Review of factors associated with prolonged hospital stay in very low birth weight infants at a tertiary hospital in South Africa

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Declaration

I, Nonceba Amelia Thambe, declare that this Research Report is my own work, and any publications consulted have been appropriately referenced. This research report is being submitted for the Degree of MMed at the University of the Witwatersrand, Johannesburg. It has not been submitted for any degree or examination at any other University.

(Signature of candidate)

_____05_____day of__July_____2022____at___Pretoria____

Dedication

This work is dedicated to my mother, Nomvuselelo Thambe, my children, Nduvho and Lindokuhle, for their love, sacrifices, prayers, encouragement and understanding throughout this study.

Acknowledgements

I would like to thank my supervisors, Professor DE Ballot and Dr TD Ramdin, for all their help, guidance and support during this research project. Special acknowledgement also to Rossella Bandini, Research Coordinator for the Neonatal Unit at the Charlotte Maxeke Johannesburg Academic Hospital, for her outstanding support. I would also like to extend my gratitude to the Department of Paediatrics and Child Health at the University of the Witwatersrand for allowing me an opportunity to pursue my dream of becoming a paediatrician.

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Abbreviations

AKI:	Acute kidney injury
BPD:	Bronchopulmonary dysplasia
CMV:	Conventional mechanical ventilation
CMJAH:	Charlotte Maxeke Johannesburg Academic Hospital
ELBW:	Extreme low birth weight
IVH:	Intraventricular haemorrhage
LOS:	Late onset sepsis
NEC:	Necrotising enterocolitis
PDA:	Patent ductus arteriosus
PHS:	Prolonged hospital stay
Preterm:	Premature neonates delivered before 37 completed weeks
REDCap™:	Research electronic data capture
ROP:	Retinopathy of prematurity
VLBW:	Very low birth weight
KMC:	Kangaroo mother care

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Submissible paper

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What is known?

Prolonged hospital stay (PHS) is associated with morbidities, mortality and high costs for both parents and the state. PHS of preterm infants increases the burden of beds on the health care system. Multiple studies highlight gestational age, birth weight, bronchopulmonary dysplasia (BPD) and nosocomial sepsis (NOS) as significant risk factors for PHS in very low birth weight (VLBW) neonates. Post-operative morbidity, including sepsis and delayed onset of enteral feeds, are associated with PHS in neonates undergoing surgery.

What this study adds

Factors associated with PHS in South Africa are the same as high-income countries (HICs). However, an association between PHS and maternal tuberculosis (TB) and PHS with patent ductus arteriosus (PDA) are unique to our current study.

Abstract

Background: Many factors have been shown to influence the duration of hospital stay, namely gestational age, birth weight and neonatal morbidities. In middle-income countries with limited resources such as South Africa, understanding factors associated with PHS will assist in resource planning, policy amendments and highlight areas for quality improvement projects.

Objectives: Our objectives were to determine the prevalence of PHS in VLBW infants and maternal, postnatal and neonatal factors associated with PHS and compare the characteristics of neonates with and without PHS.

Methods: This was a retrospective observational study. The population included all neonates with a 500 to 1500-gram birth weight, born at Charlotte Maxeke Johannesburg Academic hospital (CMJAH) in Johannesburg, South Africa, between 1 January 2013 and 31 December 2017. Pre-hospitalisation maternal and neonatal factors and complications were analysed. Maternal and neonatal characteristics of infants with PHS were compared to those without, defined by a hospital stay of 60 days or more.

Results: The survival rate in this study was 87.3%, and the prevalence of PHS was 11.8%. The mean birth weight was 993 grams (SD 186.144), and the average gestational age was 28.27 weeks (SD2.179). Lower birth weight and gestational age were associated with PHS. NOS (odds ratio 2.329; 95% Confidence interval 0.3 – 3.1), BPD (odds ratio: 4.9; 95% Confidence interval 1.93 – 5.424), PDA (odds ratio: 2.702; 95% Confidence interval:0.33 – 5.424) and maternal TB (odds ratio:25.37; 95% Confidence interval:0.43 – 488.38) were associated with PHS.

Discussion: This study showed that 12.5% of VLBW preterm infants at CMJAH have PHS. Prematurity is an independent risk factor for PHS. Complications associated with the latter, such as NOS, BPD, PDA and lower gestational age, prolongs the hospital stay further. However, an association between PHS with maternal TB and PHS with PDA are unique to our current study.

Conclusion: It is critically important to modify risk factors and morbidities associated with PHS. Measures to be improved include reducing rates of NOS, early medical closure for PDA and early identification of maternal TB. This will ultimately reduce the resource and financial burden in our hospitals.

Abstract word count: 330 Manuscript word count: 4674

Introduction

In South Africa, a middle-income country with limited resources, PHS of infants impacts resource use and availability [1]. Studies have shown that PHS leads to higher hospital costs, morbidities, mortality and adds to the problem of management and available beds. PHS of preterm infants increases the burden on parents and the health care system [1]. Neonates with medical and surgical conditions are admitted to neonatal units [2]. Therefore, it is essential to consider both medical and surgical factors associated with PHS.

Among preterm neonates with surgical conditions sampled in a study conducted in NICU in western Asia, predictors of PHS were gestational age, birth weight, post-operative sepsis and age at initiation of enteral feeds [3]. Neonatal risk factors for PHS described by other researchers were extremely low birth weight (ELBW), respiratory distress syndrome (RDS), endotracheal intubation during resuscitation at birth, need for cardiac compressions and drugs at birth, small for gestational age (SGA) neonates, hypothermia and anaemia [4-6].

Postnatal complications which have been shown to influence the duration of hospital stay were NOS, necrotising enterocolitis (NEC) and BPD [7-9]. NEC in preterm infants is associated with PHS due to complications such as poor weight gain (attributed to increased metabolic demands), morbidities such as NOS, feeding intolerance and short bowel syndrome [3, 4, 10, 11]. NOS was demonstrated to affect 37 – 44% of VLBW infants seen in three neonatal units in three different studies in Africa [8, 12, 13]. NOS is a common problem in VLBW neonates and was significantly associated with PHS in a Chris Hani Baragwaneth Academic Hospital (CHBAH) study [14]. Various factors can influence the length of hospital stay; therefore, a model consisting of all these factors was suggested in a Kenyan study [15].

VLBW infants have an increased risk of requiring ventilator support, developing complications such as pneumothorax, and more extended periods of requiring nasal prong oxygen. They are, therefore, more likely to develop bronchopulmonary dysplasia (BPD) [16, 17], which is considered one of the significant factors associated with PHS amongst VLBW neonates [18]. Understanding factors associated with PHS in neonates may assist in developing interventions to shorten the length of hospital stay and save costs [19]. There is limited information on PHS in neonates in sub-Saharan Africa. The current study reviewed the factors associated with PHS in VLBW neonates at a tertiary referral hospital in Johannesburg, South Africa.

Study Methods

Study design

The study was a retrospective descriptive study of an already established database.

Study setting and population

The study was conducted at CMJAH, a public tertiary hospital in South Africa. The study population included all VLBW infants (500 to 1500g at birth) born or admitted at CMJAH between 1 January 2013 and 31 December 2017. Infants with severe congenital defects, those who died within seven days or who were transferred to other hospitals, were excluded.

During the study period, the neonatal unit at the CMJAH had a six-bed labour ward nursery where neonates were initially stabilised and subsequently admitted to relevant wards if necessary. All VLBW neonates requiring resuscitation at birth were resuscitated using bag-mask ventilation, stabilised and admitted. Those above 700g were offered non-invasive ventilation and only those weighing 850g and above qualified for invasive ventilation. This unit protocol was set in place due to the limited resources the unit is faced with daily. There was a 35-bed high-care nursery where intravenous fluids, antibiotics, nasal continuous positive airway pressure (NCPAP), surfactant therapy, supplemental oxygen and phototherapy were provided. The discharge weight for this unit was 1600g, provided the neonate was tolerating full feeds from a cup or breastfeeding. Additionally, CMJAH had a 20-bed ward for low care and a 15-bed kangaroo mother care (KMC). Patients requiring conventional ventilation were admitted to a shared 14-bed paediatric/neonatal intensive care unit.

Data collection

Maternal, labour room and neonatal information was collected [20]. Demographics and clinical information were collected on the discharge of each baby by the attending medical staff. Data were managed using REDCap™, hosted by the University of the Witwatersrand.

Data analysis

Data were entered into a Microsoft Excel Spreadsheet (Microsoft, USA) for cleaning. The final dataset was exported to SPSS version 27 (IBM, USA) for analysis. The total sample was analysed, and categorical variables were summarised and presented in frequencies and percentages. Summaries of continuous variables were presented as means with standard deviations or median with interquartile ranges (IQR), depending on the distribution. When comparing groups with and without PHS, categorical variables were

compared using Pearson chi-squares. Continuous variables with normal distribution were compared using the Student's independent t-test. Continuous variables with skewed data were analysed using a nonparametric test (Mann Whitney U-test). The level of significance was set at $p<0.05$. In assessing factors associated with PHS, the comparison was assessed using multivariable logistic regression.

The definition of PHS and neonatal morbidities were based on those used in the Vermont Oxford Network [(20)] as follows:

- PHS was defined as more than 60 days in hospital.
- Late-onset or nosocomial sepsis was defined as the onset of culture-proven sepsis after 72 hours of life.
- BPD was defined as a persistent oxygen requirement up to 36 weeks corrected gestational age in preterm neonates or up to 28 days in term neonates with abnormal chest x-rays.
- Intraventricular haemorrhage (IVH) was defined as grade 3 and 4 using Papile grading.
- Perforated NEC was defined as stage 3 (a) or (b) using modified Bells staging.
- Very low birth weight neonates were defined as a birth weight of 500 to 1500g or less

Ethical approval

The study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Clearance certificate M180710).

Results

Maternal and prenatal characteristics of the sampled population

Maternal and prenatal characteristics of sampled VLBW neonates are shown in Table 1. Maternal age ($p=0.52$), parity ($p=0.98$) and mode of delivery ($p=0.35$) were not significantly associated with PHS. Antenatal steroids ($p=0.39$) and receiving antenatal care ($p=0.52$) showed no association with PHS. Amongst maternal comorbidities, maternal tuberculosis ($p=0.034$) was found to be a risk factor for PHS in VLBW infants (Table 3).

Population characteristics

There were 2567 VLBW infants delivered at CMJAH between January 2013 and December 2017. Of these, 38 neonates were transferred to other hospitals, 465 died within the first seven days, 59 had severe congenital defects; all were excluded from the study. A total of 2005 neonates fulfilled the inclusion criteria and were analysed. The length of stay was assessed in 2005 patients, and 237 (11.8%) had PHS.

The majority were inborn (n=1672, 84.1%) and were also black (n=1930; 97%). A large number of sampled VLBW neonates in this study, 1006 (50.5%), were delivered at a gestational age between 28 and 32 weeks, followed by those born at gestational age below 28 weeks 412 (20%), 385 (19.2%) were 31 to 32 weeks, and lastly, there were 201 (10%) above 33weeks. Of the VLBW infants, 465 (23.2%) were born with a birth weight lower than 1000g. The survival rate was 87.3% (1749/2005). The length of hospital stay was prolonged with a decrease in gestational age and birth weight. The clinical characteristics of sampled infants, complications and therapeutic interventions are shown in Table 2. Amongst VLBW neonates who were reported to have late-onset sepsis (Table 1), only 204 (30.9%) had proven sepsis with culture-positive results. More than 50% of the positive cultures were fungal sepsis, followed by gram-negative sepsis (*Klebsiella pneumonia* and *Acinetobacter Baumann*).

Continuous variables associated with PHS were birth weight (BW) and gestational age (GA), with p-values <0.001. No association was found between head circumference (HC) and PHS (p= 0.176) and duration of ventilation with PHS (p=0.18). Initial resuscitation at birth (p=0.322), Apgar scores (p=0.133), apnoea (p=0.674), gender (p=0.136) and other surgeries (p=0.517) were not included in Table 1, as they were not found to be statistically significant in this study.

Multivariate analysis

Reported associations with PHS on multivariate analysis are shown in Table 3.

Discussion

Our study showed that 12.7% of VLBW infants had a longer than 60-day hospital stay. Mortality has been inversely correlated with the risk of PHS, especially in ELBW neonates, which is observed mainly in clinical settings [7].

Maternal risk factors

The association between maternal TB and PHS was also demonstrated in our study only. This could be related to the fact that neonates of mothers with TB need to be investigated for TB, and results may take longer. The current HIV guidelines recommend screening for TB in all pregnant mothers, which means those booked for antenatal care are more likely to be treated by delivery, depending on when antenatal bookings were made.

Gestational age and birth weight

Lower birth weights and gestational age were inversely proportional to the length of hospital stay and were found to be associated with PHS. The association between length of hospital stay, birth weight and gestational age has been demonstrated in several studies previously and is not unique to the current study [21]. Gestational age of under 32 weeks has been shown as a strong predictor of length of hospital stay, mortality and morbidity in VLBW neonates [21]. Clinically, this is understandable as smaller premature babies need a more extended hospital stay to allow organ maturation.

Morbidities /complications of prematurity

Prematurity is an independent risk factor for PHS, and surgery in these individuals lengthens the duration of hospital stay even further, but this was not demonstrated in our current study [3]. The explanation for this could be the morbidities associated with respiratory support, such as sepsis, cardiovascular instabilities and possible neurological injuries during ventilation [3]. Similarly, previous studies have shown that ventilator support (invasive) has led to a prolonged hospital stay, and our results confirmed an association between the duration of ventilation and PHS [17].

In our study, VLBW infants with nosocomial sepsis had a twofold increase in their odds of having PHS. All four studies in Africa which looked at the length of hospital stay, and neonates demonstrated a strong association between NOS and PHS [7,14,16,26]. Nosocomial sepsis is one area that institutions in middle- and low-income countries should address to reduce the length of hospital stay. The association between PDA and PHS are unique to this study. Several factors could explain this; namely, neonates with PDA may have prolonged oxygen requirements because of the left to right shunt and may even be complicated by pneumonia. Also, neonates with PDA have increased energy requirements leading to slower weight gain if calories are not optimised and prolonged hospital stay. Lastly, infants with haemodynamically significant PDA that failed medical closure require anti-failure medications while awaiting surgical closure, which could prolong hospital stay further. In our clinical setting, it was unclear if the PDA cases were those who failed medical closure only or those who failed and were successfully closed medically.

In our study, factors associated with PHS were NOS, BPD, PDA and maternal TB. The odds of having PHS in VLBW infants with BPD were increased fivefold; this result is in keeping with what was demonstrated in a HIC study in ten European regions [26] and the CHBAH study [16].

Another institutional practice that may influence the length of hospital stay is the inability to adhere to sepsis-reducing measures resulting in NOS in the unit. However, in this study, adherence to sepsis-

reducing measures was not assessed, but NOS has been demonstrated as a risk factor for PHS. The unit protocol encourages breastfeeding; however, due to several factors, most neonates in this study were formula-fed, and only a few were breastfed. Some of our neonates developed NEC due to these feeding practices, prematurity, and the burden of nosocomial sepsis. A small percentage were complicated by perforation requiring surgical intervention, thereby prolonging their hospital stay. One of the major factors influencing these feeding practices is the lack of a breast milk bank, which poses a considerable challenge if the mother cannot produce breast milk[23]. NEC is one of the neonatal complications known to lengthen the duration of hospital stay in neonates in a clinical setting and has been demonstrated in several previous studies [1, 14]. However, no significant association was shown between PHS and perforated NEC in our study.

The strength of the study

The strength of this study was that there was a large sample size, and it was conducted in a tertiary institution with neonatal protocols, which gave these VLBW infants a good chance of survival. At the same time, our population was mainly from the middle-income group, demonstrating the real-life challenges South Africa is faced with daily.

Limitations

There were several limitations to this study. The first limitation was that it was a retrospective analysis of existing data, and some of the cases had incomplete information. In this study, we can only comment on the association with a prolonged hospital stay, not the cause and effect of, for example, nosocomial sepsis. The study was limited to VLBW preterm neonates, and the sample was derived from one institution, making it difficult to generalise findings to all infants.

Conclusions

It is critically important to modify risk factors and morbidities associated with PHS. Measures to be improved include reducing rates of NOS, early medical closure for PDA and early identification of maternal TB. These measures will ultimately reduce the resource and financial burden in our hospitals. Furthermore, the timeous use of postnatal steroids for infants with BPD will reduce the duration of hospital stay and improve outcomes.

Variable	Frequency (%)
Maternal age (years)	
< 20	122 (6.5%)
20 – 35	1437 (76.2%)
36 – 39	220 (11.6%)
40 – 53	106 (5.6%)
HIV* status	
Positive	620 (31.6%)
Negative	1340 (68.4 %)
Parity	
0	1726 (96.6%)
1 - 2	59 (3.3%)
3	2 (0.1%)
Antenatal care	
Yes	1560 (81.4%)
Antenatal steroids	
Yes	1560 (81.4%)
Mode of delivery	
Normal vaginal delivery	815 (41.3%)
Caesarean section	1160 (58.7%)
Maternal comorbidities	
Maternal hypertension	516 (28%)
Maternal chorioamnionitis	68 (3.7%)
Maternal diabetes mellitus	11 (0.6%)
Maternal tuberculosis	22 (1.2%)
Maternal syphilis	39 (2.1%)

*HIV=human immunodeficiency virus

Table 1. Maternal and prenatal characteristics of very low birth weight infants at Charlotte Maxeke Johannesburg Academic Hospital, admitted 1 January 2013 to 31 December 2018.

Characteristics	Frequencies (%) or mean (SD) or median (IQR)
Variables	
Males	916 (46%)
Birth weight (g), mean (SD)	1165.55 (212.994)
Head circumference (cm), mean (SD)	27.675 (2.3981)
Gestational age (weeks) mean (SD)	29.44 (2.435)
Length of stay (days) median (IQR)	32 (21-231)
Age at admission (days) median (IQR)	1.00 (1-5)
Duration of ventilation (days) median (IQR)	5.00 (3-10)
Complications	
Bronchopulmonary dysplasia	605/1861 (32.5%)
Early-onset neonatal sepsis	72/1978 (3.6%)
Late-onset neonatal sepsis	659/1989 (33.1%)
Necrotising enterocolitis	159/1990 (8%)
Patent ductus arteriosus	232/1984 (7.4%)
Hyperglycaemia	393/1998 (19,8%)
Hypoglycaemia	257/1999 (12.9%)
Intraventricular haemorrhage	97 (7.4%)
Neonatal jaundice	950/1990 (47.7%)
Pneumothorax	14/1983 (0.7%)
Hyaline membrane disease	1615/1991 (81.1%)
Management	
Invasive ventilation	430 (22.8%)
Non-invasive ventilation	1006 (70%)
Breastfeeding	770 (38.4%)
Formula feeding	1159 (57.8%)
Mixed feeding	76 (3.7%)
Steroids for bronchopulmonary dysplasia	223(60.7%)

Table 2. Clinical characteristics of very low birth weights infants at Charlotte Maxeke Johannesburg Academic Hospital, admitted 1 January 2013 to 31 December 2018

Variable	PHS N/n (%)	No PHS N/n (%)	Association test p-value	Multivariate analysis OR (95%CI)
Categorical variables			**Chi-square**	
Maternal TB	232/238 (97%)	1606/1620 (99%)	**0.034**	25.37 (0.43-488.38)
Hyperglycaemia	69/253 (27.3%)	324/1742 (18.6%)	**0.005**	0.824 (0.310-3.104)
Late onset sepsis	166/252 (65.9%)	493/1732 (28.5%)	**<0.001**	2.329 (1.00-5.424)
Nasal CPAP	152/213 (71.4%)	884/1139 (77.6%)	**0.031**	0.982 (0.310-3.10)
Ventilation	234/235 (99.5%)	1613/1640 (98.3%)	0.089	-
Patent ductus arteriosus	52/242 (21.5%)	86/1644 (5.2%)	**<0.001**	2.702 (1.336-5.424)
BPD	180/244 (73.8%)	425/1613(26.3%)	**<0.001**	4.902 (1.931-12.44)
Perforated NEC	5/251 (2%)	11/1724 (0.6%)	0.082	-
Continuous variables			**T-test**	
Birth weight (g)	993.07 (186.144)	1190.79 (204.58)	**<0.001**	
Gestational age (weeks)	28.27 (2.179)	29.61 (2.44)	**<0.001**	

CPAP = continuous positive airway pressure, BPD = bronchopulmonary dysplasia, NEC=necrotising enterocolitis, OR=odds ratio CI=Confidence interval and PHS=prolonged hospital

Table 3. Factors associated with a prolonged hospital stay in very low birth weight neonates at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 to 31 December 2018

Figure 1. Scatter plot of birth weights by the duration of hospital stay of very low birth weight infants admitted at the neonatal unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 to 31 December 2018.

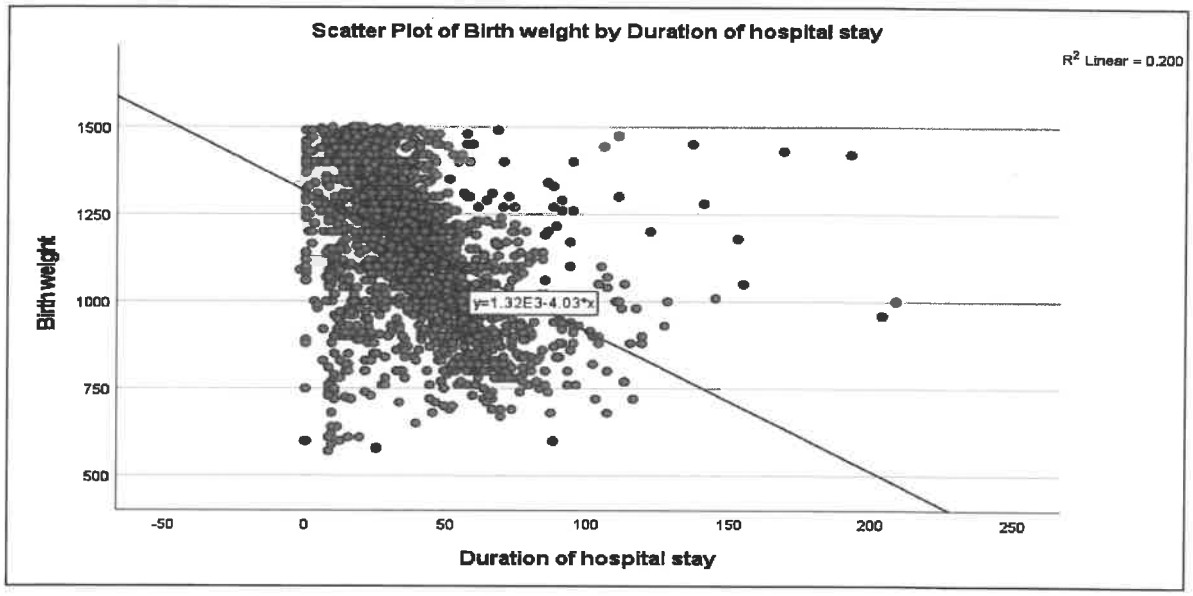
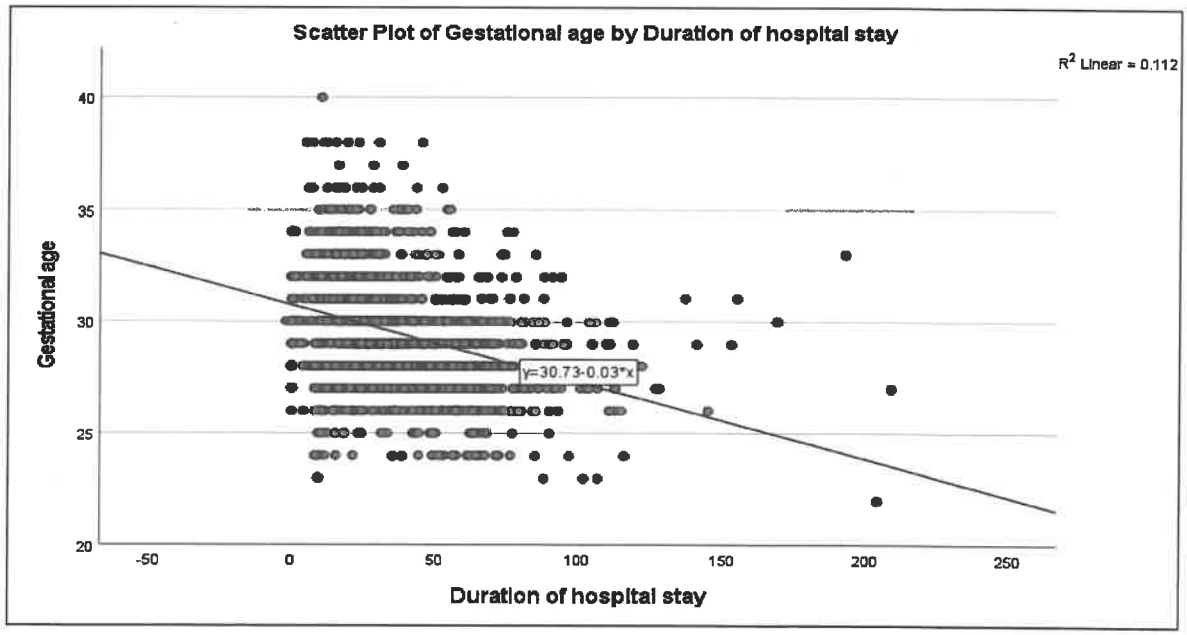


Figure 2. Scatter plot of gestational age by the duration of hospital stay of very low birth weight infants admitted at the neonatal unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 to 31 December 2018.



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Contributor's statement

Dr Thambe conducted this research in fulfilment of her MMED. She conceptualised and designed the study, collected data, carried out data analysis, drafted the initial manuscript, reviewed and revised the manuscript and approved the final manuscript as submitted. Prof Ballot and Dr Ramdin supervised Dr Thambe by assisting with the study design, data analysis and review of various drafts of the manuscript, including approval of the final manuscript as submitted.

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Abbreviations: AKI - acute kidney injury. BPD - bronchopulmonary dysplasia. CMV- conventional mechanical ventilation. CMJAH - Charlotte Maxeke Johannesburg Academic Hospital. ELBW - extreme low birth weight. IVH - intraventricular haemorrhage. NOS - nosocomial sepsis. NEC - necrotising enterocolitis. BPD - bronchopulmonary dysplasia. NNU - neonatal unit. PHS - prolonged hospital stay. Preterm - premature neonates, delivered before 37 completed weeks. VLBW - very low birth weight. PDA - patent ductus arteriosus. REDCap™ - Research Electronic Data Capture. TB - tuberculosis. HIV - Human immunodeficiency virus.

Appendix A: SAMJ author guidelines

➢ General article format/layout

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

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

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

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardised human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counsellors. J Genet Counsel 2008; 17:424-433: standard human pedigree nomenclature.

➢ Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study. Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text. Do not replicate data in tables and in text.

- *Structured abstract*

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

- *Main article*

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

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

- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

- *Results*

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

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

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

- *Conclusions*

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

- *Tables*

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

- References

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

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization, [2] and others. [3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.

- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.

➢ General submission instructions (including cover letter, title page requirements, contributors' statement page, journal style guidance, and conflict of interest statements) apply to Regular Articles.

➢ From submission to acceptance

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
    - Anonymous manuscript (unless otherwise stated)
    - Manuscript
    - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
- Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting

Appendix B: MMed Research Protocol

MMed Research Protocol

JULY 2018

Review of factors associated with prolonged hospital stay in very low birth weight neonates at a tertiary hospital in South Africa.

Investigator: Dr Amelia N Thambe

Student number: 1730628

Protocol submission for degree:

MMed (Paed)

Supervisors:

Prof Daynia Ballot, MBBCh (Wits), FC Paed (SA), PhD

Dr Tanusha Ramdin MBBCh, FC Paed (SA), DCH (SA), MMed (Paeds), Neonatology (SA)

Table of contents

GLOSSARY OF TERMS

AKI:	Acute kidney injury
BPD:	Bronchopulmonary dysplasia
CMV:	Conventional mechanical ventilation
CMJAH:	Charlotte Maxeke Johannesburg Academic Hospital
ELBW:	Extreme low birth weight
IVH:	Intraventricular haemorrhage
LOS:	Late onset sepsis
NEC:	Necrotising enterocolitis
NNU:	Neonatal unit
PDA:	Patent ductus arteriosus
PHS:	Prolonged hospital stay
Prem:	Premature neonates delivered before 37 completed weeks
REDCap™:	Research electronic data capture
ROP:	Retinopathy of prematurity
VLBW:	Very low birth weight

Definitions

Prolonged hospital stay is defined as a hospital stay of 60 days or more (1, 2).

Short hospital stay is defined as a hospital stay of fewer than 60 days (3).

Prolonged hospital stay is defined as a hospital stay of 60 days or more (1, 2).

Short hospital stay is defined as a hospital stay of fewer than 60 days (3).

Bronchopulmonary dysplasia is defined as the requirement for supplemental oxygen at 28 days of life (4).

The presence of necrotising enterocolitis is defined by stage 2 or greater, using modified Bells staging (5).

Intraventricular haemorrhage is defined as grade 3 or 4 graded using Papile grading (6).

Late-onset sepsis is defined as sepsis occurring within 4 to 90 days of life (7).

The presence of retinopathy of prematurity is defined as stages 3 and 4 (8).

Apnoea is defined as cessation of breathing for 20 seconds or any duration if associated with cyanosis, desaturation and bradycardia (9).

Prolonged ventilation is defined as greater or equal to 21 consecutive days (10).

Neonatal unit is defined as all the neonatal wards at CMJAH, including neonatal intensive care.

Very low birth weight is defined as neonates with a birth weight below 1500 grams.

Extremely low birth weight is defined as neonates with a birth weight below 1000 grams.

The presence of patent ductus arteriosus referred to those which were confirmed on echocardiography.

Introduction

South Africa is a low- to middle-income country with limited resources, and prolonged hospital stay (PHS) impacts resource use and availability (31). PHS is associated with morbidity and mortality and higher costs for both state and parents (26, 32, 33). A neonatal unit has been found to use 22 - 34% of total hospital costs (34). PHS of preterm neonates increases the burden on the health care system (4).

Neonates with medical and surgical conditions are admitted to neonatal units (5). Therefore, it is essential to consider both medical and surgical factors associated with PHS. Understanding factors related to PHS in neonates may lead to developing interventions to shorten the length of stay and save costs (1).

The present study aimed to review factors associated with PHS in a tertiary referral hospital in Johannesburg.

Background

Preterm neonates are born with immature organ systems. Usually, they require a prolonged stay in a neonatal unit to allow sufficient time for organ maturation and weight gain to survive independently (3, 11).

Campos Bannwart and colleagues (1999) reviewed predictors of PHS in very low birth weight (VLBW) neonates (6). Both maternal and neonatal factors were associated with PHS. Maternal risk factors include late antenatal bookings, maternal comorbidities and complications during delivery (1, 6, 7). Neonatal risk factors include extremely low birth weight (ELBW), respiratory distress syndrome, endotracheal intubation during resuscitation at birth, need for cardiac compressions and drugs, low Apgar score, late premature neonates, small for gestational age (SGA) neonates, hypothermia and anaemia (6, 8, 9).

The complications of prematurity are also associated with PHS. These include necrotising enterocolitis (NEC), nosocomial infection (NOS), intravenous haemorrhage (IVH), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), hypoglycaemia and prolonged vascular access (4, 7, 17, 18, 32, 35, 36). If some of these risk factors and morbidities were modified, it might result in shorter hospital stays and improved outcomes (37). PHS predisposes the neonates to LOS and has notable effects on VLBW neonate morbidity and mortality (38). OS was present in nearly 44% of VLBW neonates seen

in three neonatal units (10-12) and was significantly associated with PHS. Additional risk factors for sepsis in VLBW neonates with PHS include central lines, catheters and ventilators, amongst others (18). The association between PHS and NOS suggests that reducing the length of hospitalisation in preterm neonates will lower the institution's sepsis burden.

VLBW neonates are at increased risk of requiring ventilator support and developing complications (such as pneumothorax) and more extended periods of requiring nasal prong oxygen. They are, therefore, more likely to develop BPD (14, 15) which is considered one of the significant factors associated with PHS among VLBW neonates (16). A group of VLBW neonates with BPD were found to have a mean duration of hospital stay of 84.1 days compared to a control group without BPD which had a mean duration of 58.1 days in the hospital (16).

NEC in preterm neonates is associated with PHS in the neonatal unit due to complications such as poor weight gain (attributed to increased metabolic demands) and morbidities such as NOS, feeding intolerance and short bowel syndrome (6, 7, 17, 18). Most of these infants require prolonged use of total parenteral nutrition, which is associated with increased rates of sepsis. A study in our centre suggests that prevention of NEC and control of infections by simple measures such as breastfeeding and hand-washing should be prioritised to improve outcomes of VLBW and reduce the length of hospitalisation (10).

Neonatal acute kidney injury (AKI) is a common and independent risk factor for mortality and PHS in VLBW neonates (38). Up to two-thirds of patients admitted to the neonatal unit will be treated for AKI, and 4 – 5% will develop a severe form of AKI. Significant efforts are required for the prevention, early recognition and timely management of AKI. It is essential to understand the associated risk factors to reduce PHS.

There is limited information on PHS in neonates in sub-Saharan Africa. It is critically important to modify risk factors and morbidities associated with PHS to reduce the length of hospital stay and to improve the quality of care in the hospitals. This will ultimately also reduce the resource and financial burden on hospitals. The current study reviewed the factors associated with PHS in VLBW neonates at a tertiary referral hospital in Johannesburg, South Africa.

Aim:

To review factors associated with PHS in VLBW neonates at a tertiary referral hospital in a South African setting.

1. Objectives

1. To compare characteristics of those neonates with PHS to a group of neonates with a shorter duration of hospitalisation.
2. To determine the prevalence of PHS in VLBW neonates.
3. To determine maternal, obstetric and neonatal factors associated with PHS in VLBW neonates

2. Methodology

2.1 Study design:

A retrospective descriptive cross-sectional analysis of an already established database.

2.2 Study population:

Neonates with birth weight between 500 and 1500 grams admitted to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between 1 January 2013 and 31 December 2017.

3. Inclusion criteria:

All VLBW neonates admitted to the CMJAH neonatal unit within 48hours of birth.

4. Exclusion criteria

VLBW neonates who died within seven days of admission.

Those transferred to other hospitals and those with severe congenital defects

5. Sample size:

There are approximately 500 VLBW admissions per annum whose clinical information is captured on the in-house clinical repository. Approximately 300 of 2500 admitted from January 2013 to December 2017 had prolonged hospital stays.

6. Variables:

See the Data Collection Sheet, attached as Appendix A, for a complete list of variables analysed

Data sources

Demographics and clinical information are collected on the discharge of each baby by the attending medical staff. Data is verified against hospital records. Data is managed using REDCap™ (Research Electronic Data Capture), a product developed by Vanderbilt University and hosted by the University of the Witwatersrand (39).

Data analysis

Continuous variables were described using mean and standard deviations or median and interquartile ranges, depending on the data distribution. Categorical variables were described using percentages and frequencies. The total sample was divided into two groups: neonates with and without PHS. Neonatal and maternal characteristics were compared between the two groups.

An unpaired student t-test was used to compare continuous variables with normal distribution, and nonparametric tests will be used to compare skewed data. Chi-square tests were used to compare categorical variables. A p-value of 0.05 will be considered significant. Data were analysed using SPPS version 27 (IBM, USA). Significantly different variables were entered into a binary logistic regression model with PHS as an outcome variable.

Limitations:

This is a retrospective review of an existing database, so certain data may be missing.

Bias

Selection bias was minimised by ensuring that all eligible neonates seen at CMJAH were enrolled. All neonates are included in the database, which minimises bias.

Ethical considerations:

Application for approval of the study protocol was made to the Human Research Ethics Committee (HREC) of the University of the Witwatersrand.

Data were de-identified: no name, surname, hospital number or date of birth will be included in the data collection sheet. Neonates were allocated study numbers. Data was kept secure, and the key to the filing room was available to only the researcher collecting data.

As the study is retrospective, there is no direct risk to the participants. There is also no direct benefit, although the study's outcome may influence or change the future management of the participants or other newly admitted neonates.

Funding

An estimated R1000 was needed for photocopying and printing, and this cost was borne by the researcher.

Timing

	June 2017	July/Sept 2017	Oct-Dec 2017	Jan/April 2018	May/June/ July 2018	Aug/Sept 2018-2020	June-Aug2021
Literature review	x	x					
Protocol preparation			x	x			
Protocol assessment					x		
Ethics application					x		
Data collection						x	
Data analysis						x	
Writing thesis							x
Submission							x

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Appendix C: Data collection sheet

Appendix (page A)

Demographic data	**Birth information**	**Other factors**	**Maternal data**	**Neonatal morbidities**
Study number	Mode of delivery: C/S or NVD or Breech	Diagnosis (admission):	Maternal age:	IVH (grade 3/4): Yes/No
Length of stay in NNU:(days)	Place of birth: inborn or outborn	Congenital anomalies: Yes /No	Booked: Yes/No	Apnoea: Yes/No
Gestational age:	Singleton or multiple pregnancies	Surgical patients: Yes/No	Parity & gravidity	NEC 2/3 (surgical): Yes/No
Corrected gestational age:	Apgar score at 5min:	Required Mechanical ventilation: Yes/No	Booking bloods: Rh: positive/negative RPR: -/+	BPD: Yes/No
Birth weight	Resuscitation at birth: Yes/ No	Age of outcome:	Chorioamnionitis Yes/No	ROP: Yes/No
Head circumference:	BMV/CPR/drug use:	feeding: Formula or breastmilk	PROM: Yes/No	Late-onset sepsis: Yes/No
Length(cm):	Age of admission:	Maternal RVD:-/+	Diabetes Mellitus: Yes/No	PDA: Yes/No

Appendix D: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr Nonceba Amelia Thambe

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180710

NAME: (Principal Investigator)	Dr Nonceba Amelia Thambe
DEPARTMENT:	Paediatrics and Child Health Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A review of factors associated with prolonged hospital stay in a tertiary hospital in South Africa
DATE CONSIDERED:	27/07/2018
DECISION:	Approved Unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Daynia Ballot and Dr Tanusha Ramdin
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/08/2018

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

DECLARATION OF INVESTIGATORS

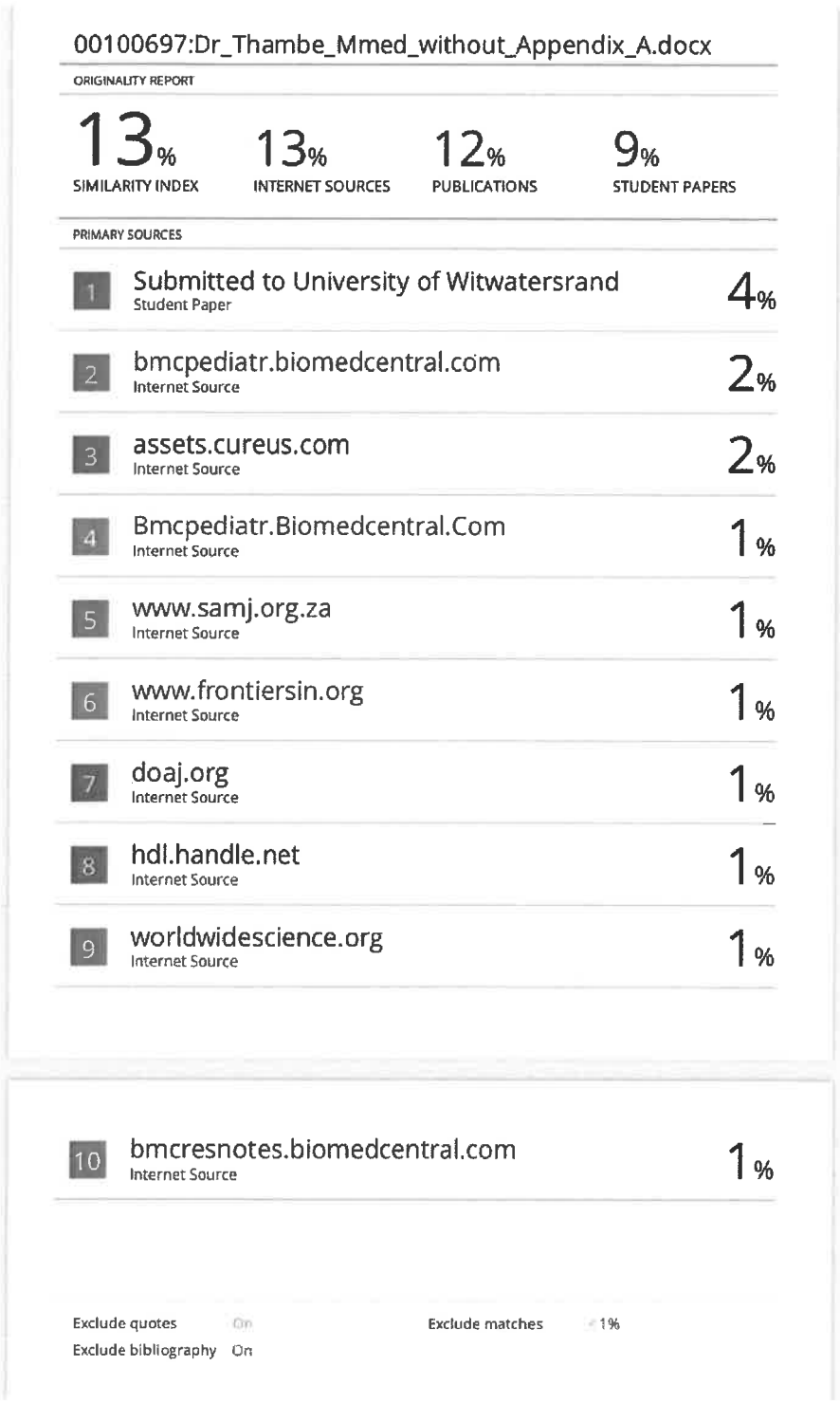
To be completed in duplicate and ONE COPY returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193. University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I agree to submit a yearly progress report. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in July and will therefore be due in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix E: Turnitin report



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