore bias the results.

Nevertheless these trials provide important and useful information with respect to outcome prediction models in critically ill obstetric patients.

1.6.1.1 General obstetric population

The APACHE II system constitutes the most commonly evaluated system in the general obstetric population[3-5, 7-9,13,14,17,20,24,25,27-29,32,50-52,86]. To date these trials have been of a retrospective nature. In some instances the researchers have reported only the APACHE II score (as a raw score and have not commented on the appropriateness of the prediction equation). This is probably attributed to one of the following reasons: -

- The aim of the trial being the stratification of disease severity, rather than outcome prediction.
- A low (or absent) mortality rate precluding the application of the outcome prediction model.

The mean or median APACHE II scores have varied from 6 to 14[20,8,9,17,25,27,32]. A retrospective study spanning a 10 year period by Taylor and Richards

(2000) reports a median APACHE II score of 14[32]. This series does however include gynaecology patients. The wide range of the score (from various centres) suggests that the patients in different ICUs exhibit variable severity of illness. The APACHE II system outcome prediction model has produced disparate results. It has been shown to over predict[3,7,14,28,51], under predict[32,52] and appropriately predict[5] outcome in critically ill obstetric patients.

The SAPS II system has been shown to either over predict[3,15,51] or appropriately[5] predict mortality in critically ill obstetric patients. The MPM model has been shown by El-Solh and Grant (1996) to appropriately predict mortality[5]. This study, which assessed the performance of the APACHE II, SAPS II and MPM II systems, represents the only one that demonstrates the appropriateness of each of these models in mortality prediction. The APACHE III system has also been demonstrated to overestimate mortality[3]. Comparison studies of some of these prediction models also show disparate results. El-Solh and Grant found the APACHE II, SAPS II and MPM II systems to have similar predictive accuracy[5]. Hazelgrove et al suggest that APACHE II demonstrated a better fit compared to APACHE III and SAPS II – although all three models had a tendency to overestimate mortality[3]. Whilst Hazelgrove *et al.* (2001), report on a large patient cohort (210 cases), it is important to note that the authors of this retrospective study (from 14 centres), acknowledge that only over half of their patients truly required ICU admission.

Afessa et al (2001) have demonstrated that SIRS is associated with a significantly higher incidence of organ failure and duration of ICU stay[29].

1.6.1.2 Hypertensive disorders of pregnancy

Although hypertensive disorders of pregnancy constitute the commonest underlying pathology necessitating ICU admission in most series, it is interesting to note that there is very little information regarding outcome prediction peculiar to such critically ill individuals A retrospective study from Durban, South Africa has shown in a cohort of 105 eclamptic patients that the organ failure score and the Glasgow Coma Scale score (GCS) are good outcome predictors. The authors also demonstrated that apart from the GCS score the other APACHE II score variables are of no value in outcome prediction[50]. It has been expressed in the literature that patients with hypertensive disorders of pregnancy are different from obstetric patients without hypertension[3,7,50,88]. The hypertensive patients are believed to be younger, exhibit specific (haematological) physiological changes and also perhaps have a lower mortality rate compared to non hypertensive pregnant patients.

1.6.2 GYNAECOLOGY PATIENTS

Outcome prediction in critically ill gynaecology patients has been addressed in very few studies[2,32]. These retrospective studies include a small number of gynaecology patients (23 patients each). In both studies the APACHE II system has been shown to be an inaccurate predictor of outcome.

Historically, gynecology cases comprise a spectrum of patients which includes early pregnancies (abnormal pregnancy states) and pure gynaecology (non pregnant) patients. Thus all gynaecology related studies, usually include early

pregnancies as part of the gynaecology cohort. I am inclined to believe that it is appropriate to do so, in view of the following:

- The physiological adaptation to pregnancy really manifests fully after at least 16 weeks gestation. Therefore the inclusion of such patients in an obstetric cohort may be inappropriate, as it may lead to the combination of physiologically heterogeneous patients.
- The physiological changes of pregnancy before 16 weeks gestation are minimal, such that anaesthetists and intensivists generally regard the physiological status of patients as equivalent to "non pregnant" individuals.
- Further, at this gestation it is also usually pointless to monitor the fetal condition.

Having stated the above, it would be interesting to compare the performance of these two subsets of the gynaecology population.

The variable and conflicting results regarding the application of general outcome prediction models to obstetrics and gynaecology is not unexpected. The solution obviously is to develop a model, designed specifically for critically ill obstetric and gynaecology patients. In light of the aforementioned reasoning it would be prudent to subcategorise the critically ill obstetric and gynaecology population into 3 subgroups – the hypertensive obstetric patients, non-hypertensive obstetric patients (pregnancies ≥ 16 weeks gestation) and gynaecology patients. Further, the comparison of the pregnant and nonpregnant gynaecology patients may provide significant additional information (to a domain that has not been explored before).

CHAPTER TWO: METHOD

2.1 DATABASE

This prospective study was conducted in the multidisciplinary surgical ICU at King Edward VIII Hospital, a teaching institution and a tertiary referral centre in Durban, South Africa. The hospital serves a predominantly underprivileged population. Obstetrics and gynaecology patients are referred to the surgical ICU if they exhibit multiorgan dysfunction and/or require ventilatory support. Critically ill obstetric and gynaecology patients who do not require ventilatory support are generally managed in a high dependency unit, which adjoins the labour ward delivery suite. The surgical ICU is geographically distinct from the obstetric unit. The ICU has 16 beds and is managed by a team of specialist intensivists. All admissions are discussed with and authorised by the specialist intensivist. The obstetric and gynaecology team provide input on a daily basis. All obstetric and gynaecology patients admitted during the period from 1 January 2001 to December 2002 were eligible for recruitment. Ethics approval was obtained from the Ethics Committee of the University of Natal. Permission from the Hospital Board was also secured. It should be pointed out that the initial intention was to perform the study over a one year period, utilising 2 centres for patient recruitment. Patient recruitment at the second site was not feasible and it was therefore decided to perform the study at a single site but over an extended period (2 years) – in order to obtain a sufficient sample size, as predetermined by the statistician. The Ethics Committee was informed of this change. The study was performed over a 2 year period.

Patients were allocated to 1 of the following categories:

- Obstetric hypertensive group (Group I)
- Obstetric non-hypertensive group (Group II)
- Gynaecology group (Group III)

Obstetric and gynaecology patients were regarded as separate groups. Based on our previous work we believe that patients with hypertensive disorders of pregnancy behave in a unique manner[50]. This was the rationale for subdividing the obstetric patients into hypertensive and non hypertensive groups. An obstetric admission was defined in the context of a pregnancy state of ≥ 16 weeks gestation up until 6 weeks post delivery. Pregnant patients < 16 weeks gestation were included in the gynaecology category. Hypertension was defined as the occurrence of a blood pressure ≥130/90 mmHg on 2 separate occasions (at least 4 hours apart), prior to ICU admission. Eclampsia was defined as follows: hypertension, significant proteinuria (> 1+mg/dl on urine dipstick analysis) and generalised convulsions at > 16 weeks gestation. Preeclamsia/eclampsia, transient hypertension, and chronic hypertension (as defined by the International Society for the Study of Hypertension in Pregnancy), HELLP Syndrome and Abruptio Placentae were included in this cohort[89]. The primary reason for ICU admission was used to decide group allocation. If a patient presented with a hypertensive disorder of pregnancy *with* postpartum haemorrhage and a pneumonia, the group allocation was decided upon as follows:

- If the patient was being admitted for hypovolaemic shock she would be allocated to Group II,

- If she was being admitted for septic shock she would also be allocated to Group II, however
- If the reason for admission was a complication of hypertension then she would be allocated to Group I

The consensus opinion was that early pregnancies (less than 16 weeks gestation) be included in the Gynaecology group (Group III) for the following reasons (apart from conventional thinking and current practice):

- The physiological adaptation to pregnancy really manifests fully after at least 16 weeks gestation. It was felt the inclusion of such patients in the obstetric cohort would be inappropriate as it would lead to the combination of physiologically heterogeneous patients.
- The physiological changes of pregnancy before 16 weeks gestation are so minimal, that anaesthetists and intensivists generally regard the physiological status of patients as equivalent to "non pregnant" individuals.
- Further, at this gestation it is also pointless to monitor the fetal condition.

Group III was analysed as a single group *and* as a subdivided group:

Group IIIa - early pregnancy group

Group IIIb - nonpregnant (gynaecology) group

This was done to ascertain if there were any differences within Group III.

There were no exclusions. Patients were managed as per the standard King Edward VIII Hospital ICU protocol, which is the same as recommended by internationally accepted guidelines.

Patient recruitment was divided into 2 phases:

- Phase I: Development Data (1 January 2001 to 31 August 2002)
- Phase II: Validation Data (1 September 2002 to 31 December 2002)

The principal investigator performed data collection. Data captured included patient demographics, indication for ICU admission, liver function tests, coagulation investigations, urine output, urea, serum magnesium, serum calcium, serum phosphate, therapy, duration of stay, outcome as well as variables required for the determination of APACHE II, SOFA score, Organ System Failure Score and SIRS. APACHE II, SOFA Score, Organ System Failure and SIRS were assessed in the entire cohort.

During the study period the HIV prevalence in the antenatal population was obtained from anonymous testing performed by the Department of Health. Patients did not routinely have an HIV test done in the ICU. Further, if a patient had a voluntary HIV test done, the result was not always displayed in the patient's chart. It was anticipated (and borne out during the course of the study) that in most cases the HIV status would be unknown and was therefore not analysed.

STATA 7® (College Station, Texas) software was utilised for data analysis. Data are presented as the mean and standard deviation. The two-tailed Student's *t*-test and Chi-square test were used for continuous and discrete variables respectively. Calculating areas under the receiver operating curves assessed discriminatory power. Calibration was assessed expressing the relation between mean predicted mortality versus observed mortality for each decile of mortality risk. The α level for statistical significance was set at $p < 0.05$.

2.2 THE APACHE II SYSTEM

The APACHE II variables were assessed during the first 24 hours of each patient's ICU stay. The most deranged value during this timeframe was identified and captured. The APACHE II score was calculated (as depicted in Appendix I) by summating points awarded for acute physiological (parameters), age and chronic health evaluation.

The GCS score was determined by assessing the non sedated patient's best eye, motor and vocal response as described by Teasdale and Jennet (1974)[41]. (Appendix V). Intubated patients were assigned a value of 1 for their vocal response .The risk of mortality (R) was calculated as advocated by Knaus et al for APACHE II (1985)[35] . Whilst ICU and hospital mortality was documented, ICU mortality was utilised to evaluate the APACHE II score. The lack of sufficient step down care facilities or adequate numbers of trained nursing personnel for all the discharged patients precluded the use of hospital

mortality. It was believed that in view of the lack of control of the patients' aftercare (following ICU discharge) in these circumstances, might lead to an erroneously higher adverse outcome. APACHE II was calculated for the entire cohort of 260 cases.

2.3 ORGAN SYSTEM FAILURE

Organ dysfunction was evaluated as stipulated in Appendix II. This is adapted from the Organ Failure Score advocated by Knaus et al (1985)[43]. Cardiovascular dysfunction (in addition to criteria defined by Knaus et al) was also diagnosed in the context of inotrope usage. The Organ Failure Score (OFS) was calculated by summating the number of organ failures. OSF was evaluated on day one.

2.4 THE SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE

The SOFA score as described by Vincent et al in 1996(Appendix III) was calculated daily for a maximum period of 35 days[79].

2.5 THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)

This was assessed in terms of the definitions proposed by the American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference Committee (1997) [81]. The two additional categories (severe SIRS and sterile shock), recommended by Muckart and Bhagwanjee(1997) were included for patients manifesting with a SIRS response but no infection[49].

An infection was diagnosed if the patient had either one of the following:

- Bacteraemia
- Fungaemia
- Breach and contamination of a normally sterile site by microorganisms

SIRS was documented on admission and on a daily basis during the course of the patients' ICU stay.

The spectrum (6 types) of the SIRS response is listed below and described in Appendix IV:

- Without a focus of infection

- SIRS
- Severe SIRS
- Sterile shock

- With a focus of infection

- Sepsis
- Severe sepsis
- Septic shock

2.6 THE OBSTETRIC AND GYNAECOLOGY OUTCOME PREDICTION (OGOP) MODEL

There exists no outcome prediction tool for this population. Therefore a select few parameters could not be chosen. It was decided that all possible relevant factors be considered, with an emphasis on the following:

- The parameter be, probably relevant in the context of the critically ill obstetric or gynaecology patient
- The parameter be generally routinely documented in the ICU setting and
- The parameter be relatively easy to access

The parameters mentioned below and the parameters mentioned in 2.1 (above) were captured and subjected to logistic regression analysis.

The following parameters were captured for each patient. The most deranged value (where applicable) in the first 24 hours was documented.

- Preadmission status
- Gestational age
- Mode of delivery
- Blood product utilisation
- Age
- Mean arterial pressure
- Temperature
- Respiratory rate
- GCS
- pH

- Haemoglobin
- White cell count
- Platelet count
- Electrolytes
- Urine output
- Creatinine
- Urea
- Liver enzymes
- International normalized ratio (INR) and Partial thromboplastin time (PTT)
- Albumen
- Total protein
- Inotrope use (adrenalin or dobutamine)
- PaO_2: FiO_2 ratio
- Aa-DO_2 (alveolar arterial gradient)

The Aa-DO_2 was calculated as follows:

$[F_{IO2} (P_B - P_{H2O}) - (P_{aCO2} / RQ)] - P_{aO2}$

The respiratory quotient was assumed to be 0.8.

760 mmHg was utilized for barometric pressure and 47 mmHg was utilized for P_{H2O}.

In the development phase, these parameters were submitted to multiple logistic regression analysis. Significant outcome predictors were identified and an outcome prediction model (Obstetric and Gynaecology Outcome Prediction

model) was developed. The accuracy of the OGOP model was subsequently tested in the validation phase.

CHAPTER THREE: RESULTS

3.1 GENERAL

During the period of study, 261 obstetrics and gynaecology cases were admitted to the ICU. One of the admissions (a pregnant cardiac patient) declined hospital care and discharged herself within 2 hours of ICU admission. The dataset thus comprises 260 admissions.

Table 1 depicts the various proportions of the ICU admission cases. Obstetrics and gynaecology cases represented 18.5% (n=260) of the total ICU population (n=1408). Obstetric admissions (n=218) were more common than gynaecology admissions (Group III, n=42), (83.8% and 16.2% respectively). The majority of obstetric patients (94%) were postpartum and only 50% had received some form of prenatal care (at least 3 antenatal visits, 3 visits was utilised as this is considered to be reasonable antenatal care by general obstetric standards). Obstetric hypertension (Group I, n= 144) and obstetric non hypertension (Group II) accounted for 66.1% and 33.9% of the obstetric admissions respectively. In total there were only 12 antenatal admissions (5.5%, n=218). As they represented a small number they were not subjected to detailed analyses. The mortality rate for the antenatal admissions was 50% (3 of 6 admissions) and 67% (4 of 6 admissions) for Groups I and II respectively. Among the obstetric cases, 5 constituted readmissions. There were no gynaecology readmissions. Eighteen (8%) obstetric admissions and 8 (19%) gynaecological admissions were direct transfers from geographically separate hospitals. The ICU utilisation of King Edward VIII Hospital obstetric patients was 1.39% or alternatively 13.9:1000 deliveries (195 patients, 14 054

deliveries). The Gynaecology admissions accounted for 16.2% of the obstetrics and gynaecology admissions. Early pregnancies and gynaecology admissions accounted for 57% and 43% of Group III admissions respectively. The nonpregnant gynaecology admissions represented 7% of the total obstetrics and gynaecology admissions.

Table 1: ICU Admissions

	Cases
All admissions	1408
Obstetrics and gynaecology	260 (18.5)*
Obstetric	218 (83.8)
• Hypertension (G I)	144 (55.4)
• Non hypertension (G II)	74 (28.4)
Gynaecology (G III)	42 (16.2)
• Early Pregnancy (GIIIa)	24 (9.2)
• Gynaecology (G IIIb)	18 (7)

( )*=% of all ICU admissions

( )=% of obstetrics and gynaecology admissions

G= Group

Table 2 depicts the underlying pathology in the admissions. The majority of Group I patients had eclampsia (68.1%, 98 of 144 admissions). Infections (64.9%, 48 of 74 cases) comprised the commonest pathology in Group II, and abortions featured most frequently in Group III (33%, 14 of 42 cases). The two

admissions with gestational trophoblastic disease did not manifest with hypertension.

Table 2: Primary diagnosis on ICU admission

Primary Diagnosis	Number (%)
• OBSTETRICS (n=218)	
Group I	
Eclampsia	98 (45)
Other hypertensive disorders	46 (21)
Group II	
Infections	48 (22)
Haemorrhage	15 (7)
Cardiac disease	5 (2.2)
Anaesthetic complication	4 (1.8)
Tumour	1 (0.5)
Para suicide	1 (0.5)
• GYNAECOLOGY (n=42)	
Group IIIa	
Abortion	14 (33)
Ectopic pregnancy	6 (14)
Infection	1(2)
Gestational trophoblastic disease	2 (5)
Anaesthetic complication	1 (2)
Group IIIb	
Infections	8 (19)
Benign tumours	8 (19)
Gynaecological malignancy	2 (5)

Table III provides a breakdown of the nature of infections in Group II. The vast majority presented with puerperal sepsis (73%).

Table 3: Group II: Nature of Infections (n=48)

DIAGNOSIS	NUMBER (%)
Puerperal sepsis	35 (73)
Pneumonia	8 (17)
Wound sepsis	3 (6)
Meningitis	1 (2)
Other (unknown)	1(2)

Table 4 illustrates that in Groups I and II the patients were young (mean age 25 and 26 years respectively) and of low parity. Group III patients were generally older (mean age 34 years). Group 3 was significantly older than Group 1 and 2 ($p=0.002$). Group I and II were of a similar age ($p=0.19$). The mean ICU stay was 4.9, 5 and 8.3 days for Groups I, II and III respectively. Group I admissions exhibited a significantly lower gestational age compared to Group II admissions ($p=0.05$). The mean hospital stay was 16.1, 13.9 and 18.1 days for Groups I, II and III respectively. Group 3 demonstrated a significantly longer ICU stay compared to Groups I and II ($p= 0.01$ and 0.02 respectively). There was no statistically significant difference in ICU stay when Groups I and II were compared ($p=0.45$). Hospital stay was not significantly different when the three groups were compared ($p>0.05$). Group IIIb admissions were significantly older

than the early pregnancy admissions ($p<0.001$). There was no significant difference in age between Groups I, II and IIIa (P.0.05). The early pregnancy group (Group IIIa) demonstrated a mean gestational age of 11 ± 1.8 and a range of 6 to 14 weeks. ICU and hospital stay was significantly longer in Group IIIb compared to Groups I, II and IIIa ($p<0.05$). Table 5 illustrates the mean values of general characteristics observed in survivors compared to nonsurvivors. There was no significant difference in mean gestation, ICU stay and parity in survivors compared to nonsurvivors for each of the subgroups ($p>0.05$ for all comparisons in each group). Groups I and II illustrated a significant difference in age between survivors and non nonsurvivors ($p= 0.03$). Groups I, II, III, IIIa and IIIb illustrated a significant difference in hospital stay between survivors and non nonsurvivors ($p< 0.003$ for each subset). In total 220 Units (U) of packed cells, 200 U of platelets and 75 U of FDP (freeze dried plasma) were utilised by Groups I and II together (n=218). This was not significantly different between the groups ($p>0.05$). Thirty Units of packed cells, 40 U of platelets and 15 U of FDP were utilised by Group III. In addition 13 cases (6%) required haemodialysis in the obstetric cohort of 218 cases. No gynaecology admission required haemodialysis. The majority of Group I and II patients were ventilated (91%, n=198) with the mean duration of ventilation being 3.8 ± 6.6 days and 4.2 ± 5.5 days for Groups I and II respectively. Ninety-three percent (n=39) of Group III patients were ventilated for 7.3 ±10.7 days. Group IIIa and IIIb patients were ventilated for 5 ±7 and 10 ± 9 days respectively. There was no significant difference in duration of ventilation on comparing Groups I and II ($p>0.05$). Group IIIb was ventilated for a significantly

longer duration compared to Group I (p=0.02), Group II (p= 0.005) and Group IIIa (p=0.005).

Table 4: General Characteristics of 260 ICU Admission Cases

	All		G I		G II		G III		G IIIa		G IIIb	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Age (years)	27	10.5	25	8	26	6	34*	12	28	6	42*	14
Gestation (weeks)	31	7.5	31.5*	5	35.6	4.5	11	1.8	11	2	-	-
Parity	2	1	2	1	2	1	-	-	1	2	2	3
ICU stay (days)	5.5	7.9	4.9	7.6	5	5.8	8.3*	10.9	6	5	11*	10
Hospital stay (days)	15.8	16	16.1	18	13.9	15.3	18.1*	15.3	15	11	23	17

(M= Mean, SD=standard deviation)

* = $p<0.05$ (refer to text)

Table 5: General Characteristics of Subgroups of ICU Admission Cases (Mean values)

	G I (n=144)		G II (n=74)		G III (n=42)		GIIIa (n=24)		G IIIb (n=18)	
	NS	S	NS	S	NS	S	NS	S	NS	S
Age (years)	26	24*	24	27*	36	33	28	28	42	42
Gestation	31.5	31.7	36.2	34.8	-	-	11	11	-	-
Parity	2	2	2	2	2	2	-	-	-	-
ICU stay (days)	5.4	8.2	3.8	6	9.9	7.1	6.8	5.5	12.4	10.2
Hospital stay (days)	6.8	19*	4.5	21*	16	19.6*	12.3*	15.5*	19*	28*

(S=survivors, NS=nonsurvivors) [SD]

- * = $p<0.05$ (survivors compared to nonsurvivors)

The overall mortality rate in the ICU was 37.8% (532 deaths among 1408 admission). Eighty-four obstetrics and gynaecology patients (32.3%) died in the ICU. The case mortality for Groups I, II and III was 23.4%, 43.2% and 42.9% respectively (Table 6). The mortality for Groups IIIa and IIIb were 33.3% and 55.5% respectively.

Table 6: Mortality of obstetrics and gynaecology admissions

Population	Mortality (%)
All ICU admissions (n=1408)	532 (37.8)
Obstetrics and gynaecology (n=260)	84 (32.3)
Group I (n=144)	34 (23.6)
Group II (n=74)	32 (43.2)
Group III (n=42)	18 (42.9)
• Group IIIa	8 (33.3)
• Group IIIb	10 (55.5)

3.2 THE APACHE II SYSTEM

The APACHE II score ranged from 7 to 43 (Table 7). The mean APACHE II score was significantly higher in nonsurvivors compared to survivors for all patient subgroups ($p < 0.0001$). Mean APACHE II scores were similar for survivors and nonsurvivors in each group yet the observed mortality differed among the subgroups. The APACHE II system over predicted mortality in Groups I, II, III and IIIa. Mortality was slightly under predicted in Group IIIb. The standardised mortality ratio (defined as observed mortality : predicted mortality) differed and was below one for each subgroup, excepting in Group IIIb (Table8). The sensitivity, specificity and predictive value of the APACHE II system at a relative risk (RR) ≥ 0.5 were demonstrated to be variable between the subgroups. Group I had a low sensitivity of 64.7% and a specificity of 88.2% whereas Group II depicted a sensitivity and specificity of 75% and

78.6% respectively. The sensitivity and specificity improved to 77.8% and 91.6% respectively in Group III (Table 9). Figures I to III illustrate the ROC (receiver operating characteristic) curves for each of the subgroups. The area under the curve differed for each subgroup. In addition it was lower in Group I (AUC= 0.8123) compared to Groups II and III.

In Group IIIa the mean APACHE II score was 16 ± 6 for survivors and 28 ± 7 for nonsurvivors. In Group IIIb the mean APACHE II score was 18 ± 7 for survivors and 29 ± 7 for nonsurvivors. The scores were significantly higher in nonsurvivors compared to survivors for both subsets. No difference in APACHE II scores was observed between the 2 subsets. The sensitivity, specificity and predictive value of the APACHE II system at a relative risk (RR) ≥ 0.5 were demonstrated to be variable for the 2 subsets. Group IIIa demonstrated a sensitivity of 38% and a specificity of 93%, whilst a sensitivity of 75% and a specificity of 80% was observed for Group IIIb. Once again the data sets were extremely small (n=24 and 18 respectively). The sample sizes were too small (Group IIIa and IIIb) and the estimates too unstable for the construction of ROC curves.

Table 7: APACHE II score of obstetrics and gynaecology cases

	All	Group I*		Group II*		Group III*	
	(n=260)	NS (n=34)	S (n=110)	NS (n=32)	S (n=42)	NS (n=18)	S (n=24)
Mean [SD]	21[8]	28 [7]	17 [6]	29 [6]	18 [5]	29 [7]	18 [6]
Maximum	43	39	34	42	26	43	40
Minimum	7	10	7	16	9	17	10

NS= Nonsurvivors

S = Survivors

SD= Standard deviation

* = $p < 0.0001$ (with respect to mean APACHE II Score in survivors and nonsurvivors)

Table 8: The Standardised Mortality Rate (SMR) for the APACHE II System

	Group I (n=144)	Group II (n=74)	Group III (n=42)		
			ALL	G IIIa	G IIIb
Observed Mortality	23.3	43.2	42.9	33.3	55.5
Predicted Mortality (APACHE II logit equation)	32.2 [22.5]	49.5 [25.9]	48.7 [26.5]	47 [25]	51 [29]
SMR	0.72	0.87	0.88	0.72	1.1

[ ] = standard deviation

Table 9: Mortality prediction with the APACHE II System

	GROUP I (n=144)	GROUP II (n=74)	GROUP III (n=42)
Sensitivity	64.7	75	77.8
Specificity	88.2	78.6	91.6
PPV	66.7	72.7	87.5
NPV	87.4	80.5	84.6

(PPV= positive predictive value, NPV= negative predictive value)

Figure 1: APACHE II: ROC curve for Group I

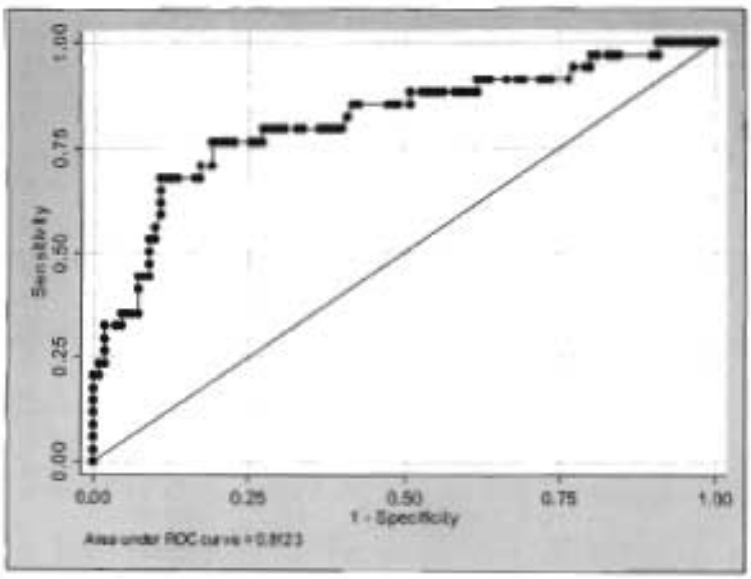


Figure 2: APACHE II: ROC curve for Group II

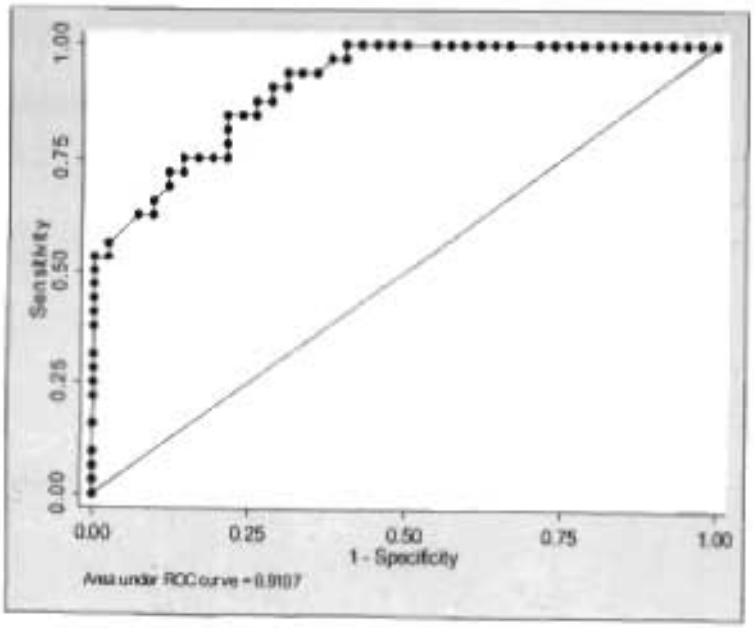
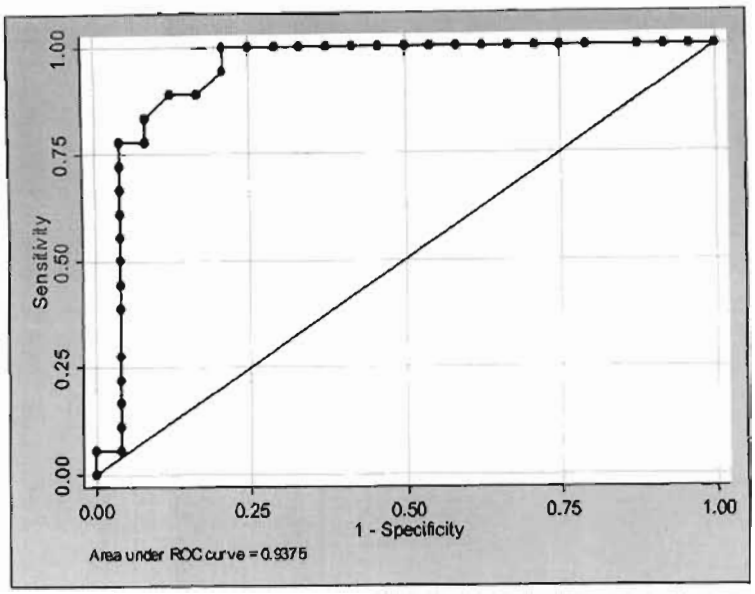


Figure 3: APACHE II: ROC curve for Group III

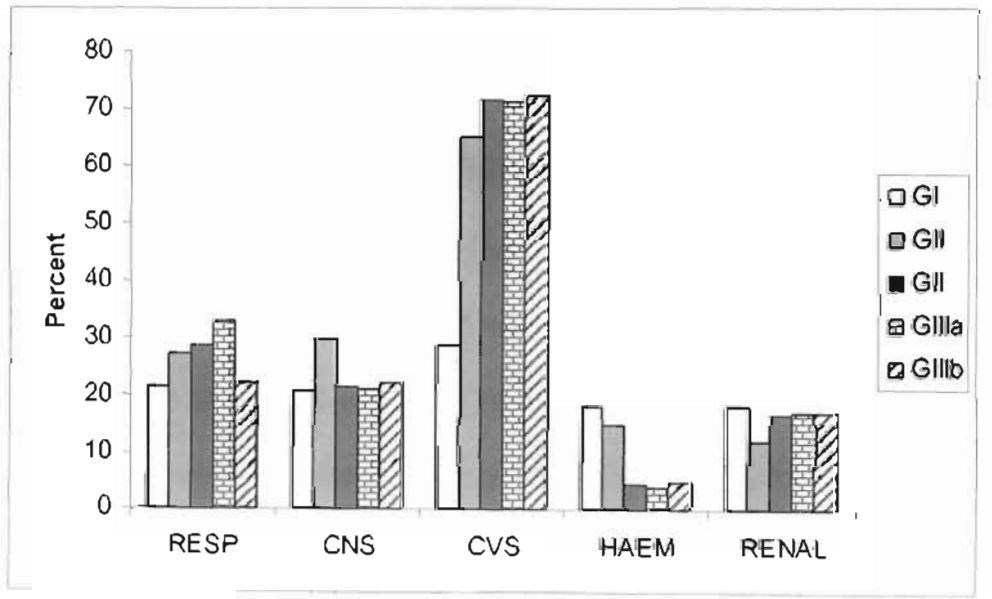


3.3. ORGAN SYSTEM FAILURE

One hundred and sixty five admissions (63.5%) of the total cohort exhibited at least one organ failure as described by Knaus et al[43]. In Group I, 55.6% (80/144) of the subjects demonstrated organ failure on Day 1(Figure4). The commonest organ failures comprised cardiac (28.5%), respiratory (21.5%) and neurological failure (20.8%). In Group II, 75.7% (56/74) of subjects demonstrated organ failure on Day 1. The commonest organ failures comprised cardiac (69.4%), neurological (29.8%) and respiratory (27%) failure. In Group III, 69% (29/42) of subjects demonstrated organ failure on Day 1. The commonest organ failures comprised cardiovascular (69%), respiratory (28.6%) and neurological failure (21.4%). In Group IIIa, 67% (16/24) of admissions demonstrated organ failure on Day 1. In Group IIIb, 72% (13/18) of the admissions demonstrated organ failure on Day 1. The commonest organ failures comprised cardiovascular, respiratory, and

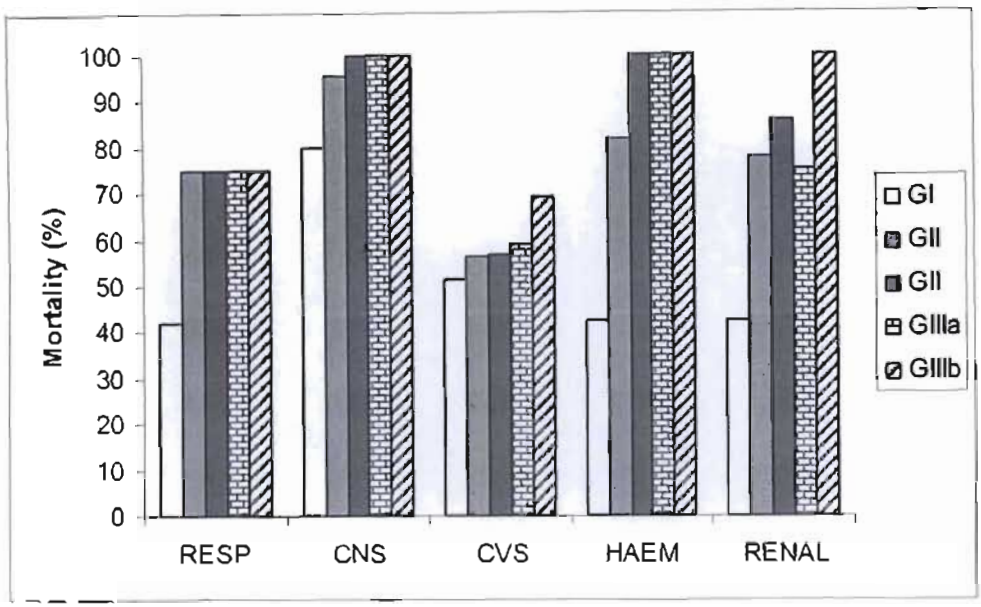
neurological failure for both subsets of Group III. Figure 5 illustrates the mortality associated with each type of organ failure in the three groups. It illustrates that the mortality associated with each organ failure differed depending on the group. Neurological failure was associated with a high mortality in all subgroups. A higher mortality was observed in Group III (for each of the organ failures) compared to Groups I and II. Haematological and renal failures were associated with a particularly high mortality in Group III. In Group IIIb, cardiovascular and renal failure were associated with a higher mortality compared to the same organ failure in Group IIIa.

Figure 4: Type of Organ Failure in each group on Day 1



(RESP=respiratory, CNS= neurological, CVS=cardiovascular, HAEM=haematological organ failure)

Figure 5: Mortality associated with each type of Organ Failure



(RESP=respiratory, CNS= neurological, CVS=cardiovascular, HAEM=haematological organ failure)

Figures 6-10 illustrate a general trend towards an increase in mortality as the Organ Failure Score increased on Day 1. For figures 6-16, the clear blocks represent survivors and the shaded blocks represent nonsurvivors. Figures 11 to 16 illustrate that generally as the number and duration of organ failures increased, mortality also increased in Groups I and II and the entire data set. In Group III (which had a numerically restricted data set), the overall trend was of an increase in mortality as the number and duration of organ failures increased (Figure 11). However a dip in mortality was observed in figures 11 and 13. The number of observations were few in these categories and may have altered the general trend. Groups IIIb illustrated a general increase in mortality as the number and duration of organ failures increased, however Group IIIa illustrated no consistent trend. This is, in all likelihood attributed to the small data set.

Figure 6: Group I: Organ Failure Score and the associated mortality

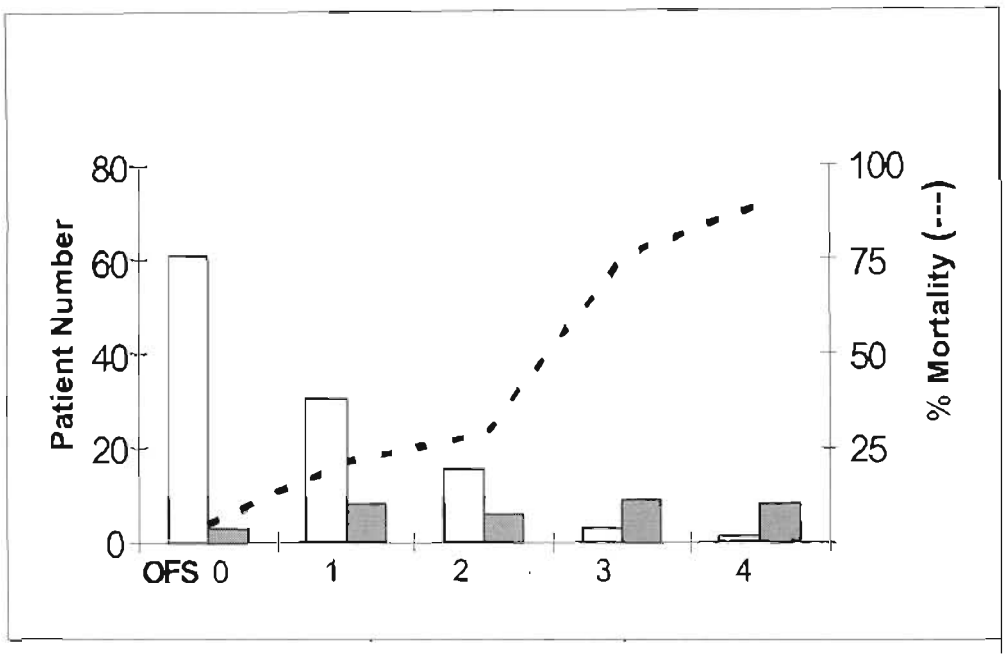


Figure 7: Group II: Organ Failure Score (X axis) and the associated mortality

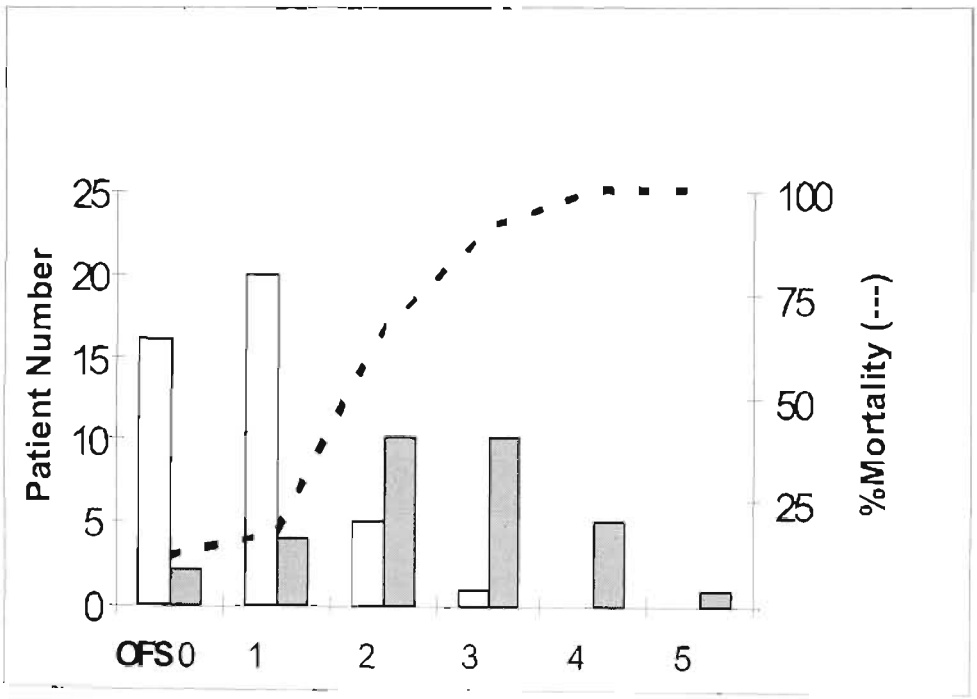


Figure 8: Group III: Organ Failure Score (X axis) and the associated mortality

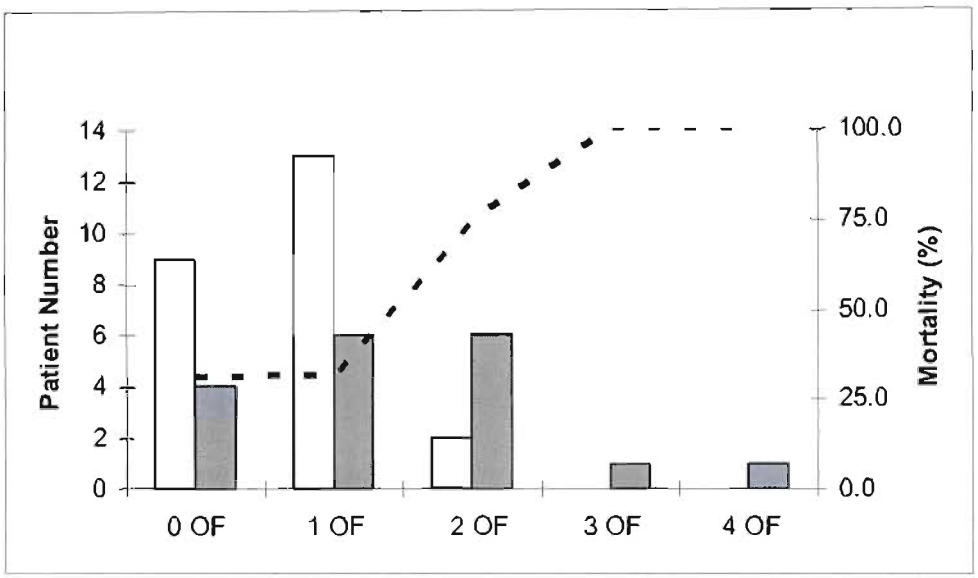


Figure 9: Group IIIa: Organ Failure Score (X axis) and the associated mortality

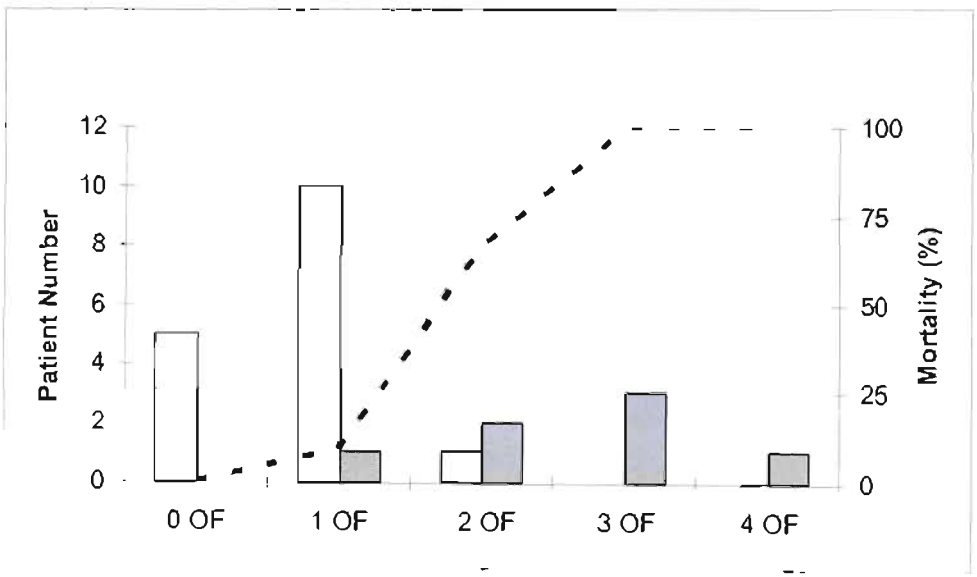


Figure 10: Group IIIb: Organ Failure Score (X axis) and the associated mortality

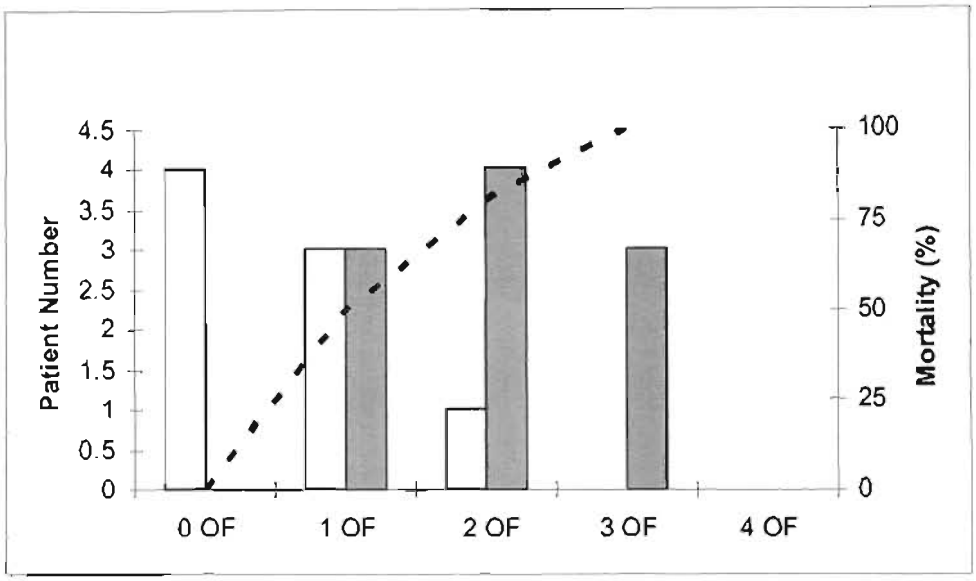
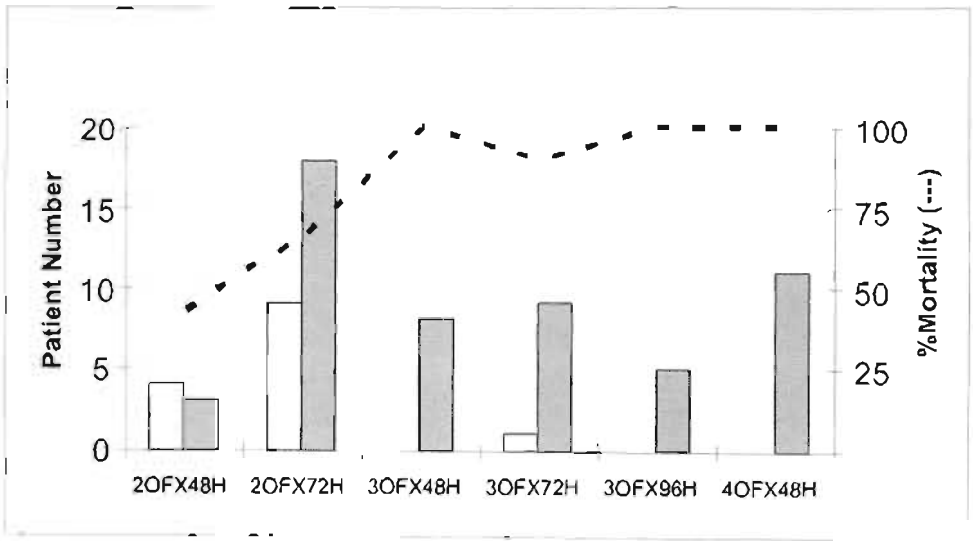
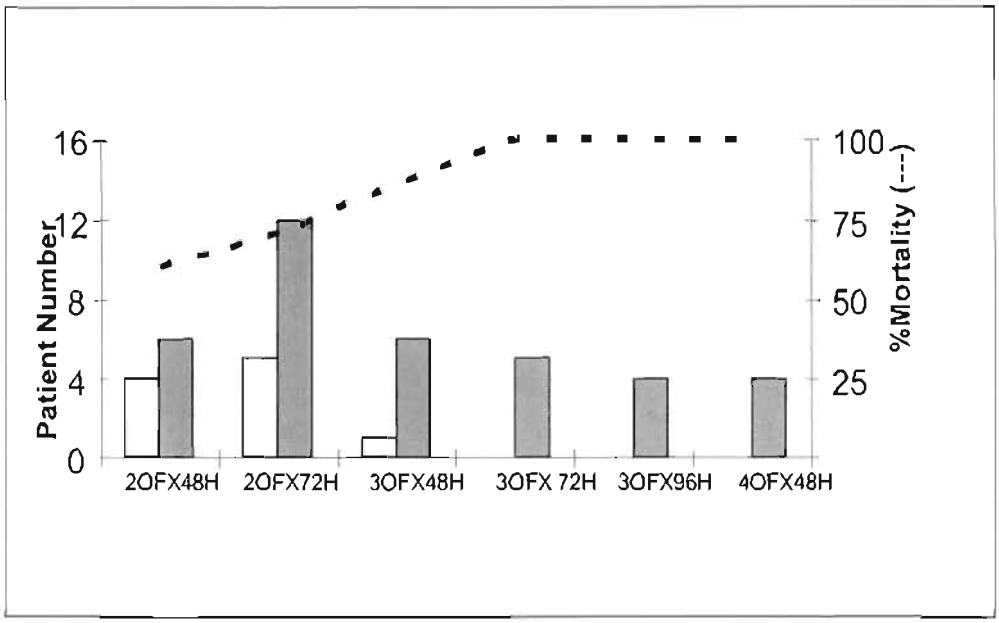


Figure 11: Group I: Number and duration of Organ Failures and the associated mortality



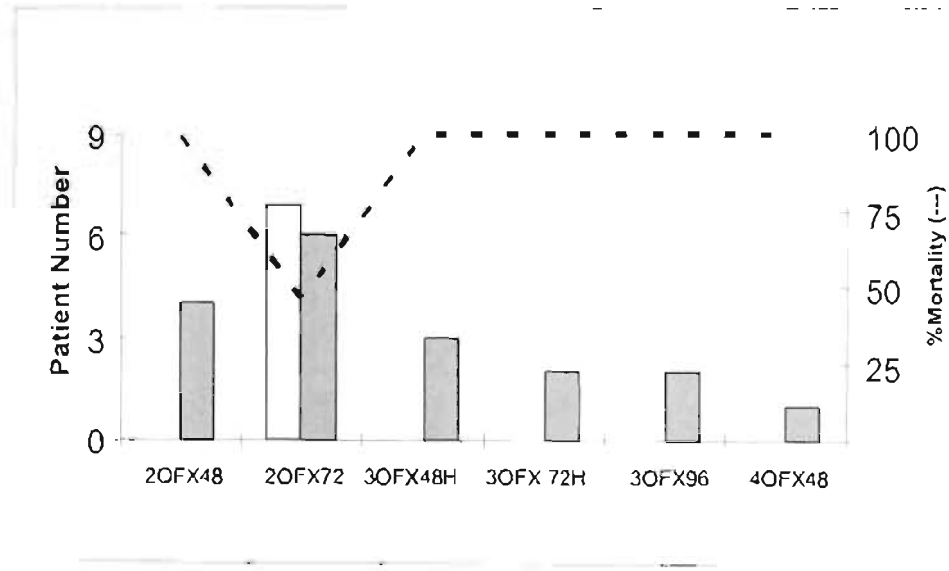
(OF= organ failures, H= number of hours)

Figure 12: Group II: Number and duration of Organ Failures and the associated mortality



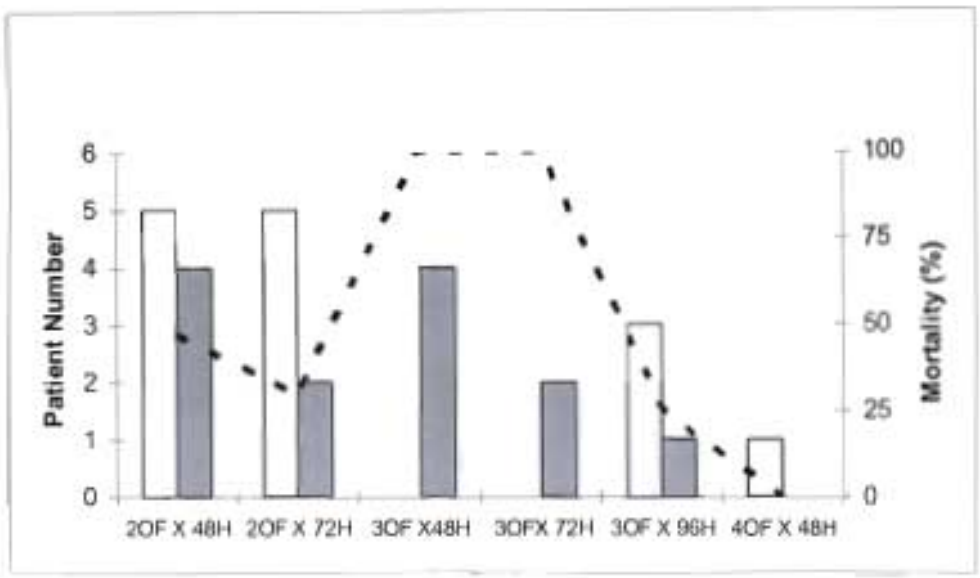
(OF= organ failures, H= number of hours)

Figure 13: Group III: Number and duration of Organ Failures and the associated mortality



(OF= organ failures, H= number of hours)

Figure 14: Group IIIa: Number and duration of Organ Failures and the associated mortality



(OF= organ failures, H= number of hours)

Figure 15: Group IIIb: Number and duration of Organ Failures and the associated mortality

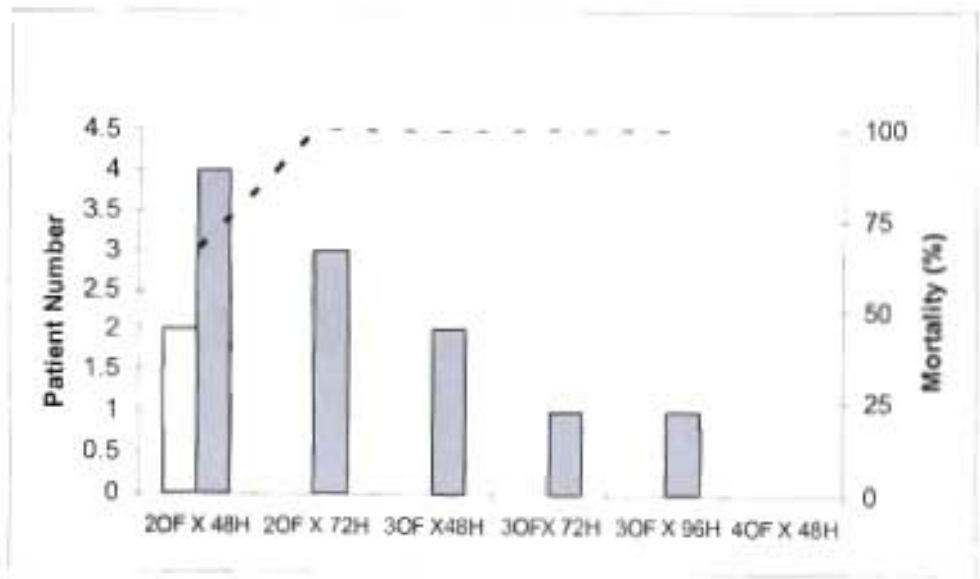
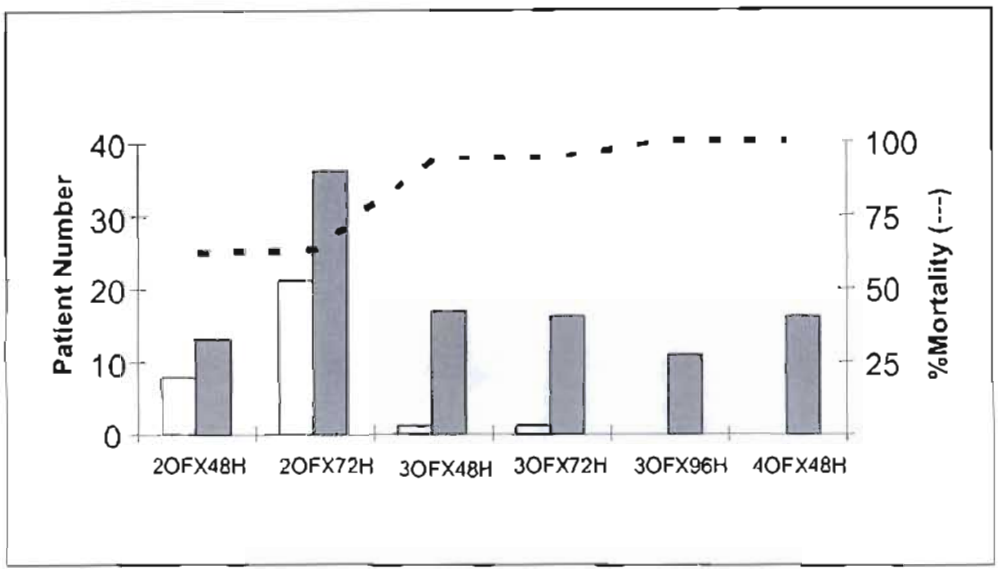


Figure 16: Entire Group: Number and duration of Organ Failures and the associated mortality



(OF= organ failures, H= number of hours)

The discriminatory ability at a decision threshold of 0.5 with 2 concurrent organ failures exceeding 48 hours is depicted in Table 10-13 for Groups I, II, III and the entire group respectively.

Table 10: Group I: Discriminatory ability at a decision threshold of 0.5 with 2 concurrent organ failures exceeding 48 hours

		True Outcome		
		Dead	Alive	Total
Predicted Outcome	Dead	21	13	34
	Alive	13	97	110
	Total	34	110	144

Sensitivity	61.8%
Specificity	88.2%
Positive predictive value	61.8%
Negative predictive value	61.8%
Correct classification rate	81.9%

Table 11: Group II: Discriminatory ability at a decision threshold of 0.5 with 2 concurrent organ failures exceeding 48 hours

		True Outcome		
		Dead	Alive	Total
Predicted Outcome	Dead	18	8	26
	Alive	14	34	48
	Total	32	42	74

Sensitivity	56.3%
Specificity	81%
Positive predictive value	69.2%
Negative predictive value	70.8%
Correct classification rate	70.2%

Table 12: Group III, IIIa and IIIb: Discriminatory ability at a decision threshold of 0.5 with 2 concurrent organ failures exceeding 48 hours

GROUP III		True Outcome		
		Dead	Alive	Total
Predicted Outcome	Dead	10	6	16
	Alive	8	18	26
	Total	18	24	42

GROUP IIIa		True Outcome		
		Dead	Alive	Total
Predicted Outcome	Dead	4	4	8
	Alive	4	12	16
	Total	8	16	24

GROUP IIIb		True Outcome		
		Dead	Alive	Total
Predicted Outcome	Dead	6	2	8
	Alive	4	6	10
	Total	10	8	18

	G III	G IIIa	G IIIb
Sensitivity	55.6%	50%	60%
Specificity	75%	75%	75%
Positive predictive value	62.5 %	50%	75%
Negative predictive value	69.2%	75%	60%
Correct classification rate	66.7%	75%	66.7%

Table 13: All Groups: Discriminatory ability at a decision threshold of 0.5 with 2 concurrent organ failures exceeding 48 hours

		True Outcome		
		Dead	Alive	Total
Predicted Outcome	Dead	49	27	76
	Alive	35	149	184
	Total	84	176	260

Sensitivity	58.3%
Specificity	84.7%
Positive predictive value	64.5%
Negative predictive value	81%
Correct classification rate	76.2%

Table 14 depicts the number and minimal duration of organ failure associated with a 100% mortality rate for each subgroup. The number and minimal duration of organ failure associated with a 100% mortality rate for Groups IIIa and IIIb was the same.

Table 14: Organ Failure associated with a hundred percent fatality rate

	Organ Failure and Duration
Group I	3 organ failures > 72 hours
Group II	3 organ failures > 48 hours
Group III /IIIa/IIIb	3 organ failures = 48 hours

3.4 THE SEQUENTIAL ORGAN FAILURE ASSESSMENT SCORE (SOFA) SCORE

Table 15 shows that the Day 1 SOFA Scores ranged from 0 to 20 (a maximum possible score is 24 points). The mean SOFA Scores were significantly higher in nonsurvivors compared to survivors in all groups ($p<0.0001$). The mean SOFA Scores were similar for survivors and nonsurvivors in each of the subgroups, yet mortality differed. The subsets of Group III exhibited similar mean SOFA scores, for survivors and nonsurvivors ($p > 0.05$).The occurrence of sepsis differed in the subgroups as depicted in Table 17. Groups II and III exhibited a higher sepsis rate compared to Group I ($p< 0.05$). Sepsis was significantly higher in nonsurvivors compared to survivors for all groups ($p<0.05$).Table 18 illustrates that Groups IIIa and IIIb demonstrated a similar incidence of sepsis.

Table 15: Day 1 SOFA Scores

	Group I (n=144)		Group II (n=74)		Group III (n=42)		All Groups (n=260)	
	S	NS	S	NS	S	NS	S	NS
Maximum	17	20	14	19	12	17	12	20
Minimum	0	3	1	5	1	6	0	3
Mean [SD]	6.4** [3.2]	11.8 [3.9]	6.8** [3.3]	11.8 [2.8]	6.7** [2.8]	11.6 [3]	6.5** [3.2]	11.8 [3.3]
Mortality*	23.6		43.2		42.9		32.3	

(S=survivors, NS=nonsurvivors, * = mortality as a percentage)

** = p <0.001 (survivors compared to nonsurvivors)

Table 16: Group III: Day 1 SOFA Scores

	Group III (n=42)		Group IIIa (n=24)		Group IIIb (n=18)	
	S	NS	S	NS	S	NS
Maximum	12	20	12	9	10	20
Minimum	0	3	2	17	0	6
Mean [SD]	6.5** [3.2]	11.8 [3.3]	7** [3]	13 [3]	6** [3.3]	11 [2.6]
Mortality*	42.9		33.3		55.5	

(S=survivors, NS=nonsurvivors, * = mortality as a percentage)

** = p <0.001 (survivors compared to nonsurvivors)

Table 17: Patients with Sepsis

	Group I (n=144)		Group II (n=74)		Group III (n=42)	
	S	NS	S	NS	S	NS
Total	110	34	42	32	24	18
Sepsis	13	8	22	28	11	14
Sepsis (%)	11.8	23.5	52.3	87.5	41.7	77.8
Sepsis (%)	14.6		67.6		59.5	

(S=survivors, NS=nonsurvivors)

Table 18: Group III: Patients with Sepsis

	Group III (n=42)		Group IIIa (n=24)		Group IIIb (n=18)	
	S	NS	S	NS	S	NS
Total	24	18	16	8	8	10
Sepsis	11	14	8	6	3	8
Sepsis (%)	41.7	77.8	50	75	37.5	80
Sepsis (%)	59.5		58.3		61.1	

(S=survivors, NS=nonsurvivors)

The mean values of the various components of the SOFA Score were significantly higher in nonsurvivors compared to survivors (Table 19), in all categories except for coagulation failure.

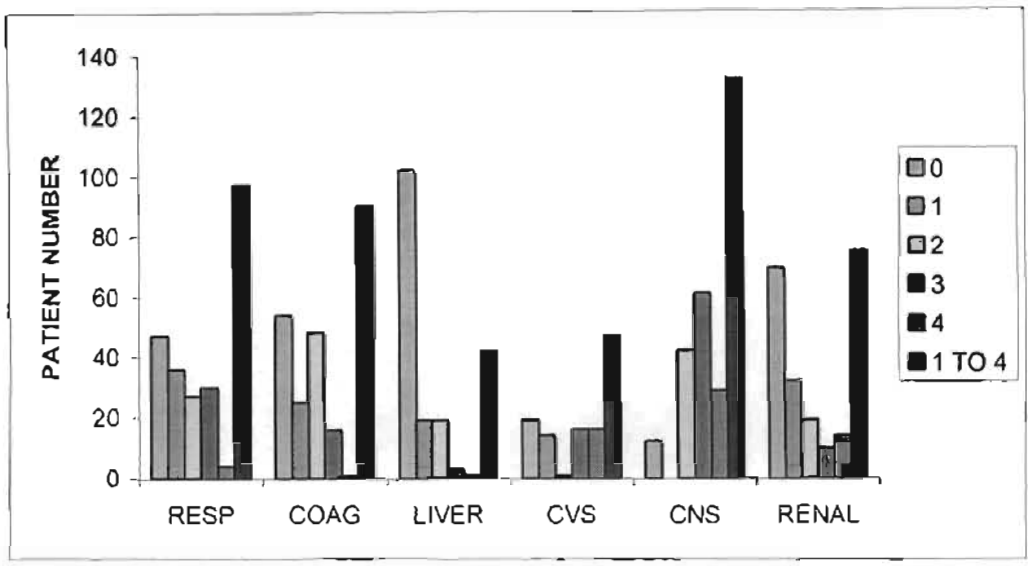
Table 19: Day 1: Mean values of the various components of the SOFA Score

	All Groups (n=260)		
	S	NS	p value
Respiratory	1.1	1.8	<0.001
Coagulation	1.1	1.3	0.06
Liver	0.4	0.7	0.01
Cardiovascular	0.9	2.9	<0.001
Central nervous system	2.4	3.6	<0.001
Renal	0.7	1.5	<0.001

(S=survivors, NS=nonsurvivors)

Figures 17-21 illustrate the contribution of the various organ dysfunctions on Day1. The graphs illustrate the various grades of dysfunction for each organ (ranging from 0 to 4). The bar "1 TO 4" summates the number of patients with that particular type of organ dysfunction. The number of patients are represented on the Y-axis. The graphs illustrate that in each group, there were variable grades of dysfunction for each of the different types of organ failures.

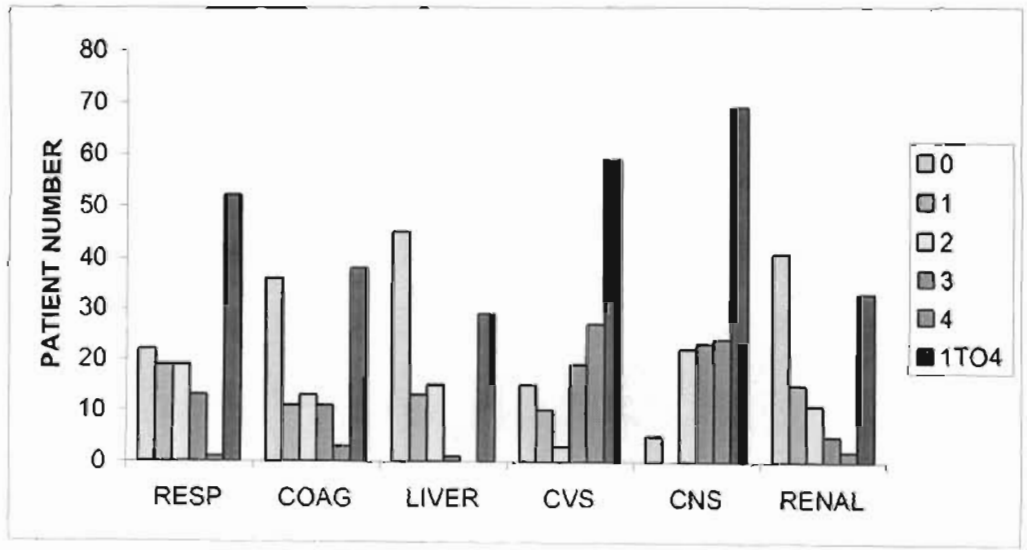
Figure 17: Group I: Components of the SOFA Score on Day 1



(RESP=respiratory, COAG= coagulation, CVS=cardiovascular,

CNS=neurological, HAEM=haematological organ failure)

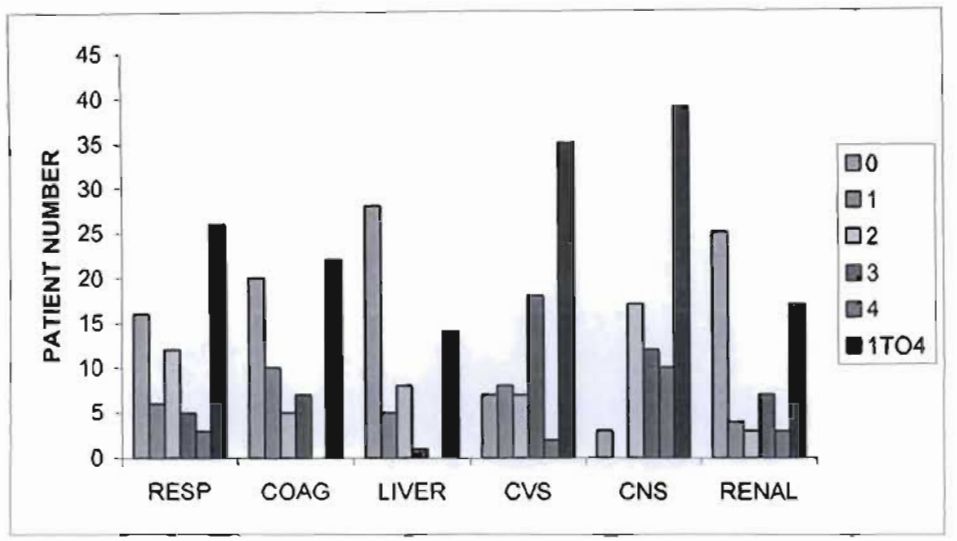
Figure 18: Group II: Components of the SOFA Score on Day 1



(RESP=respiratory, COAG= coagulation, CVS=cardiovascular,

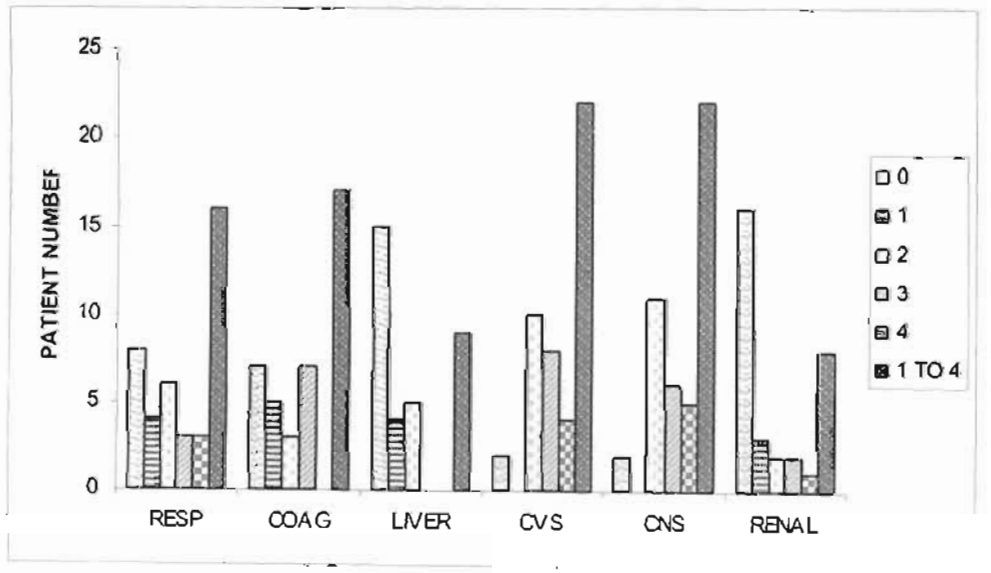
CNS=neurological, HAEM=haematological organ failure)

Figure 19: Group III: Components of the SOFA Score on Day 1



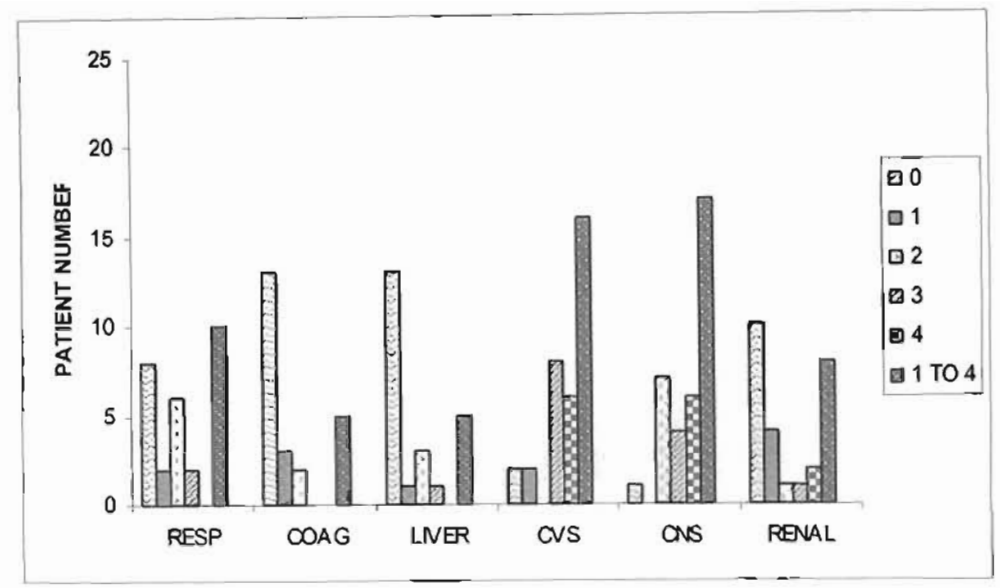
(RESP=respiratory, COAG= coagulation, CVS=cardiovascular, CNS=neurological, HAEM=haematological organ failure)

Figure 20: Group IIIa: Components of the SOFA Score on Day 1



(RESP=respiratory, COAG= coagulation, CVS=cardiovascular, CNS=neurological, HAEM=haematological organ failure)

Figure 21: Group IIIb: Components of the SOFA Score on Day 1



(RESP=respiratory, COAG= coagulation, CVS=cardiovascular, CNS=neurological, HAEM=haematological organ failure)

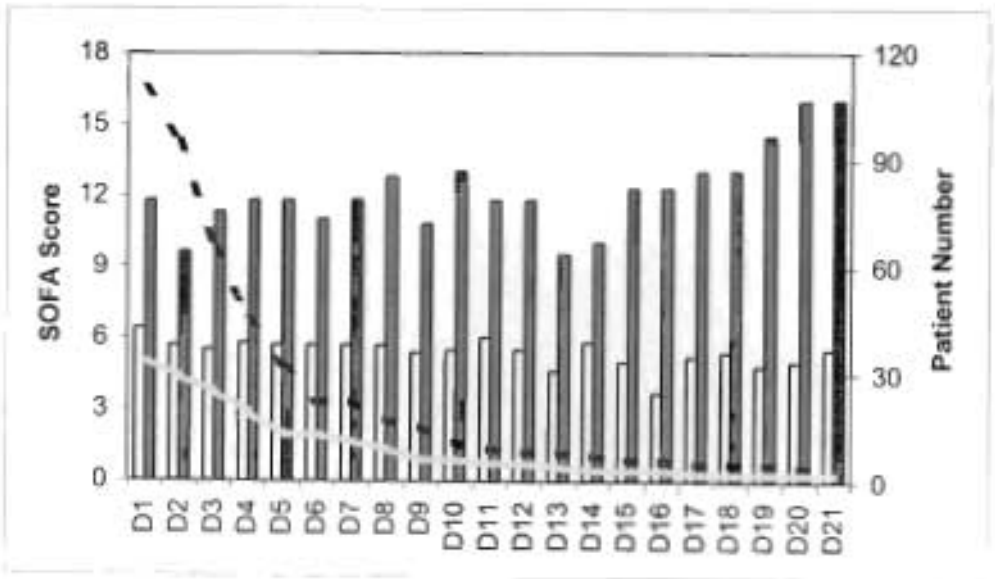
Table 20 illustrates that a minimum Day 1 SOFA Score of 18, 15 and 13 was associated with nonsurvival in Groups I, II and III respectively.

Table 20: Minimum Day 1 SOFA Score associated with a hundred percent fatality rate

	SOFA Score
Group I	18
Group II	15
Group III/IIIa/IIIb	13

Figures 22-27 illustrate the SOFA Scores on a daily basis for the different subgroups as well as the entire group. The scores were consistently higher in nonsurvivors compared to survivors ($p<0.001$) for each of the groups (Table 15). In the subgroups the scores were significantly higher in nonsurvivors compared to survivors for the first five days ($p<0.05$ for day2 to 5). However subsequently this was not true for all the subgroups (as the number of patients in Groups II and III declined considerably after day 5, as illustrated in figures 18 and 19).

Figure 22: Group I: Mean SOFA Scores



Key for Figures 22-27

D=Day

Number of Patients (survivors) - - -

Number of Patients (nonsurvivors) ——

Nonsurvivors

Survivors

Figure 23: Group II: Mean SOFA Scores

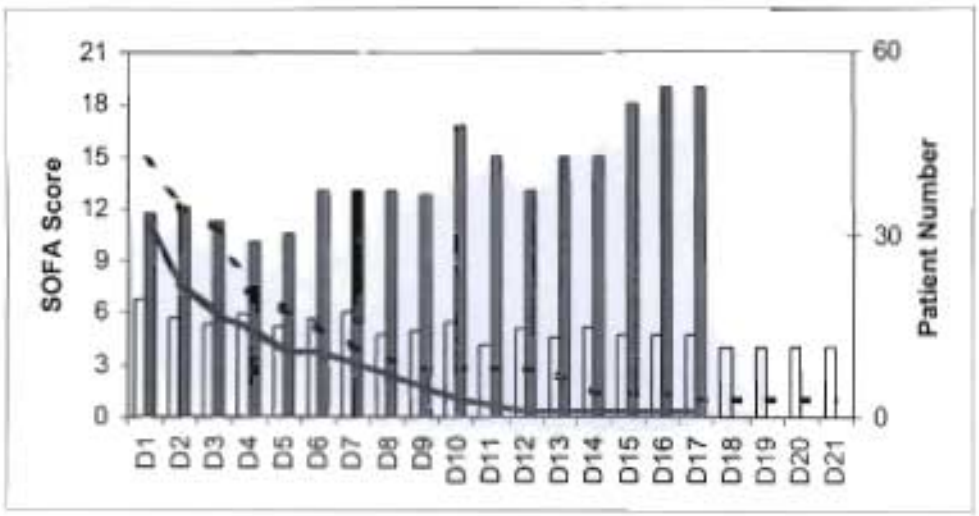


Figure 24: Group III: Mean SOFA Scores

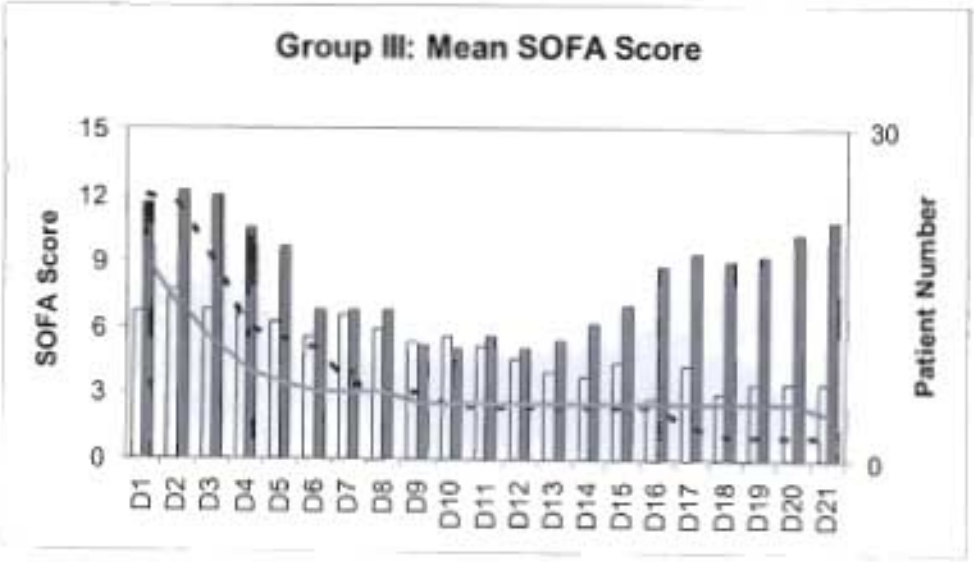


Figure 25: Group IIIa: Mean SOFA Scores

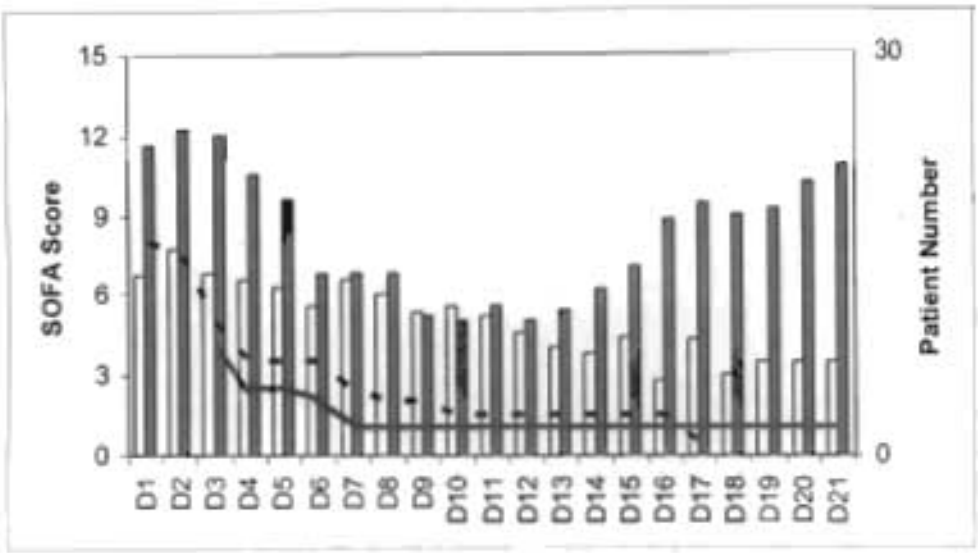


Figure 26: Group IIIb: Mean SOFA Scores

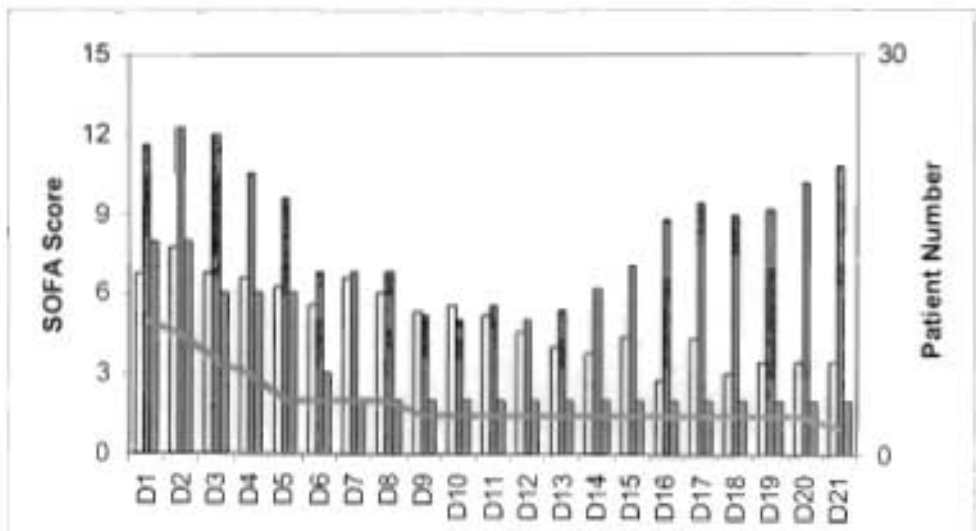
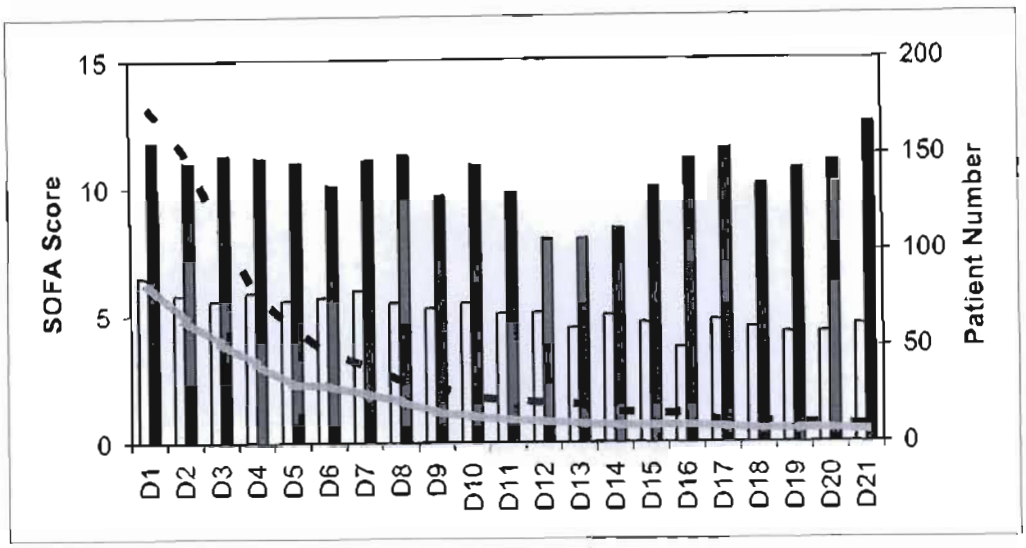


Figure 27: All Groups: Mean SOFA Scores



3. 5. THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

The spectrum of the Systemic Inflammatory Response Syndrome (SIRS) (as described by Muckart and Bhagwanjee[49]) occurred in 245 (94.2%) patients on Day 1. The vast majority (142/245, 58%) of SIRS was diagnosed on the basis of 2 qualifying criteria. Eighty three (33.9%) and 20(8.2%) patients presented with 3 and 4 diagnostic criteria on Day1 respectively. Ninety-six admissions (36.9%of all admissions and 39.2% of SIRS admissions, n=260 and 245 admissions respectively) presented with a focus of infection. Sepsis, severe sepsis or septic shock occurred in 14, 6 % of Group I patients. They were more common in Groups II and III- 67.6% and 59.5% respectively. Tables 21 and 22 provide a breakdown of the spectrum of SIRS in the different groups. Group IIIa and IIIb were too small for meaningful comparisons. In Group I the majority of patients (56/144, 38.9%) presented with SIRS. Sepsis (12/74,

16.2%) and septic shock (37/74, 50%) occurred more commonly in Group II compared to Group I.

Table 21: SIRS on Day 1

.	Group I n=144		Group II n=74		Group III n=42		All n=260		
	NS	S	NS	S	NS	S	NS	S	Mortality (%)
No SIRS	2	8	0	2	1	2	3	12	20
SIRS	1	55	0	8	0	7	1	70	1.4
Severe SIRS	8	23	1	5	0	0	9	28	24.3
Sterile shock	15	11	3	5	3	4	21	20	51.2
Sepsis	1	4	3	9	1	3	5	16	23.8
Severe sepsis	2	6	1	0	1	3	4	9	30.8
Septic shock	5	3	24	13	12	5	41	21	66.1

Table 22: Group III: SIRS on Day 1

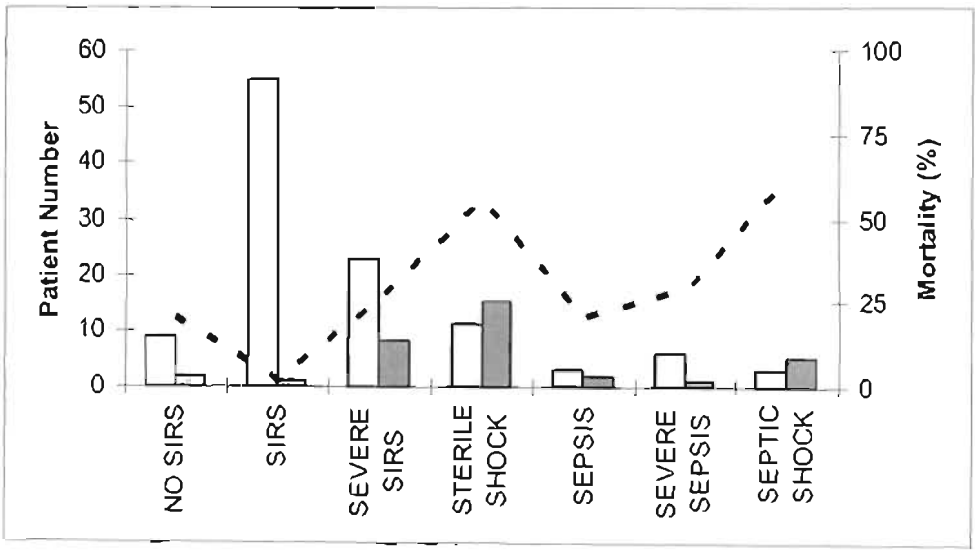
	Group III n=42		Group IIIa n=24		Group IIIb n=18	
	NS	S	NS	S	NS	S
No SIRS	1	2	1	1	0	1
SIRS	0	7	0	5	0	2
Severe SIRS	0	0	0	0	0	0
Sterile shock	3	4	1	2	2	2
Sepsis	1	3	1	1	0	2
Severe sepsis	1	3	0	3	1	0
Septic shock	12	5	5	4	7	1

(S=survivors, NS=nonsurvivors)

Figures 28-33 illustrate for each group and the entire cohort, the spectrum of SIRS response as well as the observed mortality. The figures show in Group I and III, that with an increase in the severity of either SIRS or Sepsis, the associated mortality also increased. Groups II, IIIa and IIIb did not demonstrate a consistent increase in mortality with an increase in the severity of the SIRS response. This may be attributed to the fact that few admissions presented with a severe SIRS response (that is a numerically restricted dataset).In Group I, sterile shock and septic shock were observed to have a

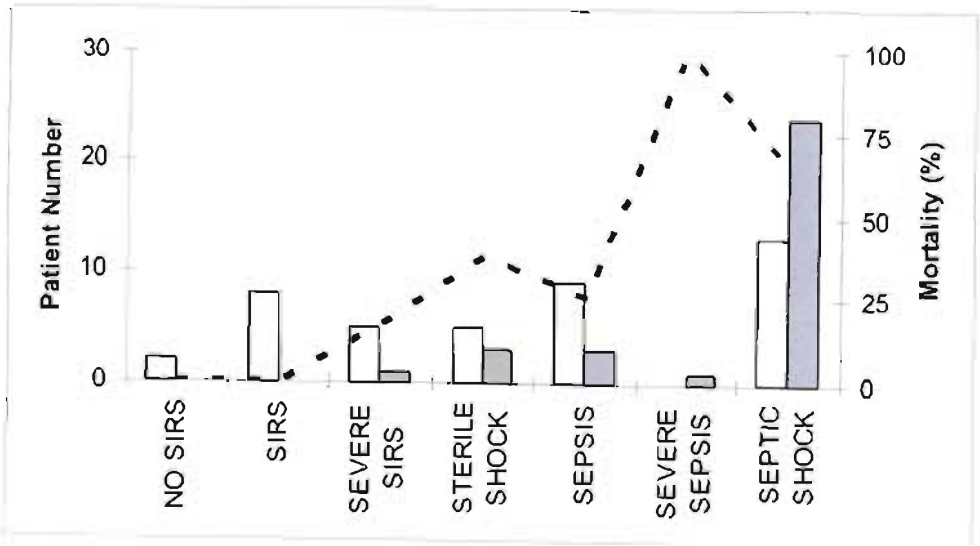
mortality of 55.6%and 62.5% respectively, whereas severe SIRS and severe sepsis exhibited a mortality of 25.8% and 28.6% respectively. The mortality observed for each category of SIRS did not differ significantly when the 3 Groups were compared.

Figure 28 Group I: SIRS subcategories and the associated mortality



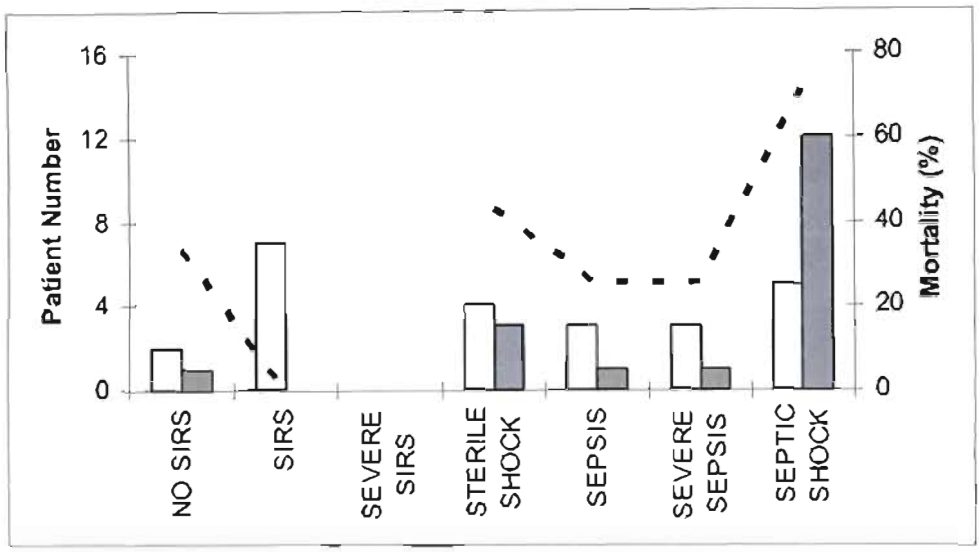
(--- = Mortality)

Figure 29: Group II: SIRS subcategories and the associated mortality



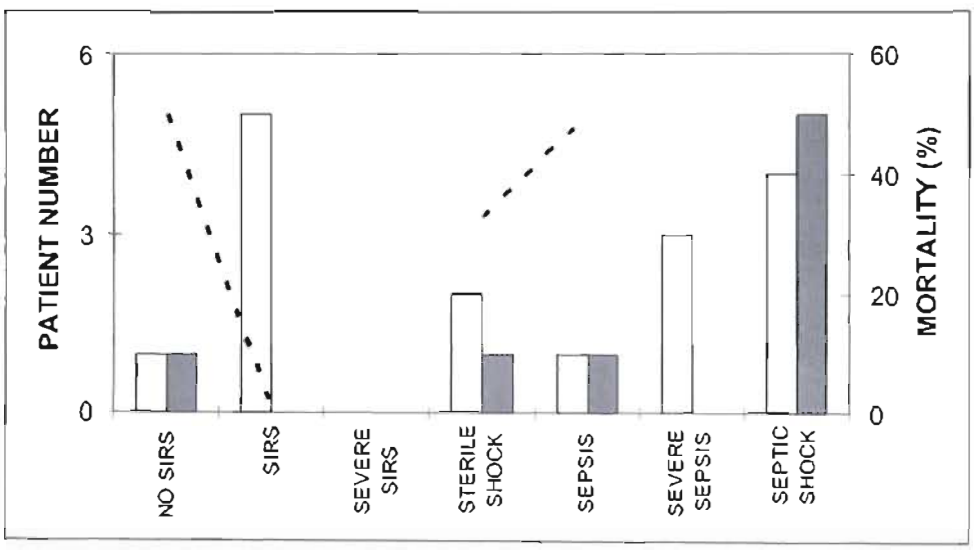
(--- = Mortality)

Figure 30: Group III: SIRS subcategories and the associated mortality



(--- = Mortality)

Figure 31: Group IIIa: SIRS subcategories and the associated mortality



(--- = Mortality)

Figure 32: Group IIIb: SIRS subcategories and the associated mortality

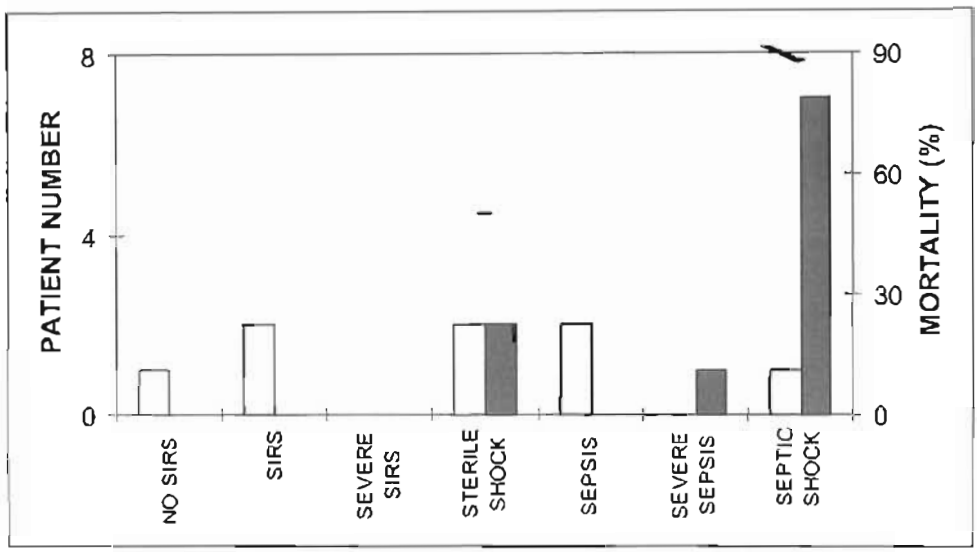
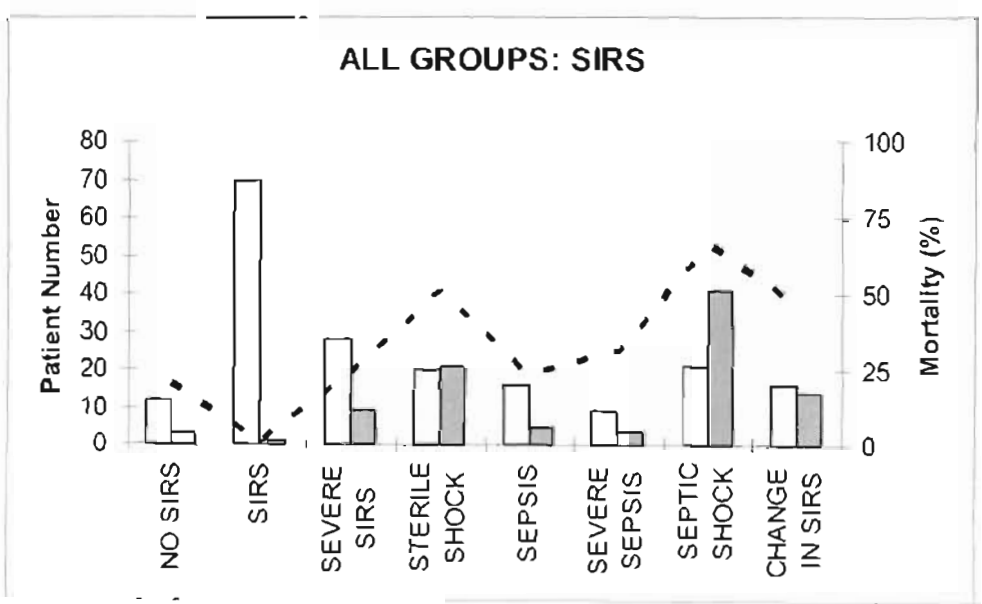


Figure 33: All Groups: SIRS subcategories and the associated mortality



(--- = Mortality)

During the course of ICU stay, 30 patients required reclassification due to the development of a more severe category of SIRS (Table 23). The observed

mortality did not increase significantly with this change. The majority of changes occurred in Groups I and II (Table 24). Table 25 indicates the mortality observed in each category with the initial classification of SIRS and compares this with the mortality observed on reclassification at a later stage during the course of ICU stay. Reclassification from the original diagnosis was associated with a higher mortality (but the severity of SIRS had increased, further the observed mortality was not significantly higher than that expected for the new category). Reclassification to a particular category was not associated with a significant change in mortality as has been previously described.

Table 23: Change in SIRS Classification and the associated mortality

	Change in SIRS	Nonsurvivors	Mortality (%)
Group I (n=144)	18	8	44
Group II (n=74)	8	5	63
Group III (n=42)	4	1	25
Group IIIa (n=24)	1	0	0
Group IIIb (n=18)	3	1	25
ALL (n=260)	30	14	47

Table 24: Change in the severity of SIRS

Change to the following category	Group I		Group II		Group III	
	NS (n=8)	S (n=10)	NS (n=5)	S (n=3)	NS (n=1)	S (n=3)
Severe SIRS		2				
Sterile shock	2	2				1
Sepsis				1		
Severe sepsis		3	2			1
Septic shock	6	3	3	2	1	1

In Group IIIa, one admission demonstrated a change to septic shock with no associated mortality. In Group IIIb, two admissions progressed to severe sepsis (both survived), and one progressed to septic shock and died.

Table 25: Mortality observed with reclassification of the SIRS response

	Mortality on Day 1	Mortality following a change from this category	Mortality following a change to this category
No SIRS	20	40	Not applicable
SIRS	1	-	-
Severe SIRS	24	40	0
Sterile shock	51	Not applicable	40
Sepsis	24	57	0
Severe sepsis	31	67	33
Septic shock	66	Not applicable	63

3.6. THE OBSTETRIC AND GYNAECOLOGY OUTCOME PREDICTION (OGOP) MODEL

The development group comprised 206 cases whilst the validation group contained 54 cases. Table 26 illustrates the breakdown of the entire cohort with respect to each group (as per the statistician's advice).

Table 26: Patient Distribution

	Development Group (n=206)			Validation Group (n=54)		
	S	NS	Total	S	NS	Total
Group I	88	31	119	22	3	25
Group II	29	24	53	13	8	21
Group III	19	15	34	5	3	8
Group IIIa	13	7	20	3	1	4
Group IIIb	6	8	14	2	2	4

(S=survivors, NS=nonsurvivors)

The data from the entire Development Group (comprising Groups I, II and III) was subjected to multiple logistic regression analysis. Age, temperature, mean arterial pressure, respiratory rate, pH and the Glasgow Coma Scale (GCS) were identified as significant independent outcome predictors ($p< 0.05$) as documented in Table 27. A logit was subsequently derived for each subgroup (Table 27). Data from Groups IIIa and IIIb was subjected to multiple logistic regression analysis. The estimation was unstable and the biostatistician was unable to fit the data into a model.

Table 27: Predictor variables and logit for each subgroup

<table>
<tr><td>All
GROUPS</td><td><u>Predictor Variables</u>
<table><tr><th>Variable</th><th>P value</th></tr><tr><td>Age</td><td>0.04</td></tr><tr><td>Temperature</td><td>0.003</td></tr><tr><td>MAP</td><td>0.005</td></tr><tr><td>Respiratory rate</td><td>0.001</td></tr><tr><td>pH</td><td>0.04</td></tr><tr><td>GCS</td><td>0.000</td></tr></table></td></tr>
<tr><td>Group I</td><td><u>Logit: R/1-R</u>
17.6626 + 0.0502 (Age) +0.0824 (T^0) - 0.0153 (MAP) + 0.1147 (Resp) -2.7096 (pH) - 0.5949(GCS)</td></tr>
<tr><td>Group II</td><td>93.419 + 0.5015 (Age) + 0.262 (T^0) - 0.2747 (MAP) + 0.4268 (Resp) -13.409 (pH) -1.324 (GCS)</td></tr>
<tr><td>Group III</td><td>3.5352 - 0.0264 (Age) +0.9132 (T^0) + 0.0088 (MAP) + 0.0196 (Resp) - 3.7096 (pH) -1.3205 (GCS)</td></tr>
</table>

(T^o = temperature, MAP = mean arterial pressure, Resp = respiratory rate, GCS = Glasgow Coma Scale)

The ROC curves for each group (in the Development phase) are illustrated in Figures 34-36. The area under the ROC curve at cut off thresholds (for R) of

0.21, 0.31 and 0.32 for Groups I, II and III respectively were 0.91, 0.99 and 0.94.

Figure 34: The OGOP Model: ROC curve for Group I (n=119)

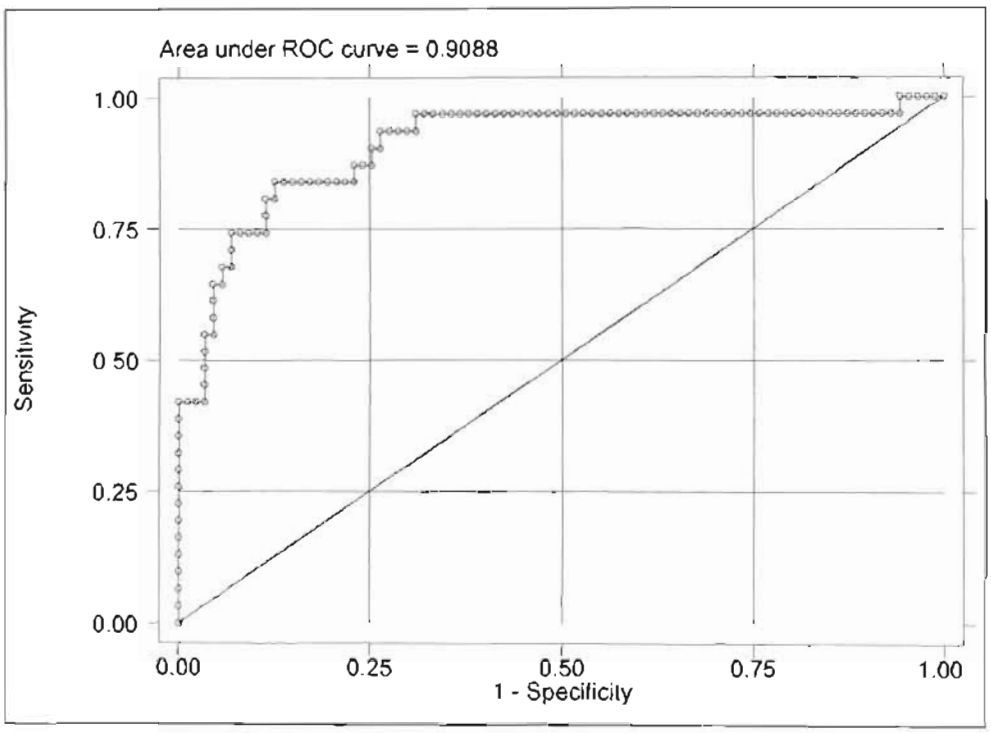


Figure 35: The OGOP Model: ROC curve for Group II (n=54)

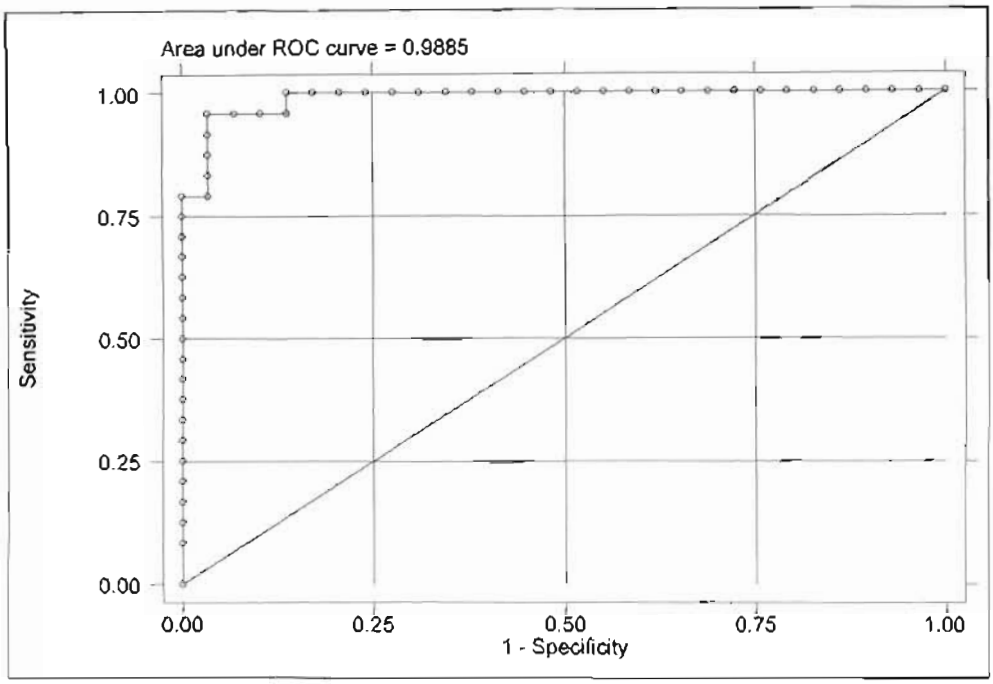


Figure 36: The OGOP Model: ROC curve for Group III (n=34)

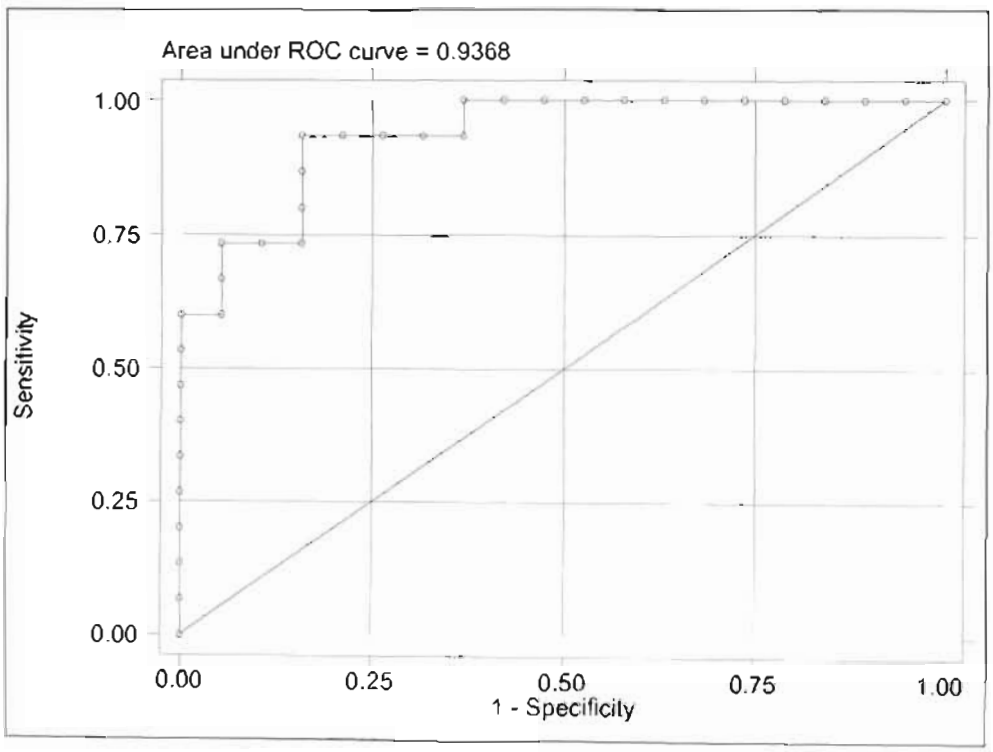


Table 28 depicts the discriminatory ability of the OGOP Model in the validation cohort. A sensitivity of 93%, specificity of 83% and correct classification rate of 85% was observed for the entire validation cohort (n=54). Groups I and II yielded a correct classification rate of 92% and 90% respectively. Group III demonstrated a sensitivity of 100%, a specificity of 60% and a correct classification rate of 75%. Group III had a numerically restricted data set, n=8). The difference between the development and validation group was not significant.

Table 28: Discriminatory ability of the OGOP Model in the Development and the Validation Group

	Development Group (n=206)			Validation Group (n-54)			
	GI (n=119)	GII (n=53)	GIII (n=34)	GI (n=25)	GII (n=21)	GIII (n=8)	GI+GII+GIII (n=54)
Sensitivity	84	95	93	100	88	100	93
Specificity	81	93	84	91	92	60	83
PPV	62	92	82	60	88	60	65
NPV	93	96	94	100	92	100	97
CCR	82	94	88	92	90	75	85

(PPV= positive predictive value, NPV= negative predictive value, CCR= correct classification rate)

3.7. THE OGOP MODEL COMPARED TO THE APACHE II SYSTEM

Table 29 indicates that the OGOP Model yielded a better sensitivity and specificity compared to the APACHE II System in each of the subgroups. Figures 37 and 38 illustrate the predicted and observed mortality graphically for the OGOP Model and APACHE II respectively. APACHE II tended to over predict mortality in most of the deciles of risk. Although the SMR illustrates that the APACHE II system over predicted mortality (Table 30), it is evident from Figure 37 that the system performed variably at different deciles of mortality risk. It clearly over predicted mortality at the extremes (at low and high deciles of predicted mortality risk). The observed mortality correlated with mortality predicted by the OGOP model more often than it did with the APACHEII System. The OGOP Model exhibited a superior coefficient of linear correlation (0.942 (r^2= 0.89) compared to the APACHE II System (0.862 (r^2=0.74). Table 30 demonstrates that the standardised mortality rates were better for the OGOP Model than the APACHE II system. Table 31 compares APACHE II and the OGOP Model in the validation group (n=42). The OGOP Model demonstrated a correct classification rate of 92% and 90% in Groups I and II respectively, compared to the 76% and 71% correct classification rate obtained with the APACHE II system. This is confirmed by the area under the ROC curves for each group. Group III was very small (n=8).

Table 29: The OGOP Model compared to the APACHE II System for the entire cohort (n=260)

	GROUP I (n=144)		GROUP II (n=74)		GROUP III (n=42)	
	APACHE II	OGOP Model	APACHE II	OGOP Model	APACHE II	OGOP Model
Sensitivity	64.7	85	75	94	77.8	94
Specificity	88.2	83	78.6	93	91.6	79
PPV	66.7	62	72.7	91	87.5	77
NPV	87.4	95	80.5	95	84.6	95
CCR	87	84	77	93	85	86

(PPV= positive predictive value, NPV= negative predictive value, CCR= correct classification rate)

Figure 37: Percentage predicted mortality versus percentage observed mortality for the OGOP Model (n=260)

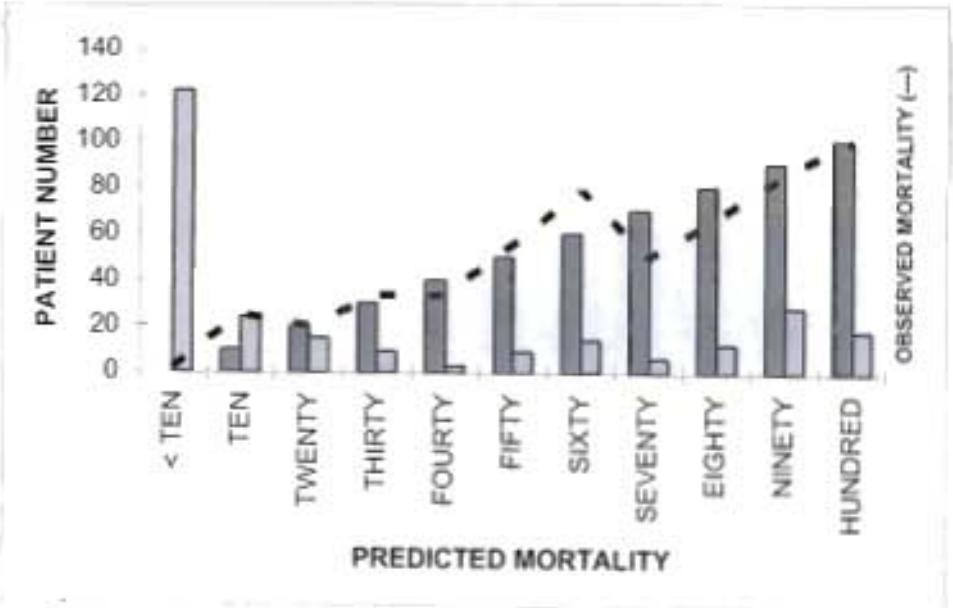


Figure 38: Percentage predicted mortality versus percentage observed mortality for the APACHE II System (n=260)

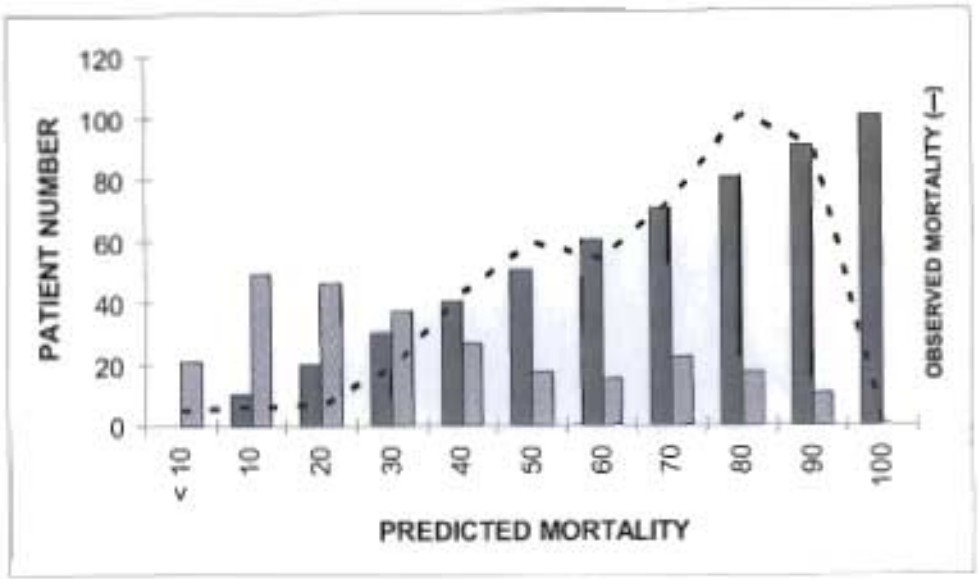


Table 30: The Standardised Mortality Rate (SMR): The OGOP Model and the APACHE II System

	Group I (n=144)	Group I (n=74)	Group III (n=42)
Observed Mortality	23.3	43.2	42.9
Predicted Mortality (OGOP Model)	25.7 [31.2]	44.4[45.8]	45.3 [40.3]
SMR (OGOP Model)	0.91	0.97	0.95
Predicted Mortality (APACHE II)	32.2 [22.5]	49.5 [25.9]	48.7 [26.5]
SMR (APACHE II)	0.72	0.87	0.88

[ ]= standard deviation

Table 31: The OGOP Model compared to the APACHE II System in the validation group

	GROUP I (n=25)		GROUP II (n=21)		GROUP III (n=8)	
	APACHE II	OGOP Model	APACHE II	OGOP Model	APACHE II	OGOP Model
Sensitivity	67	100	75	88	100	100
Specificity	77	91	69	92	100	60
PPV	33	60	60	88	100	60
NPV	89	100	82	92	100	100
CCR	76	92	71	90	100	75

3.8 THE SOFA SCORE, ORGAN FAILURE SCORE AND THE OGOP MODEL IN RELATION TO THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME ON DAY ONE

Tables 32 to 34 compare the SOFA Score, Organ Failure Score and the OGOP Model in relation to the different categories of the SIRS response for Groups I, II and III respectively. It is evident that as the severity of SIRS or Sepsis increased the above scores also worsened in each of the categories. The small number of cases in each subcategory of SIRS precluded meaningful statistical analysis. However sterile shock and septic shock (which were associated with a higher mortality) appeared to demonstrate a close correlation with the OGOP Model and an increase in the SOFA Score.

Groups IIIa and IIIb are not included (as no OGOP Model was developed for these subsets).

Table 32: Group I: SOFA Score, Organ Failure Score and The OGOP Model in relation to the Systemic Inflammatory Response Syndrome

	S/NS	n	Observed Mortality (%)	SOFA SCORE	OFS	%Mortality Risk OGOP
No SIRS	S	8	20	6 [12]	0.4 [1]	13 [17]
	NS	2				
SIRS	S	55	1.8	5 [2]	0	7 [11]
	NS	1				
Severe SIRS	S	23	26	9 [2]	1 [1]	30 [29]
	NS	8				
Sterile Shock	S	11	58	13 [3]	3 [1]	63 [34]
	NS	15				
Sepsis	S	4	20	5 [2]	0	6 [6]
	NS	1				
Severe sepsis	S	6	25	7 [3]	1 [1]	17 [8]
	NS	2				
Septic Shock	S	3	63	10 [3]	2 [1]	49 [32]
	NS	5				

(S= survivors, NS= nonsurvivors, OFS= Organ Failure Score,

[ ] =standard deviation)

Table 33: Group II: SOFA Score, Organ Failure Score and The OGOP Model in relation to the Systemic Inflammatory Response Syndrome

	S/NS	n	Observed Mortality (%)	SOFA SCORE	OFS	% Mortality Risk OGOP
No SIRS	S	2	0	8 [1]	1 [0]	5 [7]
	NS	0				
SIRS	S	8	0	5 [2]	0.3 [0.5]	15 [31]
	NS	0				
Severe SIRS	S	5	17	6 [3]	1 [1]	33 [51]
	NS	1				
Sterile Shock	S	5	38	9 [3]	2 [1]	33 [45]
	NS	3				
Sepsis	S	9	25	5 [2]	0.1 [0.2]	13 [20]
	NS	3				
Severe sepsis	S	0	100	6	1	100
	NS	1				
Septic Shock	S	13	73	12 [3]	2 [1]	67 [43]
	NS	24				

(S= survivors, NS= nonsurvivors, OFS= Organ Failure Score,

[ ] =standard deviation)

Table 34: Group III: SOFA Score, Organ Failure Score and The OGOP Model in relation to the Systemic Inflammatory Response Syndrome

	S/NS	n	Observed Mortality (%)	SOFA SCORE	OFS	%Mortality Risk OGOP
No SIRS	S	2	33	8 [2]	1 [0]	44 [40]
	NS	1				
SIRS	S	7	0	4 [2]	0.1 [0.3]	5 [10]
	NS	0				
Severe SIRS	S	0				
	NS	0				
Sterile Shock	S	4	43	10 [4]	2 [2]	52 [48]
	NS	3				
Sepsis	S	3	25	7 [7]	1 [2]	47 [55]
	NS	1				
Severe sepsis	S	3	25	8 [1]	1 [1]	31 [16]
	NS	1				
Septic Shock	S	5	71	11 [2]	2 [1]	63 [37]
	NS	12				

(S= survivors, NS= nonsurvivors, OFS= Organ Failure Score,

[ ] =standard deviation)

CHAPTER FOUR: DISCUSSION

4.1 GENERAL

Obstetric critical care constitutes a subspecialty of intensive care that is very much in the early phase of its evolution. At a casual glance there appears to be a substantial amount of data pertaining to this fascinating field of medicine[2-33,50-54,86,88,90,91]. The reality is that most of the data is retrospective and numerically restricted, which often precludes meaningful conclusions. The available literature focuses almost exclusively on obstetric patients[3-33,50-54,86]. To date there are very few reports which include critically ill gynaecology patients[2,4,32,87,90]. With respect to obstetric patients, data pertaining to ICU utilisation, pathology and mortality is extremely variable, depending largely on the available resources. In general, most developed regions report lower ICU utilisation rates and mortality is a rare phenomenon compared to reports from developing countries. The lack of well established guidelines for critically ill obstetric and gynaecology patients constitutes a further confounding variable as high dependency candidates may be admitted to ICU[3], or alternatively seriously ill patients my be denied ICU care. This confounding variable can significantly influence outcome results. Further the data emanating from the recently developed "Obstetric ICUs" is difficult to compare to data emerging from General ICUs as "Obstetric ICUs" may function differently. For example patients requiring prolonged ventilation are often transferred out of Obstetric ICUs[11,12]. Therefore one needs to be cognisant of the aforementioned factors when critically appraising the available literature.

There is general agreement that critically ill obstetric patients constitute an altogether unique population by virtue of the various anatomical, physiological and biochemical changes that occur in the gravid and puerperal state[11,17,28,92]. Further, there is a suggestion that the hypertensive subgroup of obstetric patients may exhibit unique characteristics[3,7,50]. Zakalik et al (2005) observed in a cohort of 242 patients that patients with hypertensive disorders of pregnancy demonstrated significant differences when compared with the rest of the obstetric population[7]. These differences pertained to age, number of former pregnancies and duration of ICU stay.

The results of this study confirm that obstetric and gynaecology admissions constitute a significant proportion (n=260, 18.5%) of the admissions at the Surgical ICU at King Edward VIII Hospital. The obstetric ICU utilisation rate of 13.9/1000 deliveries is high. Literature reports from developed countries range from 0.9 to 9/1000 deliveries[13,3,7,19,20,93-94,11] and poorly resourced regions quote rates ranging from 1.9 to 13.4/1000 deliveries[10,12,26]. The high utilisation rate in this series is probably a reflection of the tertiary referral and teaching status of the hospital.

The low number of antenatal admissions (5.5% of the obstetric admissions), is not a surprise. The antenatal proportion of ICU admissions is generally documented to be low worldwide and ranges from 13-42%[22,28,3]. However it was much lower in this series than that, generally reported in the literature. This is probably attributed to the following:

- Hypertensive disorders of pregnancy generally account for the most number of obstetric admissions, and this disease state is reversed by delivery of the fetoplacental unit. Therefore the patients are usually admitted post delivery for intensive care management.
- Obstetricians are often uncomfortable to admit a patient with a viable pregnancy to an ICU, unless it is absolutely necessary. There is often the fear that fetal surveillance maybe compromised.
- Alternatively the fear is that the patient may require urgent delivery and may not have immediate access to theatre facilities (unlike maternity suites, with adjoining dedicated theatres).

The associated mortality in this subset was high (50%). However this is difficult to comment upon, as the number of such admissions were small.

The point that 92% of the cases required mechanical ventilation on admission suggests that the cohort was critically ill. The vast majority of available reports on critically ill obstetric and gynaecology patients actually quote a less than 50% mechanical ventilation rate suggesting a variable severity of illness in such populations[3,13,17,22,28].

The disease profile clearly shows that hypertensive disorders of pregnancy, infections and haemorrhage represented the common primary diagnoses in the obstetric cohort (Groups I and II). Most intensive care units report hypertension and haemorrhage as their common admission diagnosis for obstetric admissions[3,16,-18,21,23,28,54,91,95] . The first striking observation is that hypertensive disorders of pregnancy constitute 66% of the obstetric

admissions, with 68% being eclamptic. This is not surprising as hypertensive disorders of pregnancy constitute a common disease and an important cause of mortality in developing countries[96,97]. There has been a change in profile of the hypertensive admissions in ICU over the last few years. A previous 1 year study by Platteau et al (1997), in the same ICU showed that hypertensive disorders of pregnancy constituted 66% (53/n=80) of the obstetric admissions. However the majority of the hypertensives were eclamptic (96%, 53/55)[4]. In the current series the increase in the proportion of preclampsia suggests that perhaps patients are presenting earlier (prior to the development of eclampsia). This may be the result of the introduction of a national policy of free public maternal care services. Nonetheless the absolute figure for hypertensive disorders of pregnancy remains high. Appropriate antenatal care is important in the prevention of hypertensive disorders of pregnancy[98,99]. The fact that only 50% of the patients received some form of antenatal care suggests either a lack of population education or service inaccessibility. In developed countries where antenatal care is accessible and appropriately utilised the hypertensive disease profile is different compared to developing countries[11,19]. With adequate antenatal care provision, the vast majority of patients present with preeclampsia rather than eclampsia.

In South Africa, Johanson et al (1995) in their series of 258 patients, report that 60% were hypertensive (with 36% being eclamptic, 55/153)[12]. Mabie and Sibai (1990) in their three year series of 200 patients, report that 46% of patients had hypertensive disorders of pregnancy however only 10% were eclamptic[11].

The second observation in this series is that the proportion of admissions in Group II with infections was high. Puerperal sepsis (73%) and pneumonia (17%) accounted for the majority of these infections. The current figure of 22% is more than double that reported by Platteau et al (1997) from the same unit[4]. In addition the associated mortality of 56% is extremely high. The series of Zakalik et al (2005) from Argentina, is the only series that describes a high rate of sepsis (30.5%, n=242) in an obstetric cohort[7]. Although the incidence of HIV infection in the cohort is unknown, the prevalence in the referring antenatal population was known to be at least 36% (personal communication: Prof J Moodley, Head Obstetrics and Gynaecology, King Edward VIII Hospital). The reality is that South Africans are living in the HIV/AIDS epidemic era. The antenatal HIV incidence in Durban at the time of the study is likely that this has impacted on the ICU patient profile- just as it has impacted on maternal mortality in South Africa[100]. The recent triennial report by the National Committee for the Confidential Enquiries into Maternal Deaths in South Africa clearly shows that pregnancy related sepsis and non pregnancy related infections (mainly AIDS) are among the top 5 contributors to maternal mortality[99]. The impact of HIV/AIDS on maternal mortality has also been documented in a recent study from Johannesburg[101].

In the current series, Group III accounted for 16.2% of the total obstetric and gynaecology admissions. Early pregnancy (Group IIIa) and pure gynaecology (Group IIIb) accounted for 9.2% and 7% of the total obstetric and Gynaecology admissions. In Group IIIa (n=24), abortions and ectopic pregnancies accounted for 58% and 25% of the admissions, whilst pelvic infections (44%)

and tumours (44%) accounted for most of the pure gynaecology admissions (n=18). There is a worldwide decline in the number of gynaecology patients admitted to ICU. All available studies include abnormal pregnancy states in their gynaecology datasets. Platteau et al (1997) previously reported 42 cases (34.4%, n=122) in a one year period in the same unit[4]. The number of gynaecology admissions (pregnant and pure gynaecology) appears to have halved. Taylor and Richards (2000) from Johannesburg cited 29 gynaecology cases over a 10 year period[32]. They do not however, document the total number of hospital gynaecology admissions during this period. There are only a few other studies that focus on gynaecology ICU admissions [2,87,90]. Heinonen et al (2002) from Finland describe 23 cases over a period of approximately 8 years and Al Jabari et al (2001) mention 18 cases over a 3 year period (18% of obstetrics and gynaecology ICU population)[2,90]. Abortions comprised the commonest indication for gynaecological ICU admission in this study; however, the proportion of abortions has declined since the audit by Platteau et al (1997) from 52% to the current figure of 33%[4]. Legislative changes in 1996 liberalised the termination of pregnancy in South Africa[102]. This may explain the decline in the proportion of abortions. Taylor and Richards (2000) demonstrated abortions to represent their commonest gynaecological indication for admission in their 10 year series (26 cases among 80 obstetrics and gynaecology patients)[32]. However, these figures allude to a period when termination of pregnancy was illegal in South Africa. In the Finnish study the majority of patients had a gynaecological malignancy[2]. The lack of cases arising from abortion is not surprising as in most rich countries family planning facilities are easily available and accessible. The fact that 71% of the abortions were septic in the current

series is extremely concerning. This may be attributed to various reasons including a lack of patient knowledge (regarding the change of law), unavailability of termination of pregnancy (TOP) services, inaccessibility of TOP services or an insufficient supply of TOP services. In addition, HIV infection may have also played a contributory role. Although the HIV status of the majority of the admissions was unknown, it is well known that the seroprevalence in the antenatal population at that time was 36% (personal communication, Professor J Moodley). Septic abortion admissions are potentially preventable and therefore strategies to effect a reduction need to be explored and implemented.

Patients in Group I, II and IIIa were significantly younger than patients from Group IIIb (mean age 42, SD 14 years). This is not unexpected as many pure gynaecology disease states manifest in the post reproductive period. The significantly lower gestational age in Group I compared to Group II probably relates to the fact that the majority of group II admissions presented with puerperal sepsis (post delivery). The mean gestational age of Group IIIb admissions is quite low (11± 1.8 weeks). However the majority of these admissions were ectopic pregnancies and septic abortions (probably induced), both of which usually present early in pregnancy. Gynaecology admissions (Group IIIb) demonstrated a significantly longer ICU and hospital stay compared to the obstetric and early pregnancy admissions. This may be attributed to the older age and higher incidence of sepsis in the gynaecology admissions.

The gynaecology subset (Group IIIb) exhibited characteristics different from the early pregnancy admissions (Group IIIa), in that they were older, were ventilated for a longer period, had a longer duration of ICU as well as hospital stay and they had a much higher mortality. The younger and possibly healthier state of Group IIIa admissions might explain the aforementioned differences with respect to duration of ICU stay and associated mortality. The need for ventilation in the majority of patients, the duration of ICU and hospital stay, the duration of ventilation and the need for vast amounts of blood and blood products illustrates the severity of illness in this cohort.

The ICU stay in Groups I and II is similar to that reported by Platteau et al (1997), but much higher in Group III in the current series (8.3 versus 5.2 days)[4]. Although Platteau et al (1997) did not categorise the severity of illness of their patients it may well be that the admissions in the current cohort were sicker, as is reflected by the higher mortality compared to the 1997 data. Additional factors that also warrant consideration are changes in ICU management practices (with advances in medical science). However these factors cannot be commented upon as they were not documented in either or both studies. It would be inappropriate to compare ICU and hospital duration of stay with reports from developed regions as most series report low mechanical ventilation rates and variable severity of illnesses[6,16,20,25,31]. The disparate populations preclude meaningful comparisons. For example Hazelgrove et al (2001) found that only just over half of their patients had really required ICU admission[3]. On the other hand Mabie and Sibai (1990) and Johanson et al (1995) managed their patients in the obstetric ICU for a predefined period[11,12].

Patients requiring prolonged ICU necessitated transfer to more specialised units. It is quite clear that there exists a wide variation with respect to patient population profiles. It is therefore impossible to make scientifically sound comparisons.

Interestingly obstetric survivors (Group I and II) had a longer ICU stay compared to nonsurvivors. This is not surprising as the survivors were discharged back to the antenatal wards. Hospital stay was longer but not significantly different between survivors and nonsurvivors for the gynaecology admissions. Group III survivors demonstrated a shorter ICU stay compared to nonsurvivors. Thus it is evident that although obstetrics and gynaecology patients belong to a single discipline, their behaviour is distinctly different from each other, validating the hypothesis that risk stratification in obstetrics and gynaecology patients is different.

Whilst gestational age, parity and duration of ICU stay were not significantly different between survivors and nonsurvivors, the age (Groups I and II) and duration of hospital stay (all groups) did demonstrate a significant difference.

The obstetric mortality of 30.2% is high, although a slightly higher rate (38%) has been reported by Taylor and Richards (2000) from Johannesburg, South Africa[32]. The mortality in the current setting has increased compared to the 21.3% reported by Platteau (17 of 80 patients) et al in 1997[4]. This may be attributed to the increase in sepsis in the current series. Group I and II exhibited a variable mortality (23.6% and 43.2%) reaffirming the belief that

patients with hypertensive disorders of pregnancy behave differently compared to other obstetric patients. The lower mortality in Group I compared to Group II may be attributed to the rapid resolution of the disease following the delivery of the feto-placental unit in the hypertensive admissions. Dao et al (2003) from Burkina Fasso report an exceptionally high mortality of 60 % in a cohort of 82 patients over a two and a half year period[26]. Developing countries generally report high maternal mortality rates [103]. Developed countries on the other hand report mortality rates ranging from 0 to 36%, but are below 10% in most series[17,3,5,6,11,14,18,20,21,28,29,53,93,52].

The overall mortality in Group III was high at 42.9%. Interestingly Group IIIa and IIIb demonstrated mortalities of 33.3% and 55.5% respectively. The lower mortality in the former group suggests that these patients behave differently from the pure gynaecology group. Further the mortality in Group IIIb is different from that observed in Group II, suggesting that early pregnancies are perhaps an altogether distinctively unique group.

Platteau et al (1997) previously reported a mortality of 26.2% in their total gynaecology cohort[4]. However the overall ICU mortality in that series was 23% compared to 37.8% in the current series. Platteau et al (1997) documented an admission sepsis rate of 27.9 %(34 of 122 patients), whilst the day one sepsis rate in the current series was 36.9% (96 of 260 admissions). This may partially explain be due to an increase in the mortality rate in the unit. Taylor and Richards (2000) reported a 39% mortality rate in their group of patients presenting with abortions[32]. Heinonen et al (2002) and Al Jaberi (2001) report a

0% mortality among gynaecology patients[2,90]. Heinonen et al do however state that 26% of the patients (n=23) died within 6 months of ICU discharge. In the context of gynaecology patients, documentation of day 28 mortality may be of assistance, particularly in units with low or no ICU deaths.

4.2 THE APACHE II SYSTEM

The mean APACHE II score of 21 ±8 (range 7- 43) for the entire cohort was high. This is not surprising considering that more than 90% of the admissions required ventilatory support on ICU admission. In this cohort it is possible that the patients, in addition, presented late for health care and thus manifested with severe physiological derangement. The APACHE II system has demonstrated its limitations in this study. However the high scores documented, suggest severe physiological derangement on admission. This may explain the high mortality observed in the current series. Taylor and Richards (2000) documented a median APACHE II score of 14 (n=61) and a highest score of 32[32]. Karnad et al (2004) and Munnur et al (2005) from India observed in 2 separate retrospective series over 5 and 10 years a median APACHE II score of 16 (in both series) and an observed mortality of 21.6% (n=453) and 25% (n=754) respectively[9,25]. The majority of reports from developed regions quote mean or median APACHE II scores of below 10 [6,10,11,20,23,30,] although mean or median scores of up to 14 have been documented[9,28]. The majority of studies have found that the APACHE II system over predicts mortality in obstetric patients[3,7,8,17,20,27]. Taylor and Richards (2000) and Koch (1988) have observed it to under predict mortality[32,52]. Interestingly Karnad et al (2004) of India found that the predicted

mortality rate of 26.3% in obstetric patients with medical disorders closely matched the observed mortality rate of 28.6%, however in patients with purely obstetric disorders, the APACHE II system over predicted mortality[25]. El-Sohl et al (1996) from Buffalo, New York also found the APACHE II system to appropriately predict outcome in a cohort of 93 obstetric patients[5]. Eighty percent of El- Solh's cohort was adrnitted with medical problems. These findings illustrate that APACHE II does not perform uniformly in all obstetric patients.

There is little data pertaining to APACHE II in patients with hypertensive disorders of pregnancy. Bhagwanjee et al (2000) from the same unit in Durban demonstrated in a cohort of 105 eclamptic patients that, apart from the Glasgow Coma Scale score, the other variables in the APACHE II score were of no value for outcome prediction[50].

There are only two studies that have evaluated the APACHE II scores in the general gynaecology population[2,32]. Both these series included early pregnancy states, had small numbers of patients (n=23 for each report) and did not find the APACHE II score to be an appropriate outcome predictor[2,32].

The observation of the APACHE II score being significantly higher in nonsurvivors (in all groups including the gynaecology subset) compared to survivors has been reported previously for the general obstetric and gynaecology poplation[32,50]. A striking observation was that the APACHE II scores for all 3 groups (survivors and non survivors) were similar, yet the

observed mortality ranged from 23.6% to 43.2%. The APACHE II system performed most poorly in Group I (AUC=0.81). It performed better in Group III (AUC=0.9375) compared to Group II (AUC = 0.9107). This clearly illustrates the point that obstetric and gynaecology patients need to be divided into physiologically distinct subsets. It is unfortunate that ROC curves could not be constructed for the subsets of Group III.

The low mortality in Group I is not surprising. Previous reports from the same unit support this[4,50]. The APACHE II system over predicted mortality in the three main groups. However in group III, it over predicted mortality for Group IIIa (SMR=0.72) and under predicted (SMR=1.1) mortality for Group IIIb. This suggests that these two subsets behave differently. However a larger sample size is required to confirm this opinion.

Mortality over prediction in the obstetric admissions is understandable, as the physiological changes of pregnancy may falsely elevate the APACHE II score. In addition it is well documented that many obstetric complications resolve rapidly following the delivery of the fetoplacental tissue, with the physiological return to a pre-pregnancy state lagging behind.

The APACHE II system was not designed with the obstetrics and gynaecology patient in mind[35]. In fact the original database did not have a specific subgroup for obstetrics and gynaecology patients. Obstetrics and gynaecology subjects (if there were any) were probably included in other disease/injury categories. However the APACHE II system remains the most commonly evaluated outcome prediction tool in reports pertaining to critically

ill obstetric and gynaecology patients[2-4,7-9,12,17,120,25,27,28,32,50,52-54]. An important point to note is that all these studies are retrospective. In addition many of the reports have a long data collection period (in order to obtain an adequate number of patients), which may bias results as medical management principles do change with time, and have so in recent times. Further in order to evaluate outcome the majority of studies utilise the APACHE II score (a raw score) rather than the calculated prediction equation (APACHE II system). It is not surprising that the APACHE II system (raw score or logit) has not been shown to consistently either overpredict or underpredict outcome in all obstetric and gynaecology patients.

The conflicting reports regarding the APACHE II System's utility as well as the current observations clearly supports the point that obstetrics and gynaecology patients, by virtue of their unique differences require their own outcome prediction model.

4.3 ORGAN SYSTEM FAILURE

Organ dysfunction and ultimately organ failure are the end points of physiological deterioration in the critically ill patient. It is clearly documented in the literature that the number and duration of organ failures impacts on patient outcome[43,77,104,105]. The attractive quality of utilising organ failure as an outcome prediction tool lies in the fact that it need not be assessed singly at a fixed point in time. Serial (daily) monitoring of organ failure permits the detection of improvement or alternatively deterioration.

The challenge for the intensivist lies in the method of defining organ failure. Unfortunately there exists a lack of consensus regarding these definitions. There are two methods that may be utilised to do so. Firstly one can ascertain the presence or absence of organ failure based on strictly defined criteria (for the various organs). The number of failed organ systems are then summated to yield a score such as the Organ Failure Score[79]. The alternative method is to define various levels of dysfunction for each organ system, as is the case for the Sequential Organ Failure Assessment Score.

In the current series 63.5% (165/260) of the patients presented with at least one organ failure as described by Knaus et al (1985) on the first day of ICU admission[43]. At least one organ failure was present on Day one, in 55.6%, 75.7%, 67% and 69% of Groups I, II, IIIa and IIIb respectively. Cardiac, respiratory and neurological failures were most commonly involved in each subgroup. Mortality increased with an increase in the Organ Failure Score for most subgroups. In numerically restricted groups, this trend was not always clearly demonstrated. However, the mortality increased as the number and duration of organ failures increased for the entire group. Further, organ failure was associated with a higher mortality (for each of the organ failures) in Group III compared to Groups I and II. In addition, renal and cardiovascular failures were associated with a higher mortality in Group IIIb compared to Group IIIa. The last two observations need to be interpreted with caution, in view of the small number of data points.

The presence of 2 organ failures for 48 hours was not a sensitive marker of mortality in all the subgroups. An important observation was that 3 organ failures greater than 72 hours (Group I), 3 organ failures greater than 48 hours (Group II) and 3 organ failures equal to 48 hours (Group III/IIIa/IIIb) was associated with a hundred percent mortality. It is generally accepted by intensivists that three organ failures for a period of three days usually equates to 100% fatality.

Generally outcome is influenced by a multitude of factors which includes the number of organ failures, precise combinations as well as the patient population[43,46,77]. Cardiovascular, renal and respiratory failure are generally associated with a higher mortality compared to haematological or liver failure[43,46,76,77].

Organ failure has been reviewed in very few obstetric patients[7,9,25,28,50]. There are no reports on organ failure assessment in gynaecology patients (except for the series by Zakalik et al (2005) which included abortion cases in an obstetric cohort)[7]. All the series are retrospective and they utilise different organ dysfunction assessment tools. In addition, only one study has evaluated the effect of the number and duration of organ failure[50]. Afessa et al (2002) from Florida assessed organ failure as defined by Knaus et al (1985) with some modification. In their series of 74 patients, organ failure occurred in 65% of the patients which is similar to that noted in the current series[28]. Zakalik et al (2005) from Argentina demonstrated in a retrospective series of 242 patients that 45.45% of patients had at least 1 organ dysfunction (MODS

Score) with haemodynamic dysfunction being the most common organ dysfunction[7]. In addition, they observed the number of organ dysfunctions to be a good indicator of mortality. Karnad et al (2004) of Mumbai noted 30.5% of patients to have single organ failure (n=453). The presence of neurological, renal and cardiovascular failure or a DIC was associated with an increase in mortality. Munnur et al (2005) retrospectively compared critically ill obstetric patients from a tertiary hospital in Mumbai (n= 754) to a tertiary hospital in Houston (n=174), over a ten year period[9]. The Indian cohort presented predominantly with neurological, renal and cardiovascular failure. The MODS score on admission was low (4), but the patient population was probably not very ill (18.65% ventilation rate). The Texan cohort also had a low MODS score (3). Respiratory and haematological failure predominated in this group. The different organ failure profile was attributed to the difference in the disease profiles of the 2 cohorts[9]. Bhagwanjee et al (2000) from the same unit in Durban, assessed organ failure as described by Knaus et al in a group of 105 eclamptic patients[50]. They observed that 3 organ failures exceeding 48 hours were associated with a hundred percent mortality. In addition nonsurvivors had a significantly greater number of organ failures compared to survivors (1.3 versus 0.9). The use of variable classification systems in disparate populations is responsible for the variable results. This is further compounded by the retrospective nature of all the available reports.

4.4 THE SEQUENTIAL ORGAN FAILURE ASSESSMENT SCORE

The Day one SOFA Scores ranged fro 0 to 20 and the mean SOFA Score was significantly higher in the nonsurvivors compared to survivors for all the subgroups. Respiratory, cardiovascular, neurological and renal dysfunctions were significantly different between survivors and nonsurvivors. All groups exhibited similar mean SOFA Score values for survivors and nonsurvivors, yet the mortality for Group I was 23.6% and it was 43%, 33.3% and 55.5% for Groups II, IIIa and IIIb respectively. Interestingly sepsis was noted in 14.6% of Group I admissions but in 67.6%, 58.3% and 61.1%% of Groups II, IIIa and IIIb admissions. Group I patients exhibited neurological, respiratory or coagulation dysfunction most commonly. Cardiorespiratory and neurological dysfunction comprised the common organ dysfunctions in Groups II and III. Coagulation dysfunction was found be more prevalent than cardiovascular dysfunction in Group I with the application of the SOFA Score, yet the reverse was noted with the application of the Organ Failure Score. The SOFA score allows the inclusion of variable grades of organ dysfunction. The difference in the results of organ dysfunction for Group I merely illustrate the point that different classification systems do not yield similar results. An important observation was that an admission SOFA Score of 18 (Group I), 15 (Group II) and 13 (Group III/IIIa/IIIb) was associated with a hundred percent mortality. It is reported that two organ failures (a minimum score of 4 per organ) is associated with a 60 -74% mortality[106]. The SOFA Scores remained significantly higher in nonsurvivors compared to survivors for the first five days in the entire cohort. The small number of patients after day five precluded meaningful statistical analysis.

Karnad et al (2004) of Mumbai also found the SOFA score to be higher in nonsurvivors than in survivors[25]. They also noted a clear trend of increasing mortality rate with increasing number of organs that had failed.

Organ failure assessment has not been standardised and there are therefore various definitions or systems to classify the degree of organ dysfunction. Nonetheless it emerges that the number and duration of organ failures correlate with outcome. ICU mortality is not usually directly attributed to the admission indication, but rather the progressive development of organ dysfunction, which is often remote from the site of the initial insult. It makes sense that the time factor probably allows for more accurate outcome prediction compared to a system where the data is obtained within the first 24 hours of ICU admission.

4.5 THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

Systemic Inflammatory Response Syndrome describes the human body's response to either an infective or noninfective insult. The severity of this response (which has a wide spectrum of responses) is believed to influence patient outcome. The SIRS response may therefore be considered as a type of an outcome prediction tool.

The occurrence of SIRS on admission was high at 94.2% (245/260). Sepsis occurred in 14.6% of Group I but in 67.6%, 58.3% and 61.1% of Group II, IIIa

and IIIb admissions.3a 3b sepsis As the severity of SIRS or sepsis increased mortality was observed to increase as well (in Groups I and III). This was not consistently demonstrated in all admissions, due to the small number of admissions with a severe SIRS response in some groups (Group II, IIIa and IIIb), Sterile shock, severe sepsis and septic shock (appendix IV), were associated with a mortality of 51.2%, 30.8% and 66.1 % respectively. The vast majority of Group I patients manifested with SIRS, severe SIRS or sterile shock. Group II and III patients presented mainly with sepsis, severe sepsis or septic shock. Interestingly reclassification of SIRS to a more severe category during the course of ICU stay (30 of 260 patients) was not found to be associated with a mortality higher than that expected for the new category. This was surprising as Muckart et al (1997) documented an increase in mortality following a change in the SIRS response[48].

SIRS has been evaluated rather superficially in 2 retrospective studies in the obstetric population[7,28]. Afessa et al (2002) noted in their cohort of 74 patients over a eight year period that the SIRS response occurred in 59% of their patients. Eighty two percent of the patients with SIRS had at least 1 organ failure as described by Knaus et al[42]. Organ failure occurred in only 12% of patients in the absence of SIRS. The median APACHE II score was higher in patients with SIRS compared to patients without SIRS (15 versus 10)[28]. Zakalik et al (2005) demonstrated that 30.5% of their patients presented with severe sepsis or septic shock. The majority of these patients had either septic abortions or puerperal sepsis[7].

4.6 THE OBSTETRIC AND GYNAECOLOGY OUTCOME PREDICTION MODEL

Initial management of the critically ill obstetric or gynaecology patient encompasses the achievement of physiological homeostasis. Hypotension constitutes a life-threatening phenomenon. Mean arterial pressure is utilised more commonly than systolic blood pressure in most outcome prediction tools. Hypoxia is known to be associated with organ dysfunction and mortality[107-109]. Hypothermia can lead to cardiac and coagulation dysfunction. It is not unexpected to find that temperature, mean arterial pressure, respiratory rate and the Glasgow Coma Scale were identified as significant outcome predictors. Hypotherrnia, hypotension and neurological dysfunction (especially in eclampsia) are commonly noted on admission in this patient population.

The OGOP Model incorporates 6 variables, all of which are readily available and routinely documented in all ICUs. This minimises detection error. Raw values are utilised, as the model does not require weighting of the variables. This minimises the bias introduced when specific cut-off points are utilised in weighting variables. Admittedly a logit is required, however it is far simpler compared to existing general outcome predictive models.

Prognostic markers of poor outcome have been identified in a few retrospective series[25,32,50]. Karnad et al (2005) from Mumbai observed that an increased maternal age, a lack of antenatal care and admission to ICU more than 24 hours following the onset of the acute problem were associated with

an increase in mortality (n=453)[25]. Bhagwanjee et al (2000) reported that temperature, respiratory rate and the Glasgow Coma Scale score were significantly different between survivors and non survivors in a group of 105 eclamptic patients[50]. Taylor and Richards (2000) identified significant differences between survivors and nonsurvivors in terms of the admission platelet count, serum creatinine and INR in a cohort of 23 incomplete abortions[32]. There is no data pertaining to the development of an outcome prediction model for this population. This may well be due to the fact that in most developed regions the ICU utilisation and mortality in this group is generally low. As a result, very large numbers of patients would be required to develop and validate such a tool. Further, data collection would span a long period (as most of the available studies are numerically restricted despite the data collection periods being more than a few years).

The gynaecology cohort was unexpectedly small in this study. Further, the subdivision of the admissions (into pregnant and nonpregnant groups) rendered the two cohorts to be extremely small. As a result a predictive equation could not be developed for these subsets of the gynaecology group. The point that Group IIIa and IIIb admissions demonstrated differences with respect to mean ages, duration of ICU and hospital stay, mortality rates and SMRs (APACHE II) strongly suggests that these two groups are heterogeneous. The observation that Groups IIIa and IIIb demonstrated similar Organ failure scores, APACHE II Scores, SOFA Scores and sepsis rates, yet a difference in mortality rate also suggests that these 2 groups are different compared to each other. Perhaps the fundamental difference lies in

the pregnancy status, albeit early in Group IIIa. In view of the small cohorts, this needs to be further evaluated in a larger cohort. The challenge obviously lies in recruiting an appropriate number of patients. The global decline of general gynaecology admissions to ICU will indeed render this a difficult task. Perhaps Group IIIb (pure gynaecology) patients, will one day, be regarded in the same as light as general ICU patients.

In the context of general outcome prediction tools, it is clear that tools evaluating data serially over a period of time generally perform better than tools that evaluate data just at a single point in time of ICU stay. Nonetheless tools utilised at a single point in time (for example the APACHE II System) do provide important outcome information. There has been a move in general critical care towards "ongoing assessment" of patients in order to improve outcome prediction. For obstetric and gynaecology patients there exists no specific outcome prediction tool to begin with. The OGOP Model constitutes the first step with respect to outcome prediction for this unique population. The APACHE, MPM and SAPS systems have all evolved during the last decade[35-38,1110,111]. The rationale for evaluating the APACHE II system in this cohort was simply based on the fact that it represents the most commonly evaluated general outcome prediction model in the obstetric population. For the OGOP Model the road ahead is long but the route is predictable. The road map for its evolutionary cycle will include, validation (nationally and internationally), refinement and in all likelihood further modification.

As an outcome prediction tool the OGOP Model's advantages include the points that it is a simple tool, the prediction equation is easily calculated, it recognises and corrects for the subtle differences within the obstetric and gynaecology population and it has been prospectively demonstrated to have a good discriminatory power in a validation group. It also represents the first model that has been developed for this subgroup of critically ill individuals.

The recently published SAPS 3 Score appears to be an attractive general outcome prediction tool as it incorporates important predictor variables including pre ICU admission data[110,111]. The SAPS 3 system will probably become the gold standard for general ICU patients as it also incorporates the clinical condition and management of the patient prior to ICU admission. The current study did not evaluate SAPS 3 as it (SAPS 3) was not in existence at the time of development of the study protocol. SAPS 3 needs to be validated in other general ICU patients. In addition its performance in obstetric and gynaecology patients is unknown.

The OGOP Model needs to be validated locally and internationally in ICUs where pathology, age and co morbidities may differ. It may be argued by some, that, the patient profile in this series is somewhat different from critically ill obstetric and gynaecology patients managed in many centres internationally. These differences relate to pathology, ICU utilisation rates, ICU stay and outcome. However, it is difficult to compare patients if severity of illness assessment is not standardised (and currently it is not for obstetric and gynaecology patients). This is all the more reason to evaluate the OGOP

Model in different countries. Currently the OGOP Model is being evaluated in an international cohort (as a separate collaborative study).

South Africa is a unique country. The health sector is divided into two distinct subsets; a wealthy private sector and a much larger but extremely poor public sector. Poor antenatal attendance, nutritional problems (such as anaemia) and diseases associated with poor economic status (such as eclampsia) result in disparate populations within the same country. Thus the OGOP Model needs to be validated in both the public and private institutions in South Africa. This could be easily achieved by the establishment of a national database, which would facilitate the acquisition of epidemiological information.

A limiting factor in the study is the small number of patients in the validation group. Group III in particular was numerically restricted. It had been initially envisaged that the development and validation group would have had sixty and twenty admissions respectively. The number recruited in the current series was unexpected as the unit previously admitted about 40 gynaecology cases per year. However, as has been previously mentioned, the decline in the number of gynaecology admissions appears to be a global phenomenon.

Outcome prediction models, once validated in an ICU may be utilised to stratify patients for interventional therapeutic trials in a population of that particular unit. This can be used to provide scientifically informed management protocols. It needs to be emphasised that outcome prediction models are not designed for individual application. No prediction model has to

date, shown a hundred percent correct classification rate. As a result it would be unacceptable to use such a tool for the purposes of triage or treatment withdrawal.

4.7 THE OBSTETRICS AND GYNAECOLOGY OUTCOME PREDICTION MODEL COMPARED TO THE ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II SYSTEM

In comparing the discriminatory power of the OGOP Model to the APACHE II system, the former appeared to yield better results (sensitivity, specificity and area under the ROC curves) for the entire cohort and each of the development groups. In the validation group a similar observation was made for Groups I and II. Group III was too small (n=8) for a meaningful comparison. Groups IIIa and IIIb were not analysed as a predictive equation had not been developed for these subsets (explained above). The APACHE II system performed most poorly in Group I (AUC=0.8). The OGOP Model yielded an AUC of 0.9 in the same group. The OGOP model is superior to the APACHE II system as it performed equally well in all subgroups, demonstrated a better standardised mortality rate and in addition it is extremely easy to utilise.

4.8 THE SEQUENTIAL ORGAN FAILURE ASSESSMENT SCORE, ORGAN SYSTEM FAILURE AND THE OBSTETRICS AND GYNAECOLOGY OUTCOME PREDICTION MODEL IN RELATION TO THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

Evaluation of the data with respect to the spectrum of the SIRS response clearly revealed that as the severity of SIRS increased, this was associated with a worsening of the Organ Failure Scores, SOFA Scores and the risk of mortality with the OGOP Model. Mortality prediction by the OGOP Model correlated closely with the observed mortality for all subgroups in most instances (except for a few categories which had a very few number of patients). The observation that the predicted mortality by the OGOP Model correlated with the magnitude of the inflammatory response and organ failure (as adjudged by the Organ Failure Score and SOFA Score) also lends support it to being a reasonable outcome prediction tool. The OGOP Model has been demonstrated to be a good outcome prediction tool. Organ failure assessment and the SIRS response provide important adjunctive information.

CHAPTER FIVE: CONCLUSION

5.1 COMMENT

It is clearly evident that in the current series critically ill obstetrics and gynaecology patients constitute a substantial proportion of the ICU population at this centre. This study of critically ill obstetric and gynaecology patients is unique by virtue of being the first to:

- Prospectively describe mortality outcome in this population,
- Separate patients into physiologically distinct groups,
- Develop and attempt to validate an outcome prediction model,
- Evaluate the entire spectrum of the SIRS; including severe SIRS and Sterile Shock and
- Simultaneously evaluate APACHE II, Organ Failure Score, SOFA Score and SIRS in a large patient cohort.

The results have confirmed that critically ill obstetric and gynaecology patients are not an entirely homogenous population, and that the subgroups need to be perceived as separate groups. The APACHE II system, which is labour intensive and complex to utilise, performed variably in the subgroups. On the other hand, the OGOP Model is simple and easy to utilise. In addition, it demonstrated an excellent goodness of fit in all the subgroups. Organ failure assessment, as adjudged by the Organ Failure Score and the SOFA Score, provides significant supplementary information. The number and duration of organ failures impact on outcome. Further, the admission day SOFA Score may identify nonsurvivors. SIRS has been demonstrated to occur in the majority of critically ill obstetric and gynaecology patients. In addition the

severity of the SIRS response helps to complement outcome prediction information. It should be emphasised that in the acutely ill individual subjective and objective outcome prognostication is extremely difficult, with outcome prediction tools providing supplementary information to one's subjective but scientifically informed judgement.

Although the entity of critical care medicine is almost 50 years old, "critically care obstetric and gynaecology" is only now being recognised as a discipline with more question than answers. This study has attempted to evaluate existing outcome prediction tools and further develop and validate an outcome prediction model for this unique population. The findings are distinctive and important. However it should be acknowledged that this study has merely addressed the *tip of the iceberg.* It would be prudent to conclude with a remark made by Scarpinato (1998) in an editorial highlighting the paucity of information in this subdiscipline of critical care: "Every large journey begins with a small step" [112].

5.2 RESEARCH AGENDA

Critically ill obstetric and gynaecology patient populations represent a very fertile ground for research. In the current era of practising evidence based medicine, ICU research focusing on improving the quality of care, the efficient use of limited resources and informed decision making is crucial. The issues of interest for this patient population include the following:

- Validation of the OGOP Model at other local and international (currently in progress) institutions

- Verification of the findings pertaining to Organ Failure Score, SOFA Score and SIRS in other critically ill obstetric and gynaecology patients.
- Utilisation of the aforementioned outcome prediction tools to "risk-stratify" patients for various therapeutic or intervention trials. This can assist in the development and refinement of management protocols for issues of specific import in the critically ill obstetric and gynaecology patient.
- Further work to address the issue of the definition of the gynaecology patient.

Continued research of available outcome prediction tools as well as the exploration of novel methods may, one-day result in "near-perfect" prediction estimates and further broaden their application.

5.3 RECOMMENDATIONS

Based on the findings of the current study the following is suggested:

- ICUs admitting this subset of patients should include an obstetric and gynaecology category in their databases. Early pregnancies be captured as a separate group rather than be included in the general gynaecology category. This will permit definition clarification, future audits and focused research.
- There is a need for the development of international standardised guidelines pertaining to severity of disease stratification, indications for high dependency care or intensive care, discharge criteria and patient management. Research focusing on these issues is crucial.

- In this study both ICU utilisation and mortality were substantial. Certainly from a South African perspective it is hoped that this study creates an impetus to formalise obstetric critical care in the country. The College of Medicine of South Africa allows obstetricians to gain accreditation in critical care. Perhaps it is time for College of Obstetricians and Gynaecologists of South Africa to take note, become actively involved and utilise this window of opportunity in creating a subdiscipline that has been neglected for too long a time.
- The high utilisation of critical care services by obstetric patients in the study raises the issue of what constitutes the ideal location for such a service. The possible options include the establishment of an obstetric ICU (located within the confines of the maternity unit) or the use of a general multidisciplinary ICU (which is often geographically separate from the maternity unit). Obstetric ICUs although few in number have been established in both developed and poorly resourced regions[14,15]. A major advantage is the presence of an on-site obstetrician – this facilitates management of antenatal patients as well as the early detection and timeous management of complications. Intensivists in multidisciplinary ICUs however in most cases, manage critically ill obstetric patients. The geographic location as well as the absence of an on-site obstetrician often results in reluctance in the transfer of antenatal patients. The proportion of antenatal patients in general ICUs is usually much lower than that reported by Obstetric ICUs. addition (depending on the utilisation rate) the intensivist may not always be too familiar with obstetric patients. Although each option has potential

advantages and disadvantages, the ultimate ideal is probably the obstetric ICU. The reality however is that it is not an inexpensive option. Cost containment is an issue of paramount import in a field where fiscal discipline is crucial. Looking at the evolution of intensive care medicine, it has been shown that the introduction of specially trained medical personnel has resulted in favourable outcome. Perhaps the answer may lie in adopting a "middle path" approach of training obstetric intensivists to manage such patients in multidisciplinary ICUs.

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APPENDIX I

APACHE II SCORE (A+B+C BELOW)

A: Acute Physiology Score

Points	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature ^{0}C	≥ 41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean arterial pressure mmHg	≥160	130-159	110-129		70-109		50-69	50-69	≤49
Heart rate/min	≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory rate/min	≥50	35-49		25-34	12-24	10-11	6-9		≤5
A-aDO_2 mmHg if (FIO_2<0.5) *PO_2 if (FIO_2>0.5)*	≥500	350-499	200-349		<200 >70	61-70		55-60	≤55
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	≤7.15
Sodium*	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Potassium*	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		≤2.5
Creatinine* *double points for acute renal failure*	≥300	171-299	121-170		50-120		<50		
Haematocrit %	≥60		50-59.9	46-49.9	30.45.9		20-29.9		≤20
Leucocytes/mm^3	≥40		20-39.9	15-19.9	3-14.9		1-2.9		≤1
Neurological points	15 – GCS score								

* = mmol/l

B: Age Points

Years	≤44	45-54	55-64	65-74	≥75
Points	0	2	3	5	6

C: Chronic Health Points

If patient has significant chronic liver disease, cardiovascular, respiratory, or renal disease or is immunocompromised:

2 points for elective post operative admission

5 points for emergency operation or non operative admission

APPENDIX II

ORGAN FAILURE SCORE

ORGAN	ORGAN FAILURE DIAGNOSIS (At least one criterion for the organ concerned)
Cardiovascular	• Heart rate < 55/minute • MAP <60 mmHg • Ventricular tachycardia/ ventricular fibrillation • pH <7.24 and $PaCO_2$ <50 mmHg
Respiratory	• Respiratory rate ≤ 4/minute or ≥ 50/minute • $PaCO_2$ > 50 mmHg (6.4 KPa) • A-aDO_2 >350 mmHg (46 KPa) • Ventilation >72 hours
Renal	• Urine output < 160 ml/ 8 hours • Serum urea > 16.6 mmol/l (100mg/dl) • Serum creatinine > 310 mmol/l (>3.5mg/100/ml)
Haematologicical	• White cell count <1000 x 10^9/ l • Platelet count < 20 x10^9/ l • Haematocrit <20%
Neurological	• GCS ≤ 6 (in the absence of sedation)

APPENDIX III

SOFA SCORE

ORGAN SYSTEM	POINTS			
	1	2	3	4
Respiration • P_aO_2/FIO_2 mmHg	<400	<300	<200	<100
Coagulation • Platelets $x10^3/mm^3$	<150	<100	<50	<20
Liver • Bilirubin mg/dl • Bilirubin umol/l	1.2-1.9 20-32	2.0-5.9 33-101	6.0-11.9 102-204	>12 >204
Cardiovascular • Hypotension	MAP <70 mmHg	Dopamine≤5 or Dobutamine (any dose)*	Dopamine > 5 or Epinephrine ≤0.1 or Norepinephrine ≤0.1	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1
Central nervous system • Glasgow coma Scale score	13-14	10-12	6-9	<6
Renal • Creatinine mg/dl • Creatinine umol/l or • Urine output ml/day	1.2-1.9 110-170	2.0-3.4 171-299	3.5-4.9 300-440 <500	>5 >440 <200

* Adrenergic agents need to be administered for at least 1 hour (dose in ug/kg.min)

APPENDIX IV

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

SIRS	Two of the following: • Temperature >38° C or < 36°C • Heart rate >90/minute • Respiratory rate > 20/minute or $PaCO_2$ <32 mmHg (4.3 KPa) • White cell count: - >12 000cells/mm^3 or - < 4000 cells/mm^3 or - 10% immature/band forms
Sepsis	• SIRS with infection
Severe sepsis	• Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria or an acute alteration in mental status
Severe SIRS	• Identical to severe sepsis but in the absence of infection
Septic shock	• Sepsis associated with hypotension, despite adequate fluid resuscitation along with the presence of perfusion abnormalities as listed for severe sepsis. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured
Sterile shock	• Identical to septic shock but in the absence of infection

Appendix IV depicts the criteria utilised to define the various categories of SIRS. Infection was diagnosed in the context of a positive microbial culture, contamination of the gastrointestinal tract or the presence of overt sepsis. SIRS was evaluated on admission and on a daily basis.

Infection: Microbial phenomenon characterised by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.

Hypotension: A systolic blood pressure of < 90 mmHg or a reduction in blood pressure of >40 mmHg from the baseline, in the absence of other causes of hypotension.

APPENDIX V

GLASGOW COMA SCALE

The score is calculated by summating points achieved for the best eye opening, best verbal and best motor response. The score achieved may range from 3 to 15. points are allocated as follows:

PARAMETER	RESPONSE	POINTS
Eye opening	Spontaneous	4
	To verbal command	3
	To pain	2
	No response	1
Motor	Obeys verbal command	6
	Response to painful stimuli: localises pain	5
	Response to painful stimuli: flexion-withdrawal	4
	Response to painful stimuli: decorticate rigidity	3
	Response to painful stimuli: decerebrate rigidity	2
	Response to painful stimuli: no response	1
Verbal	Orientated and converses	5
	Disorientated and converses	4
	Inappropriate words	3
	Incomprehensible words	2
	No response	1