DURATION OF HOSPITAL STAY AND FACTORS ASSOCIATED WITH PROLONGED HOSPITAL STAY IN VERY LOW BIRTH WEIGHT INFANTS SURVIVING TO HOSPITAL DISCHARGE

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the Branch of Paediatrics

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DECLARATION

I Rugare Mahovo declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in the Branch of Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

(Signature of Candidate)

_____09th _____day of _____June_____2020_____

DEDICATION

To

my mother

Florence Mahovo

Who made this dream a reality.

PRESENTATIONS

1. Witwatersrand Paediatrics Research Day: 26 October 2018

2. 38th Conference on Priorities in Perinatal Care in Southern Africa Hartenbos, Western Cape: 15 March 2019

ABSTRACT

***Background*:** Ongoing care of surviving very low birth weight infants (VLBWI) is associated with increases in medical costs. Thus, knowing their length of hospital stay (LHS) will assist in counselling parents and budgeting for their neonatal care.

***Objective*:** To determine the LHS among VLBWI surviving to hospital discharge and factors associated with prolonged LHS.

***Methods*:** This was a retrospective descriptive study performed at Chris Hani Baragwanath Academic Hospital, South Africa. Records of VLBWI who survived to hospital discharge between January 2015 and October 2016 were reviewed. Data on maternal and infant characteristics, morbidities and LHS were recorded. Comparison between those with and without prolonged LHS as defined by being discharged beyond 41 weeks of postmenstrual age was performed.

***Results*:** Records of 435 VLBWI who survived to hospital discharge were reviewed. Their mean birth weight and gestational age were 1234±192 grams and 30±2 weeks, respectively. The median duration of LHS was 39 days, with a range of 11 to 183 days. The LHS increased proportionally with decreasing gestational age or birth weight. Thirty-four VLBWI (7.82%) had prolonged duration of hospital stay. On multiple logistic regression analysis factors associated with prolonged LHS were gestational age (OR: 2.01; 95% CI 1.6-2.61), chronic lung disease (OR: 9.40; 95% CI 2.53-34.72), and nosocomial infections (OR: 31.86; 95% CI 6.75-150.3).

***Conclusions*:** The median LHS stay for the VLBWI was noted to be 5.5 weeks (39 days) and neonates with morbidities, namely chronic lung disease and nosocomial infections are more likely to have prolonged LHS**.**

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ABBREVIATIONS

ANC	antenatal care
BBA	born before arrival
BPD	bronchopulmonary dysplasia
CHBAH	chris hani baragwanath academic hospital
CLD	chronic lung disease
CMV	conventional mechanical ventilation
Cpap	continuous positive airway pressure
DBM	donor breastmilk
EBM	expressed breastmilk
ELBW	extreme low birthweight
EONS	early onset neonatal sepsis
GA	gestational age
HIC	high income country
HFOV	high frequency oscillation ventilation
HIE	hypoxic ischaemic encephalopathy
IQR	interquartile range
KMC	kangaroo mother-care
LHS	length of hospital stay
LMIC	low middle-income country
LONS	late onset neonatal sepsis
NEC	necrotising enterocolitis
NICU	neonatal intensive care unit
SD	standard deviation
SGA	small for gestational age
TPN	total parenteral nutrition
VLBW	very low birth weight
VLBWI	very low birth weight infants
PHS	prolonged length of hospital stay

DEFINITION OF TERMS

Extreme Low Birth Weight : Birthweight less than or equal to 1000grams

Very Low Birth Weight : Birthweight less than or equal to 1500grams

Small for Gestational Age : Birthweight below the 10^{th} percentile for the gestational age

Chronic Lung disease /Bronchopulmonary dysplasia : Requiring oxygen for more than 28 days of life

Early onset sepsis: Presence of sepsis at ≤72 hours of age

Late onset sepsis: Presence of sepsis at ≥72 hours of age

Prolonged Length of hospital stay : Discharge beyond 41 weeks postmenstrual age

PUBLICATION SUBMISSIBLE FORMATTED RESEARCH REPORT

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Introduction

Survival of very low birth weight infants (VLBWI) (birthweight <1500grams) or infants born preterm has improved over the years (1). Though survival rates of VLBWI are higher in high income countries (HIC) than in low middle income countries (LMIC), both groups of countries have shown an in improvement in overall survival of VLBWI over the years (2). The ongoing care of surviving VLBWI is associated with high medical costs (3). Preterm/low birth weight infant stays averaged $15,100, with a mean length of stay of 12.9 days versus $600 and 1.9 days for uncomplicated new-borns in the United States in 2001(4).These high medical costs cause stress and anxiety to families of infants cared for in the private health sector and place more financial demands to the private and public health systems. Thus, both parents and health systems are interested in knowing upfront the financial costs of caring for VLBWI that survive till hospital discharge. The length of hospital stay (LHS) has been used as a surrogate for assessing the medical costs, therefore knowing the average LHS of VLBWI will assist in budget planning and in counselling parents.

Numerous factors have been reported to influence LHS and these include gestational age, birth weight, neonatal morbidities like chronic lung disease, necrotizing enterocolitis and nosocomial infections(5). Local hospital practices or protocols, namely the weight used to discharge VLBWI have been reported to influence the LHS (6-8). Many studies have reported on average LHS of VLBWI, but most of them are from HIC(9). The mean duration of hospital stay for VLBWI in a LMIC in 2013 was noted to be 28.2 (±21.8) days while another study reported the median LHS for VLBW infants to be 44 (28-66) days in UK, a HIC and it was longer for extreme low birth weight (ELBW) (birth weight less than 1000 grams) at 86 (65-102) days (10, 11).The LHS vary from country to country even in HIC. The average length of hospital stay in Italy was reported to be 46.2 (95% CI 44.5-47.8) days while in Sweden it was reported to be 61.0 (95% CI 60.0-62.0) days during the same period, 2006 to 2008 (12).Variations were postulated to be as a result of differing practices and organisation of care for these infants from one country to another. The LHS in LMIC may differ from those reported in HIC, because of differences in local practices. Therefore, in this study we sought to determine the LHS amongst the VLBWI

born and admitted to a public hospital in a LMIC and to determine factors associated with prolonged LHS defined in our study as discharge beyond 41 weeks post menstrual age.(PMA)

Patients and Study Methods

Study design: This was a retrospective descriptive study

Study setting: The study was conducted at Chris Hani Baragwanath Academic Hospital (CHBAH), a public tertiary hospital, in South Africa. The hospital records about 22 000 births per annum and is a referral centre for the local clinics which record 8000 births per annum. It has 185 neonatal beds, of which 66 beds are Level 3 or acute care nurseries. The hospital protocol is that viable (>500grams) neonates requiring resuscitation at birth are offered resuscitation, but because of limited resources non-invasive ventilation is offered only to those weighing ≥750 grams and invasive ventilation only to those weighing ≥900 grams. All VLBWI are offered in-hospital continuous Kangaroo Mother Care once they weigh ≥1000g, are on full feeds and not requiring any treatment. During the study period, the weight used to discharge VLBWI was 1650 grams.

Study Population: All VLBWI born and/or admitted at CHBAH from January 2015 up to October 2016 inclusive and survived to hospital discharge were included in this study. These infants had to have been delivered at CHBAH or were admitted to CHBAH within the first 72 hours of life. Infants excluded were those transferred out of the CHBAH neonatal unit to another hospital and did not return to CHBAH or came back after more than a week or died before discharge. Those who had missing information on discharge were also excluded from the study. The exclusion of infants that were admitted after 72 hours or returned after 1 week or more to CHBAH was to eliminate the effect that varying hospital treatment policies, resources and level of care available may have on the assessment of LHS for these infants and for the overall study population largely treated at CHBAH.

Data Collection: On admission to the neonatal unit, each patient is assigned a paper file into which all available maternal and patient data is entered. Clinical notes of each patient are handwritten into the file on a daily basis before and after the patient has been reviewed by the most senior clinicians assigned to those patients on that day. On discharge, all patients exit the hospital with a discharge letter summarising the patients' stay in the hospital and the files are then stored in the records department in the neonatal unit. Maternal and neonatal data were gathered from these patients' hospital notes and entered into a data collection sheet designed specifically for this study (Appendix B). All data

collected was then entered into an electronic data base using Microsoft Excel (Microsoft Seattle, WA, USA).

Maternal data collected included age, parity and gravidity as well as the HIV status, and neonatal data included gestational age, birthweight, place of delivery, diagnosis and management namely, need for mechanical ventilation, milk feed types, insertion of central lines, parenteral nutrition and whether the infant received phototherapy or not. Those who received mechanical ventilation were categorised into those who received non-invasive mechanical ventilation that is continuous positive airway pressure (CPAP) only and those who received invasive ventilation. The milk feed types were divided into exclusive breast milk, formula feeds and mixed feeds. Information on time to full enteral feeds and the duration on parenteral nutrition, neonatal complications namely chronic lung disease or, necrotizing enterocolitis, and sepsis were collected. Chronic lung disease was defined as need for supplemental oxygen for more than 28 days. Sepsis was defined as growth of an organism considered to be a pathogen from blood and/or cerebrospinal fluid. Nosocomial infection was defined as infection diagnosed after 72 hours of being admitted to the hospital.

Data analysis: Infants were stratified according to gestational age in weeks from ≤26 to ≥35 weeks and according to birth weight in 100 grams from 600 grams to 1400-1499 grams. Continuous data were assessed for normality and where appropriate presented as means (±SD). Non-normal or count data were presented as medians (±IQR). T-tests (normal) and the Mann-Whitney test were used to assess sex differences and differences between categories of length of hospital stay (prolonged vs not prolonged) for continuous data. Differences in proportions were assessed using the Pearson chi-squared test.

In assessing factors associated with prolonged LHS, comparison was assessed using multivariable logistic regression. Included in the regression model were infant characteristics namely gender, gestational age and birthweight, morbidities included were CLD and nosocomial infection and interventions namely ventilation. Variables in the regression model with p-value <0.05 on univariate analysis were considered statistically significant and included in the regression model to assess factors associated with prolonged LHS. All statistical analysis were performed using STATA MP version 13.0 StataCorp LLC, Texas, USA.

Ethics: Permission to conduct the study was acquired from the hospital management and ethical approval was given by the University of the Witwatersrand Human Research Ethics Committee (Medical) (Clearance number M161170).

Sample size estimation: Sample of VLBWI planned to be enrolled in the study was 448, calculated based on the assumption that the standard deviation for the duration of hospital stay will be 27 days similar to that reported by Bannwart et al (5), with a precision of 2.5 days and level of confidence of 95%. Selection of patients was that of a convenient sampling based on the first 448 files of VLBWI who survived to hospital discharge. The sample size was calculated using the formula : ($n=Z^2SD^2/E^2$) where n = sample size, Z= 1.96, SD= standard deviation, E=Precision. This then worked out to $[(1.96x27)/2.5]^2=448$

Results

Of 2204 VLBWI delivered at CHBAH from January 2015 to October 2016, 1661 (75%) survived to hospital discharge.. A total of 435 hospital records were retrieved for the study. Majority of mothers of infants enrolled in this study were of age group 20-35 years, 28.5% were primigravida, and 29.9% were HIV positive (Table 1). Most of mothers (90.6%) gave birth in hospital with only 3.4% giving birth outside a healthcare facility and 92.0% had attended antenatal care.

TABLE 1. MATERNAL CHARACTERISTICS

Variable	Number	Percentage(%)
Maternal Age		
<20	35	8.0
20-35	348	80.0
>35	52	12.0
HIV status		
Positive	130	29.9
Negative	305	70.1
Parity		
<1	124	28.5
1 - 4	305	70.1
>4	6	1.4
Place of Delivery		
Inborn	394	90.6
Local Clinic	20	4.6
Other hospitals	6	1.4
Home	15	3.4
Antenatal care		
Yes	400	92.0
No	35	8.0

Characteristics of VLBWI enrolled in the study and diagnosis on admission are presented in Table 2. The average birth weight and gestational age of infants were 1234±192 grams and 30±2 weeks, respectively. Less than 20% of infants weighed less than 1000 grams or were of gestational age less than 28 weeks, with 85.1% weighing between 1000 and 1499 grams, and 76.6% having a gestational age of 28-32 weeks. Fifty five percent of infants

were males. In addition to being VLBW, respiratory system diagnoses were found to be the most common primary reason for admission to the neonatal unit with 335 (77.0%) of infants being admitted with a diagnosis of respiratory distress syndrome and 75 (17.2%) with transient tachypnoea of the newborn.

TABLE 2. INFANT CHARACTERISTICS

Variable	Number	Percentage (%)
Birthweight(g)		
<1000	65	14.9
1000-1499	370	85.1
Gestational age(weeks)		
<28	50	11.5
28-30	223	51.3
31-32	110	25.3
33-44	52	12.0
Gender		
Male	238	54.7
Female	197	45.3
Admission diagnosis		
Respiratory distress syndrome	335	77.0
Transient tachypnoea of the newborn	75	17.2
Very Low birthweight	17	3.9
Intrauterine growth restriction	4	0.9
Congenital Pneumonia	3	0.7
Congenital Anaemia	1	0.2

Sixty five percent of VLBW required mechanical ventilation, with the common mode of ventilation used being nCPAP (196/284; 69.1%) (Table 3). Only 53.6% were exclusively breast fed on discharge from hospital. Fifty-five percent received parenteral nutrition at some stage during their stay in hospital. The average time to full feeds was 11 (±6) days and the average duration on parenteral feeds was 6 days. Proportion of infants who developed different morbidities during their stay are reported in (Table 3). About a third of patients (152/435; 34.9%) had late onset sepsis and of these patients there was a total of 125 culture confirmed episodes of sepsis with some patients having more than one episode during their hospital stay whilst others were presumed to have late onset sepsis and treated

as such but did not have any positive cultures. Patients who developed chronic lung disease were 139 (32%) of the total population.

TABLE 3. MANAGEMENT AND COMPLICATIONS

Variable	Number	Percentage (%)
Management		
Ventilation (N = 435)		
Yes	284	65.3
No	151	34.7
Ventilation Type (N = 284)		
Non invasive	196	69.1
Invasive	88	31.0
Feed Type (N = 435)		
Expressed Breast Milk	233	53.6
Formula	65	14.9
Mixed	137	31.5
Central Line (N=435)		
Yes	109	25.1
No	326	74.9
Complications		
Chronic Lung Disease (N=435)		
Yes	139	32.0
No	296	68.0
Chronic Lung Disease by Gestation (N=139)		
<32 weeks	125	89.9
≥32 weeks	14	10.1
Early Onset Sepsis (N=435)		
Yes	26	6.0
No	409	94.0
Late Onset Sepsis (N=435)		
Yes	152	34.9
No	283	65.1

Median LHS amongst VLBWI was 39 (29-53) days and average LHS was 45 (±25) days. Duration of hospital stay was inversely proportional to the birthweight and gestational age (Tables 4 and 5). Each birth weight increase of 100 grams was associated with a reduction of LHS by 4.3 days and each gestational age increase of one week being associated with a decrease in LHS by 0.4 days.

TABLE 4. MEDIAN AND AVERAGE LENGTH OF HOSPITAL STAY ACCORDING TO BIRTHWEIGHT

		LHS	LHS
Birth weight in grams	Number	Median (25th -75th centile)	Mean±SD
600-799	6	68 (61-81))	71±14
800-899	22	68 (57-103)	69±40
900-999	37	59 (51-82)	68 ±24
1000-1099	39	50 (45-62)	54 ±17
1100-1199	59	44 (39-62)	54 ±26
1200-1299	83	37 (30-46)	42 ±22
1300-1399	85	32 (27-39)	36 ±14
1400-1499	104	32 (27-39)	30 ±15
All	435	39 (29-53)	45 ±25

TABLE 5. MEDIAN AND AVERAGE LENGTH OF HOSPITAL STAY ACCORDING TO GESTATIONAL AGE

		LHS	LHS
Gestational age in weeks	Number	Median (25th -75th centile)	Mean±SD
≤26	27	64 (50-74)	71 ±38
27	23	49 (41-58)	55 ±27
28	64	47 (34-79)	59 ±32
29	74	43 (35-53)	47 ±21
30	85	38 (30-53)	42 ±16
31	62	35 (25-41)	35 ±15
32	48	31 (27-39)	35 ±16
33	24	27 (23-32)	35 ±27
34	11	27 (23-30)	30 ±16
≥35	17	30 (15-57)	38 ±27
All	435	39 (29-53)	45 ±25

On univariate analysis prolonged hospital stay was associated with lower birth weight ($p<0.001$), need for ventilation ($p=0.012$) or parenteral nutrition ($p=0.009$), and having been diagnosed with necrotizing enterocolitis ($p=0.002$) or nosocomial infection ($p<0.001$) and chronic lung disease ($p<0.001$) (Table 6). On multiple logistic regression analysis, factors associated with prolonged LHS were gestational age (OR: 2.01; 95% CI 1.6-2.61), having a diagnosis of chronic lung disease (OR: 9.40; 95% CI 2.53-34.72), and nosocomial infections (OR: 31.86; 95% CI 6.75-150.3) (Table 6).

TABLE 6. FACTORS ASSOCIATED WITH PROLONGED LENGTH OF STAY

	Total	**Not Prolonged**	**Prolonged**	**Association tests (chi squared or T test)**	**Multivariate analysis**
	N=435 n (%)	N=401 n (%)	N=34 n (%)	p-value	OR (95%CI)
Gestational Age (weeks) Mean ±SD	30±2	30±2	31±4	0.065	2.0(1.6-2.6)
Birthweight (grams) Mean ±SD	1230±190	1240±190	1110±200	<0.001	0.99(0.99-1)
Male	238(54.7)	222(55.4)	16(47.1)	0.350	1.2(0.5-3.3)
Chronic Lung disease	139(32.0)	112 (27.9)	27(79.4)	<0.001	9.4(2.5-34.7)
Ventilation	284(65.3)	257(64.1)	29(85.3)	0.012	0.7(0.2-3)
Nosocomial Infections	152(34.9)	123(30.7)	29(85.3)	<0.001	31.9(6.8-150.3)

Discussion

In this study we report on LHS of VLBWI from a LMIC, where discharge weight is much lower(1650g) than that used in an upper middle income country and HIC (2200g)(13, 14). The findings in this study have shown that the LHS vary with gestational age and birth weight and is inversely related to the birth weight and gestational age. Overall, the average LHS of VLBWI was found to be 45 days, with a median of 39 days. One week increase in gestational age resulted in a decrease in LHS by 0.4 days. A 100g increase in birthweight was associated with 4.3 days decrease in LHS. Factors associated with prolonged LHS were gestational age at birth, a diagnosis of chronic lung disease and nosocomial infections.

Due to improved survival of the preterm infant, research is now focused on models that can be used to predict LHS in this population of patients. Birthweight, gestational age, antenatal and perinatal factors are known to influence the LHS and can be used to estimate LHS (5, 10, 15). There is a paucity of data reporting on the LHS of the VLBWI in the LMIC. The median LHS in VLBWI delivered in Brazil (5), a LMIC, from January 1992 to December 1993, was reported as 45 (35-62) which was just 6 days longer than our observed median LHS of 39 (29-53) and similar to findings in Salford UK whose median LHS for the same population of patients over April 1986 and November 1990 was 44 (28-66) (10).Differences between our study and that in Brazil were most notable among the extremely premature neonates. The mean LHS was 92.2 ($\pm$26.7) in infants weighing <1000g in Brazil compared to 73.1 ($\pm$30.3) in our study. Infants in our study were discharged home once they were ≥1650g and feeding well with no other complications whereas those in Brazil were discharged once they reached a weight of ≥2000g (5). This would account for the longer LHS in the Brazilian study a LMIC similar to South Africa in addition to differences in hospital practices as well as availability and distribution of resources. Similarities were observed when one assessed the overall relationship between birthweight and LHS. The infants born with lower birthweights had longer LHS overall as compared to the babies that higher birthweights in both studies.

A study conducted in HIC including 10 European regions, reported that average LHS of infants with gestational ages between 22+0 and 31+6 was 63.1(±36) days with a median LHS of 55 (interquartile range 40-75).(16). Variation in patient clinical characteristics, patient populations, in hospital morbidities and planning/organisation of discharge as well as lack of availability of home care and step down facilities, resource limitations directing hospital policies may explain the difference in LHS between HIC and LMIC (17). There is evidence that being small for gestational age (SGA) will increase the odds of having shorter LHS (18). In our study, we did not assess for SGA because of unreliability of gestational age. HIC offer advanced interventions like invasive mechanical ventilation to almost all VLBWI and discharge infants when they achieve weights of ≥1800 grams, whereas in our study settings, invasive ventilation is only offered to those weighing above 900 grams and infants are discharged at weights ≥1650 grams because of limited resources. Offering advanced care to all weight groups results in more smaller infants surviving and using higher weights to discharge are the most likely explanations for longer LHS in HIC compared to LMIC. It has been reported that the extremely premature infants have a high risk of mortality and those who survive have a six fold risk of increase in LHS (19) and thus mortality has been inversely correlated to the risk of having prolonged LHS(20).

One of the objectives of our study was to investigate factors associated with prolonged LHS. Knowing that most extremely preterm infants are discharged by 42 weeks postmenstrual age (PMA) (20), we defined prolonged LHS as discharge beyond 41 weeks PMA. Gestational age at birth, development of chronic lung disease or bronchopulmonary dysplasia (BPD) and nosocomial infections was associated with PHS. Gestational age has previously been reported to be a strong predictor of LHS (6, 10, 21, 22) with one study reporting that each day of increase in gestational age was associated with a one day decrease in LHS (6). BPD (oxygen dependency at ≥28days) is known to prolong LHS in the premature neonate. In Israel over a 9-year period (1995 to 2003) the relationship between BPD and LHS in the VLBWI was investigated and they reported that LHS was prolonged if the infant had

BPD (23). It was reported that the adjusted mean LHS of infants <999g without BPD was 89.8 days and 112.9 days for those with BPD. The adjusted mean for LHS for VLBW infants with BPD overall was 84.1 days and 58.1 days for those without BPD. In our study patients with CLD or BPD had mean LHS of 55 days and those without had mean LHS of 39 days and the odds of having PHS were nine-fold higher if a VLBWI had CLD. Another factor that was found to be associated with an increase in risk of prolonged LHS was nosocomial infection with its presence increasing the odds of having PHS by 32 folds. The association between infections and PHS has been reported previously (5). Necrotizing enterocolitis, one of relatively common morbidities of infections has also been reported with PHS (24). Parenteral nutrition was significantly associated with prolonged LHS in univariate analysis (p=0.009) but not in multivariate analysis (OR 0.52 ; 95% CI ;0.15-1.82). This may be due to the increased risk of infection when on parenteral nutrition or perhaps the infants were already too sick to take oral feeds and therefore required parenteral nutrition. We did not compare the risks of morbidity in those that were exclusively breastfed against those that received cow's milk formula or mixed feed in this study though this has been studied elsewhere (25).

The LHS in LMIC countries has not been well studied and what this study adds is information in an area where there is paucity of published data in the literature. The information that we have gathered in this study will allow parents to better understand the approximate date of discharge of their premature infants. Continued counselling can be given to parents whose infants may have any morbidities as these parents and caregivers can be counselled about the high likelihood that their infant may have a more prolonged length of stay than as originally estimated. This will allow them to plan accordingly and will allay any anxiety or fear that the parents may have should their infant not be discharged around the timeframe initially advised. Hospital managers can now plan according to these findings and will direct budgets towards prevention and treatment of morbidities associated with prolonged LHS.

The strength of this study was that it was conducted at one tertiary centre which has a large number of VLBWI who stay in the same centre from admission to discharge with negligible outward transfer rates and has uniform policy with regards to labour room practices, management protocols and discharge criteria so this enabled us to make the assessment of LHS without having to account for variations that may be seen in different units that may have differing practices and protocols to our neonatal unit. Our study population was a good representation of the VLBWI that one encounters in a LMIC as it is a state hospital. We were able to explore for factors associated with PHS.

Limitations to our study was the fact that it was a retrospective study. Files were manually retrieved from the archives and this was a lengthy exercise, thus we were not able to enrol the calculate sample size of 448 as the study period came to an end, but we were able to retrieve 97% of the files. Again, being a retrospective study, it was difficult to determine as to how was the gestational age determined as the method of determination was not recorded, thus unable to rely on its accuracy. The other limitation is that maternal details were often incomplete, and literature has shown that including in-hospital comorbidities with antenatal and perinatal factors in estimation of LHS gives more clinically applicable and accurate data to determine LHS for future hospital planning and parental counselling (19).

Conclusion

The median LHS stay for the VLBWI in this study was 39 days (5.5 weeks) with a range of 11 to 183 days and the average LHS of 45 days. Birthweight can be used as a predictor of LHS, but gestational age may not be so accurate in our setting. Neonates with morbidities stay longer in the hospital. Chronic lung disease and nosocomial infections are significantly associated with prolonged LHS. Infection control measures and lung protective ventilation strategies are recommended to decrease the LHS in these VLBWI.

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APPENDICES

APPENDIX A : PROTOCOL

DURATION AND DETERMINANTS OF HOSPITAL STAY IN VERY LOW BIRTH WEIGHT INFANTS SURVIVING TO HOSPITAL DISCHARGE

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ABBREVIATIONS

ANC	antenatal clinic
BW	birth weight
CHBAH	chris hani baragwanath academic hospital
CW	current weight
DTD	date to discharge
ENCPAP	early nasal positive airway pressure
ELBW	extreme low birth weight
GA	gestational age
IQR	interquartile range
KMC	kangaroo mother-care
LOS	***length of hospital stay***
NEC	necrotising enterocolitis
NICU	neonatal intensive care unit
NNJ	neonatal jaundice
SD	standard deviation
SGA	small for gestational age
TICU	transitional intensive care unit
TPN	total parenteral nutrition
VLBW	very low birth weight

BACKGROUND

Survival of infants with very low birth weight (VLBW)(birth weight <1500 grams) or infants born preterm has improved over the years. In the tertiary hospitals in Johannesburg, South Africa the survival rate in VLBW infants has been reported to be 71-74% (2, 26). Though VLBW infants account for only 3% of total live births, they have been reported to constitute a significant proportion (21%) of total admissions in one of the neonatal units in Johannesburg hospitals (2), therefore they place high demands on specialist neonatal services.

Clinical care of VLBW infants is labour intensive and is associated with a prolonged hospital length of stay (LOS). Although some of the VLBW infants are discharged within a few weeks, some remain critically ill in neonatal intensive care units (NICUs) while some remain chronically ill in the neonatal unit for weeks or months (5, 24). The long duration of hospitalization associated with VLBW or preterm infants compared to term infants contributes significantly to high hospital costs in neonatal care and is also associated with psychological stress in parents and caregivers (3). Each additional day of inpatient stay bears a cost on the health system, therefore the improved survival is more likely to contribute to increased hospital cost (27).The length and cost of hospital stay are both major concerns for parents, healthcare providers and healthcare managers. Thus, it is important to assess the hospital LOS of VLBW or preterm infants and determinants thereof as this can then be used to calculate costs associated with caring for VLBW or preterm infants during their hospital stay. A study done in California over a one-year period from January to December 1996 concluded that prematurity is in itself a risk factor for elevated hospital costs and that there is a direct relationship between birth weight, gestational age (GA) and the hospital cost of care, with an increase in cost being shown with every decrement in either one of the two variables (3). Some population-based studies have shown that VLBW infants account for less than 1% of new-borns but 35% of costs, and that hospitalization costs for VLBW infants were more than twice those for infants weighing between 1500 and 2500g (4, 28).

The LOS appears to vary from country to country. The median LOS for VLBW infants has been reported to be 44 days with an interquartile range (IQR) of 28-66 days in the UK, and it was longer (86 days; IQR, 65-102 days) for extreme low birth weight infants (birth weight <1000g) compared to those weighing 1251 to1500g (30 days; IQR, 22-43 days). In the EuroHOPE study, a large multicentre study conducted in Europe from 2006 to 2008, the LOS in Italy was reported to be 46.2 days (95% CI, 44.5-47.8 days) while in Sweden it was reported to be 61.0 days (95% CI, 60.0-62.0 days) during the same period (12). In Finland, LOS for VLBW infants born between

2000 and 2003 was 53 days (IQR, 38-76 days) (6). The variation in patient characteristics observed in the EuroHOPE study was assessed to have impacted on the management and care of neonates and ultimately the LOS which was then translated to resource utilisation (12).Extremely long hospitalisations (> 6 months or 179 days) have been documented in the USA (24).

Several factors are reported to influence the LOS. These include perinatal risk factors, infant characteristics and diagnosis, and local hospital practices or protocols. Perinatal risk factors include types of delivery and delivery complications (5, 29). Infant characteristics include GA and birth weight, while the medical diagnosis include neurological complications at birth or during hospital stay, chronic lung disease, necrotizing enterocolitis and infections (5, 30, 31). Local hospital practices or protocols might also influence the LOS (6-8).

Delivery room protocols such as early nasal continuous positive airway pressure (nCPAP) or early kangaroo-mother care (KMC) have been noted to decrease the LOS, and lead to good outcomes and less expense in the VLBW infant (2, 32). Discharge protocols which vary among neonatal units are noted to contribute to variations in LOS observed between different regions of a single country (6). A number of neonatal morbidities namely chronic lung disease, NEC, and late onset sepsis have been noted to be recurring factors in the literature linked to prolonged LOS defined in one study as >42 weeks' postmenstrual age for those infants born at ≤ 28 weeks' GA (20).

A South African study, conducted in a Private Sector health care facility, interrogated the factors which predicted LOS and mortality in preterm infants admitted to NICU (33). Birth weight, mode of delivery, maternal ethnicity, head circumference and Apgar scores were the variables tested. Increases in both Apgar scores at one minute and birth weight had a good correlation with shortened LOS in this study population. Other studies propose GA to be the most significant predictive factor in determining LOS with an inverse relationship to the LOS (33). (2). (34) .

Treatments such as multiple doses of surfactant, postnatal steroids and H_2 Blockers, when given to infants, indicate a higher likelihood of a prolonged LOS (35). Models to predict the LOS use these indicators, and severity of illness scores among other factors in formulating some of these models. A retrospective study conducted in the USA at a large academic children's hospital from June 2007 to May 2013 formulated a model that could be used to try and predict the date to discharge (DTD) from NICU (36). If one could predict date to discharge (DTD), then one could prepare

accordingly for the impending discharge to prevent a delay in discharging a patient that was otherwise medically fit for release from hospital. The study highlights some of the factors that influence DTD and, indirectly, LOS. Of note, amount of oral feeds, GA and birth weight were some of the predictive factors in the determination of DTD. An unexpected finding in this study was that early enteral feeding, which had the greatest positive impact on DTD from the NICU and invariably LOS, had the greatest effect on DTD across all the patient categories, regardless of the subpopulation the patient belonged to. These subpopulations comprised premature infants, post cardiac surgery infants, gastrointestinal and neuro-surgical infants (36).

Nutritional variables such as late enteral feeding and lower rates of weight gain increased the odds of a prolonged hospital stay. Provision of breast milk to VLBW infants has been associated with reduction in the incidence of NEC and late onset sepsis, and fewer days required to achieve full enteral feeding (37). Exclusively breast fed infants are also found to have shorter and less costly hospital stays with less feeding intolerance when compared to those fed a combination of breastmilk and cow's milk formula or cow's milk formula alone (25).

Premature infants have an immature immune system, and thinner more permeable skin which predisposes them to infection. They are prone to ventilator-associated pneumonia and line-associated infections due to the increased likelihood of such interventional therapies being performed during their stay in hospital resulting in late onset sepsis which is a risk factor for prolonged LOS (36, 38).
The length of hospital stay at CHBAH and determinants associated with prolonged hospital stay at CHBAH are not known. Factors which prolong or shorten the LOS can be evaluated and considered when planning or putting institution-specific protocols in place, planning budgets around neonatal care and counselling mothers antenatal and postnatal. Therefore length of hospital stay for premature infants can be used as a surrogate for assessing the resource utilisation of neonatal units and indirectly assess whether the resources are being utilised efficiently, appropriately and effectively (34). The LOS has also been put forth as a guiding tool when assessing the appropriateness of discharge of a high risk neonate (34).

Determination thereof may assist policy makers at a national level and protocol contributors at a hospital level in determining what variables exist which negatively affect LOS and whether current protocols allow for effective resource utilisation and appropriate discharge of high-risk neonates. Determination of factors which impact on LOS may assist in the counselling of parents regarding estimated duration of stay of these infants. This may assist parents to better prepare themselves for likely

hospital outcomes of their preterm infants. Great financial burden is placed on some of the families of these infants. Parents and caregivers may need to make alternative arrangements within a specified time frame with regards to continued care for the patient's siblings and other dependants. Determining better estimates of the LOS will assist these families as it provides a time frame for them to reference when making the necessary arrangements, be it with their employers or other parties involved.

OBJECTIVES

1. To determine the hospital length of stay (LOS) of VLBW infants surviving to hospital discharge at CHBAH.
2. To determine the proportion of VLBW infants with prolonged LOS defined as stay beyond 41 weeks postmenstrual age.
3. To describe the common morbidities in VLBW infants and identify those associated with prolonged LOS.
4. To describe determinants of prolonged hospital stay

METHODS

Study Setting

Chris Hani Baragwanath Academic Hospital (CHBAH) is the third largest hospital in the world. It is in Soweto, south of Johannesburg. It is one of 40 Gauteng provincial hospitals and is one of the teaching hospitals for the University of Witwatersrand. The hospital offers maternity and neonatal services to the Southern Johannesburg area and is a referral centre for the clinics in the Soweto area and for provincial hospitals in southern Gauteng for patients who need surgical services. The neonatal department of the hospital statistics for January 2015 to December 2015 recorded a total of 18513 live births of which 758 (4.0%) were VLBW infants. All VLBW infants are admitted to one of the neonatal wards (neonatal intensive care unit, transitional care unit and ward 66) depending on their birth weight and severity of illness. They are transferred to a step-down facility that offers 24-hour KMC if they weigh more than 1000g and are on full feeds, not on oxygen and gaining weight. Infants are considered fit for hospital discharge if medically stable, on full oral feeds and at least 1650g in weight.

Study design and population

This will be a retrospective descriptive study**.** All VLBW infants born and/or admitted at CHBAH from January 2015 up to and including October 2016 will be eligible for enrolment to this study.

Inclusion criteria:

1. VLBW infants (<1500g) that are born and/or admitted at CHBAH within the first 72 hours of life.
2. VLBW infants that survive to hospital discharge

Exclusion criteria

1. Infants transferred out of the CHBAH neonatal unit to another hospital, who did not return to CHBAH.
2. Infants transferred to another hospital for a period of ≥1 week before returning to CHBAH.
3. Infants who are missing information on date of discharge home.

Sample Size Estimation

Sample of VLBWI planned to be enrolled in the study will be 448, calculated based on the assumption that the standard deviation for the duration of hospital stay will be 27 days similar to that reported by Bannwart et al (5), with a precision of 2.5 days and level of confidence of 95%. Selection of patients will be that of a convenient sampling based on the first 448 files of VLBWI who survived to hospital discharge. The sample size was calculated using the formula: ($n=Z^2SD^2/E^2$) where n = sample size, Z=1.96, SD= standard deviation, E=Precision. This then worked out to $[(1.96x27)/2.5]^2=448$.

Definitions

Length of hospital stay- Differences in days between date of discharge and date of admission (date of discharge subtract date of admission)
Age at onset of feeds: Difference between date of initiating feeds and date of birth
Duration on parenteral nutrition: Difference between date of initiating parenteral nutrition and date of stopping parenteral nutrition, and sum of all days on parenteral nutrition
Average weight gain: Difference in discharge weight and weight regained to at least birth weight after the initial expected weight loss post-delivery.
Presence of sepsis: Early (≤72 hours of age) and late (≥72 hours) culture negative sepsis (started on antibiotics and CRP>20), and early (≤72 hours of age) and late (≥72 hours) culture positive sepsis (positive blood or cerebrospinal fluid or urine culture with organisms other than contaminants).
Hypoxic ischaemic encephalopathy: Required resuscitation (bag mask ventilation or more), base deficit >12 within 1 hour of delivery with a diagnosis of HIE 2 or 3 in the hospital records.
Intraventricular haemorrhage and its grades: As recorded in the hospital files.

Necrotizing enterocolitis (NEC): A diagnosis recorded as definite NEC or stage 2 or 3 NEC.
Chronic lung disease/ Bronchopulmonary dysplasia: Requiring supplemental oxygen for more than 28 days.

Study Procedures

Data collection

Data on each infant admitted to the CHBAH neonatal unit has been routinely collected and entered into an electronic database using Microsoft Excel (Microsoft, Seattle, WA, USA) and REDCap (Vanderbilt University, Nashville, TN, USA). For the purposes of this study, data will be abstracted from the departmental electronic database, with permission, and additional data will be obtained from archived patient folders. Data relevant to this study will be entered into a data collection sheet (Appendix 1), and then captured into a study-specific Excel spreadsheet for further analysis. Data collected will include all eligible patients born from January 2015 to December 2015.

Data analysis

Infants will be stratified according to gestational age in weeks from < 26 weeks, 27 w, 28 w, 29w, 30w, 31w, 32w, 33w, 34w and 34-36w and according to birth weight in 100 gram differences from <700 grams to 700-799 g, 800-899g, 900-999g, 1000-1099g, 1100-1199g, 1200-1299g, 1300-1399g and 1400-1499g. An average with standard deviation and median with ranges will be used to summarize the duration of hospital stay for each group as stratified above. Different medical managements and diagnoses on discharge will be presented as frequencies and proportions. Anthropometric characteristics, clinical management and medical diagnosis will be compared between those with prolonged hospital and those who did not using the Chi-squared or Fisher's exact test for categorical variables and Student t-test or Whitney-Mann U test for continuous variables to determine for statistical differences. A difference with a p-value <0.05 will be considered statistically significant.

ETHICS

Submissions for approval of the study will be made to the University of the Witwatersrand Human Research Ethics Committee (Medical). Thereafter, approval will be sought from the Medical Advisory Board at CHBAH and the head of department of paediatrics at CHBAH to conduct the study. Patient names will not be used in this study except to retrieve files to collect information that will be required in the study. There will be no interventions, therapies or clinical trials involved in this study, so a waiver of parental informed consent will be motivated for.

IMPLICATIONS OF THE ANTICIPATED STUDY FINDINGS

Findings in this study will assist in assessing the burden of prematurity or VLBW infants in the current system and will also assist in counselling mothers about the expected duration of stay of their infants. Determinant factors associated with

prolonged hospital stay will assist in emphasizing on the importance of preventing the implicated factors, therefore reviewing the current protocols around prevention and management of these factors.

ANTICIPATED LIMITATIONS

Retrieval of some patient files may be lengthy. Some files may be lost and tracing these patients may prove to be difficult. Excel database backup of patients treated in the Neonatal Unit from January 2006 to end April 2016 will be available for analysis, however.

BUDGET

There will be no external funding or sponsorship for this study. The costs for materials used in this study will be carried solely by the investigator.

STUDY TIMELINE

	Jun 2016	Jul	Aug	Sept	Oct	Nov	Dec	Jan 2017	Feb	Mar	Apr	May	Jun
Literature review	■	■											
Protocol preparation	■	■											
Protocol Assessment	■	■											
Ethics Application			■										
Data collection								■	■				
Data Analysis									■	■			
Write up-thesis										■	■	■	
Write up-paper											■	■	■

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APPENDIX B : DATA COLLECTION SHEET

STUDY NUMBER:

1.MATERNAL DETAILS

AGE :_____ BOOKED: YES/NO

PARITY :_____ HIV RESULT: POS/NEG/UNK

GRAVIDA :_____ HAART : YES/NO/UNK

GESTATIONAL AGE (OBGYN) :____ BIRTHPLACE: BARA/LOCAL CLINIC/OTHER

2.INFANT DETAILS

AGE (CHRONOLOGICAL): _____ weeks

GESTATIONAL AGE (BALLARD): _____weeks

BIRTHWEIGHT: _____g

SEX : MALE/FEMALE

3.ADMISSION DIAGNOSIS:

4.MANAGEMENT

MODE VENTILATION: YES/NO

LINES: UVL/UAL/PICC

5.NUTRITION

TYPE OF FEED: EBM/DBM/COWS MILK ITN: YES/NO

DATE OF INITIATION OF FEEDS: DATE OF INITIATION :

AGE AT FULL ENTERAL FEEDS: TOTAL DAYS ON ITN :

6.MORBIDITY

EARLY ONSET SEPSIS: YES/NO IF YES: CULTURE CONFIRMED/PRESUMED SITE : Blood and/or Cerebral Spinal Fluid

LATE ONSET SEPSIS : YES/NO IF YES: CULTURE
CONFIRMED/PRESUMED SITE : Blood and/or Cerebral Spinal Fluid

NEC STAGE 2: YES/NO

NEC STAGE 3: YES/NO

ANY SURGERY : YES/NO

HIE STAGE 2: YES/NO BPD: YES/NO

HIE STAGE 3 : YES/NO NNJ : YES/NO

OTHER MORBIDITIES :

7.OUTCOME

WEIGHT AT DISCHARGE:

POST-CONCEPTUAL AGE AT DISCHARGE:

DISCHARGE DIAGNOSIS :

TOTAL DURATION OF HOSPITAL STAY

APPENDIX C : ETHICS CLEARANCE CERTIFICATE

R14/49 Dr Rugare Mahovo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M161170

NAME: (Principal Investigator)	Dr Rugare Mahovo
DEPARTMENT:	Paediatrics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Duration and Determinants of Hospital Stay in Very Low Birth Weight Infants Surviving to Hospital Discharge
DATE CONSIDERED:	25/11/2016
DECISION:	Approved unconditionally
CONDITIONS:	Title Change (17/02/2017)
SUPERVISOR:	Prof Sithembiso Velaphi
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	01/02/2017

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in November and will therefore be due in the month of Novemper each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 1/03/2017

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX D : TURNITIN REPORT

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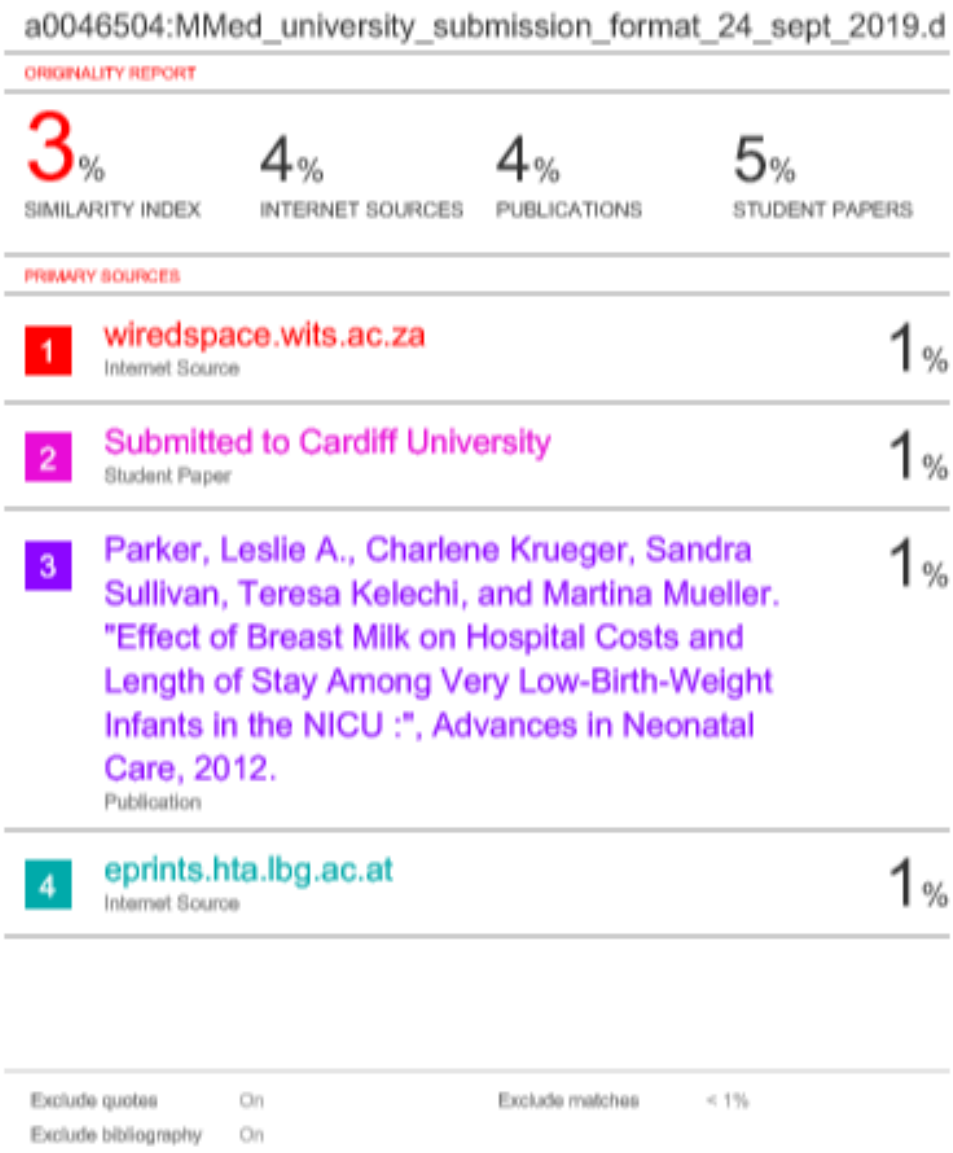

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ORIGINALITY REPORT

3%	4%	4%	5%
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PRIMARY SOURCES

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3	Parker, Leslie A., Charlene Krueger, Sandra Sullivan, Teresa Kelechi, and Martina Mueller. "Effect of Breast Milk on Hospital Costs and Length of Stay Among Very Low-Birth-Weight Infants in the NICU :", Advances in Neonatal Care, 2012. Publication	1%
4	eprints.hta.lbg.ac.at Internet Source	1%

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Exclude bibliography	On		

APPENDIX E: JOURNAL AUTHOR GUIDELINES

Journal format :Journal of Pediatrics, Perinatology and Child health.

Cover letter: The articles must always be accompanied by a cover letter, stating the type of the article and that the article submitted is neither published nor is under consideration by any other journal. It should also have a statement of the main point of the article. Names, affiliations, and e-mail addresses of five potential referees can be mentioned.

The tables, figures with legends and the supplemental material (if any) must be cited appropriately in the text and should be submitted in separate word files

- The submission has not been previously published, nor is it before another journal for consideration (or an explanation has been provided in Comments to the Editor).
- The submission file is in OpenOffice, Microsoft Word, or RTF document file format.
- The text is single-spaced; uses a 12-point font; employs italics, rather than underlining (except with URL addresses); and all illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end.

Main submission:

1. The title of the article must be with relation to the content and should not be similar to any other published article.
2. All the contributing author names must be mentioned with their affiliations and email addresses. The corresponding authors telephone number is requested in case of any quick correspondence required in accordance with the submission.
    A. Research articles must contain an abstract, keywords, introduction, material & methods, results & /or discussion and a conclusion
    B. Review articles must contain abstract, keywords and the main text. Conclusion is optional
    C. All the remaining types of articles have the abstract, keywords and conclusion as optional
        i. Abstract must summarize the concept being addressed, how the study was performed, the primary results and the authors brief conclusion from these results. It should be not more than 250 words.
        ii. Keywords are the highlights of the article and be from 4-10 in number.
        iii. Abbreviations, if any must be mentioned.
        iv. Introduction must be a concise review of the subject area and the rationale for the study
        v. Materials & Methods must include all the methods used in the study in sufficient detail so that other researchers would be able to reproduce the research. When established methods are used, the author need only refer to previously published reports; however, the authors should provide brief descriptions of methods that have been modified. Identify all materials used. The populations for research involving humans should be clearly stated and enrollment dates provided.

vi. Results must be in a proper sequence with reference to tables, figures, and supplemental material as appropriate.
vii. Discussion must include the new and important findings of the study as well as any conclusions that can be drawn. The Discussion must analyze the present data with the previous findings. Limitations of the experimental methods should be indicated, as should implications for future research. New hypotheses and clinical recommendations are appropriate and should be clearly identified.

3. The tables, figures with legends and the supplemental material (if any) must be cited appropriately in the text and should be submitted in separate word files
4. Acknowledgements for the work can be mentioned. Funding if any, must be clearly mentioned in the acknowledgement section
5. Conflicts of interest must be clearly stated
6. References of all the citations mentioned in the text must be given along with the author name, year of publication and the title of the article.
   E.g: Aleksandra M, Stokic E, Plecas-Duric A, Popovic D, Ilincic B. Is Qtc Interval Associated With Insulin Resistance in Metabolic Syndrome?. Cardiology and Cardiovascular Medicine 1 (2016): 26-36.