DISEASE PROFILE AND OUTCOMES OF NEONATES ADMITTED TO THE PAEDIATRIC INTENSIVE CARE UNIT AT THE RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL IN CAPE TOWN, SOUTH AFRICA

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Table of contents

TABLE OF CONTENTS **2**

DECLARATION **3**

ABSTRACT **4**

ACKNOWLEDGMENTS **5**

LIST OF TABLES **6**

LIST OF FIGURES **7**

CHAPTER 1: INTRODUCTION **9**

CONTEXT *9*
ETHICAL CONSIDERATIONS *12*
AUTHOR GUIDELINES OF THE JOURNAL OF PAEDIATRICS AND CHILD HEALTH *13*
REFERENCES *14*

CHAPTER 2: MANUSCRIPT **16**

INTRODUCTION *16*
METHODS *16*
RESULTS *17*
DISCUSSION *19*
CONCLUSION *22*
REFERENCES: *23*
TABLES AND FIGURES *25*

APPENDIX A: AUTHOR GUIDELINES FOR THE JOURNAL OF PAEDIATRICS AND CHILD HEALTH **31**

APPENDIX B: VARIABLES COLLECTED **36**

APPENDIX C: ETHICS APPROVAL **39**

APPENDIX D: RCWMCH PERMISSION LETTER **40**

APPENDIX E: DISTRIBUTION OF ADMISSIONS BY MONTH AND SEASON **41**

DECLARATION

I Linda Jane Riemer hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Aim

Neonatal healthcare is an area of focus in reducing global child mortality. Unwell neonates are usually managed in neonatal intensive care (NICU) but sometimes are admitted into paediatric units (PICU). This study aimed to describe the profile of neonates admitted to a South African PICU and to identify risk factors associated with mortality.

Methods

Patients with a post-menstrual age of <44 weeks, admitted to the PICU between November 2018 and October 2019, were included in a prospective observational study. Associations with mortality were evaluated with univariate and multivariable logistic regression analyses.

Results

266 neonates (median birthweight 2210g (IQR 1397 – 2995g); chronological and post-menstrual age at admission 11 days (IQR 2 – 28) and 38 weeks (35 – 40) respectively were included, accounting for 18.4% of PICU admissions. The largest referral source were tertiary NICUs. Surgical admissions accounted for most patients. Congenital abnormalities occurred in 50.4% of the cohort. Neonatal mortality at ICU discharge was 10.9% compared to 3.8% in older patients (OR 3.08. CI 1.89 – 5.02; p = <0.001). Congenital abnormalities were the most common group of conditions associated with mortality, followed by NEC and infections. After logistic regression analysis the only variables independently associated with death/palliation were oscillatory ventilation, TPN and feeds received.

Conclusion

We describe a cohort of predominantly term and normal birth weight neonates but also includes ex-premature babies. Closer analysis of neonatal referral pathways can build on this study. All of this data can help policymakers and unit managers improve neonatal care.

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LIST OF TABLES

Table 1: Cohort Demographics 25
Table 2: PICU interventions, complications, investigations and outcomes 26
Table 3: Variables associated with death/palliation after logistic regression analysis 27

LIST OF FIGURES

Figure 1: Comparison of total admissions and survival across birth weight categories. 27
Figure 2: Comparison of total admissions and survival across categories of 'age on admission'. 28
Figure 3: Comparison of total admissions and survival across PMA on admission categories. 28
Figure 4: Underlying causes of death 29
Figure 5: Proportion of underlying causes of death by Post-menstrual age group 29
Figure 6: Proportion of congenital abnormalities per system 30

ABBREVIATIONS

RCWMCH	Red Cross War Memorial Children's Hospital
PICU	Paediatric Intensive Care Unit
NICU	Neonatal Intensive Care Unit
SNAP	Score for Neonatal Acute Physiology
PMA	Post-menstrual Age
SD	Standard deviation
IQR	Interquartile Range
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
NEC	Necrotising Enterocolitis
NIV	Non-invasive Ventilation
MV	Mechanical Ventilation
HFOV	High Frequency Oscillatory Ventilation
CPAP	Continuous Positive Airway Pressure
TPN	Total Parenteral Nutrition
EBM	Expressed Breast Milk
AKI	Acute Kidney Injury
RRT	Renal Replacement Therapy
FFP	Fresh Frozen Plasma
VIS	Vasoactive Infusion Score
PIM	Paediatric Index of Mortality
SNAPPE	Score for Neonatal Acute Physiology with Perinatal Extension
KDIGO	Kidney Disease Improving Global Outcomes
VA ECMO	Venoarterial Extracorporeal Membrane oxygenation
CT	Computed Tomography
MRI	Magnetic Resonance Imaging

CHAPTER 1: INTRODUCTION

CONTEXT

Neonatal care is a key area of focus in reducing global under-five child mortality. Driven by the United Nations Millennium Development Goals, neonatal mortality has improved, falling from 37/1000 live births in 1990 to 17/1000 in 2019.(1) The rate of decline however has been slow when compared to older infants and children. There is an increased call to focus on neonatal deaths as a cause of mortality in children under five.

Globally, sub-Saharan Africa has the most neonatal deaths (42%) followed by Central and Southern Asia (37%)(1). The Western Cape province in South Africa accounts for 5.2% of the under-five mortality nationally and has the lowest under-five mortality of the nine provinces at 24.2/1000 live births (2). The city of Cape Town has a population of four million people, of which approximately 330 000 are under the age of five years (3). It falls into the highest socioeconomic income quintile in South Africa but even so, roughly 75% of the population are dependent on state funded health care (4). Sub-Saharan Africa is also synonymous with a high burden of disease due to Human Immunodeficiency Virus (HIV). The HIV prevalence within the Western Cape province in 2019 was reported to be 17% and the HIV vertical transmission rate was last reported as 3.5% (5, 6). The Red Cross War Memorial Children's Hospital (RCWMCH) provides a state funded health care service, offering regional, tertiary, and quaternary levels of care. Additional funding is generated by a non-profit organisation called The Children's Hospital Trust. The patients are primarily referred from district, regional and tertiary level facilities within four of the city's eight health sub-districts. Due to its many paediatric sub-specialities and being only one of two dedicated paediatric hospitals in Sub-Saharan Africa, it also takes referrals from other provinces (7). Almost all the patients that are managed are referrals from within the relevant health sub-districts, but the hospital does see walk-in patients in the emergency department if they are triaged and found to be too unwell to down refer.

Neonatal care is dependent on functional health facilities, skilled health care workers and life-saving drugs and equipment, as stated in the 2018 United Nations Children's Fund report (8). There are limited neonatal and paediatric intensive care services in South Africa (9). In some settings where resources are limited, specialised equipment, monitoring and skills are combined into a unit that functions as both a neonatal and paediatric intensive care space. A typical neonatal unit admits premature, low birth weight newborns who need specialised care, or critically unwell term babies with complications such as birth asphyxia, meconium aspiration or pulmonary hypertension(10, 11). In the Western Cape, standard neonatal care is provided in neonatal units at district, secondary and tertiary levels. At district level babies receive standard inpatient care which includes incubators, oxygen, intravenous fluids, or tube feeding, and basic monitoring of oxygen saturation levels, glucose, and bilirubin. At this level, care is provided by family physicians and general practitioners. Secondary level care provides a high care space for babies that require more intensive cardio-respiratory monitoring, non-invasive ventilation, and short-term invasive ventilation. These units are typically managed by general paediatricians. Tertiary services offer highly specialised neonatal care by sub-specialist doctors and nurses including neonatologists, paediatric cardiologists and paediatric surgeons. Advanced ventilation, haemodynamic support, total parenteral nutrition, therapeutic cooling, and neurological monitoring are available (12). There are two tertiary units in the drainage area of the RCWMCH. The Groote Schuur unit admits 3200 of the 40 000 neonates born annually in the Metro West district of Cape Town. More than 15% of the admissions are less than 1500 grams and 5% less than 1000 grams at birth. They report a 91% survival rate for neonates weighing between 1000g and 1500g at birth (13, 14). The unit also admits a significant population of term neonates with birth asphyxia, and have published several studies on this population (15, 16). The neonatal mortality rate for the area that RCWMCH drains is reported as 8.2/1000 live births but In the tertiary centre where high risk babies are admitted it is as high as 28.5/1000 live births (17).

The RCWMCH is a 300-bed paediatric centre with a 22-bed Paediatric Intensive Care Unit (PICU) providing care in an upper middle-income country(18). In addition to managing medical patients, it supports centralised paediatric surgical services including cardiothoracic, ear nose and throat (ENT), trauma and neonatal/paediatric surgery, together with neurosurgery, and burns management. The unit offers ventilatory and cardiovascular support, renal replacement therapy, invasive and non-invasive monitoring systems, as well as bed-side ultrasonography for vascular access and diagnostic procedures. There is limited Venoarterial Extracorporeal membrane oxygenation (VA ECMO) for select post-operative cardiac patients. Additionally, CT and MRI are available on site. Patients are admitted to the hospital via two pathways. Firstly, from the emergency or outpatient services to a short-stay ward from where they are either down-referred to an appropriate level of care closer to home, transferred to an appropriate specialist or long-stay ward, or they are discharged. The second pathway involves direct referral to a specialist ward or PICU from outside public and private centres. The hospital is not directly attached to an obstetric unit and does not have a dedicated Neonatal Intensive Care Unit (NICU). Approximately 1350 patients are admitted to the PICU per annum and approximately 13% of these are neonates. RCWMCH sees a small proportion of the population of neonates requiring intensive care and is not responsible for providing standard neonatal care for prematurity or complications of birth such as asphyxia. The neonates seen at RCWMCH present with a different spectrum of conditions to that seen in the surrounding neonatal units and are either referred from these units for centralised and specialised surgical management or have been discharged from the neonatal services and now present with late diagnosis of congenital abnormalities or with acquired infection.

There is a paucity of literature around the profile of neonates that are admitted in a PICU. In a literature search on the topic only two articles were identified that specifically describe these patients and both were primarily studies designed to validate the Score for Neonatal Acute Physiology (SNAP)(19, 20). There is a gap in the available literature to help policy makers and unit managers anticipate the risks and resources associated with such a niche population.

By auditing the disease profile of neonates as a sub-population of PICU admissions, including when in their lives and where they accessed care, as well as their outcomes, we have an opportunity to create policy and health system strengthening activities that will focus on this high-risk population. For example; in situations where unwell neonates are being readmitted after discharge there may be benefit in reviewing how long neonates remain in the care of neonatal services. Where the pregnancy and delivery are uncomplicated, neonates may be discharged within hours of birth with limited screening for conditions such as congenital heart disease. Focus could then be on providing adequate follow-up resources in the first 72 hours of life. Lastly, another group at risk after discharge from neonatal services are the ex-premature infants and very low birth weight babies. They are sometimes discharged at weights of 1.6kg depending on season and unit bed pressure. Focus again is on providing adequate neonatal services but also follow-up and educational resources for parents of such at risk babies. Ultimately there may be many areas other than simply increasing PICU capacity and resources to deal with this population.

The aim of this study was to describe the population of neonates admitted to the PICU at the RCWMCH and identify risk factors for mortality in these patients, to ultimately inform and improve the care of neonates managed within the health care system

ETHICAL CONSIDERATIONS

The study was designed as an observational study and as such the participants were not subjected to any additional procedures or therapeutic advantages beyond the care that they would ordinarily receive during an admission to PICU. To ensure confidentiality specific measures were taken to ensure that any personal data collected was protected. Initially names and hospital numbers were used for verifying data entry accuracy and stored in a password protected database. Following that identifiers were replaced by participant codes.

Children are a vulnerable group when used for research due to their lack of autonomy in the consent process. Balancing against this risk is that the knowledge which we hope to gain through this study is pertinent to providing better care to neonates specifically.

We were granted a waiver for the requirement of parental informed consent by the Human Research Ethics Committee, taking the following into consideration:

- All parents of children admitted to the PICU at RCWMCH standardly received general information sheets with contact numbers of the ICU staff. This pamphlet states that some information about their children’s condition and/or treatment and outcomes may be used for research purposes unless they specifically refuse permission (providing an opt-out option).
- Parents are assured that no interventional research will be done without their express permission.
- The research design was purely observational and involved no additional risk to the patient above that of standard care.
- The autonomy of the patient was preserved by de-identification in the database.
- The process of getting informed consent may add stress and anxiety to the parents who are often overwhelmed by having a critically ill child and the intimidating nature of an intensive care unit.
- If the parent was not available to provide consent the exclusion of these children could potentially lead to information bias.”

Ethics approval for the study was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town – HREC: 695/2018

AUTHOR GUIDELINES OF THE JOURNAL OF PAEDIATRICS AND CHILD HEALTH

The Journal of Paediatrics and Child Health is the official journal of the Paediatrics and Child Health Division of The Royal Australasian College of Physicians. It is also affiliated with the Perinatal Society of Australia and New Zealand, the Paediatric Research Society of Australia, and the Australasian Association of Paediatric Surgeons. It has an impact factor of 1.95.

This Journal was chosen for its international impact as our study adds new data to a limited body of literature which could be beneficial to other low- and middle-income countries. The scope of the journal targets a wide range of specialties including perinatal and paediatric surgeons who could also benefit from our data.

Instruction for authors can be found in Appendix A or at https://onlinelibrary.wiley.com/page/journal/14401754/homepage/forauthors.html.

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CHAPTER 2: MANUSCRIPT

INTRODUCTION

Deaths in the neonatal period account for 47% of deaths in children under the age of 5 years globally (1). Neonatal and paediatric intensive care services are limited in South Africa (2). Neonatal intensive care units (NICU) typically admit premature, low birth weight newborns or term babies with complications such as birth asphyxia, meconium aspiration or pulmonary hypertension (3). Neonates admitted to paediatric intensive care units (PICU) likely have a different patient profile.

Neonatal care (within the Provincial health services) in Cape Town are primarily provided within the neonatal services (district, regional and tertiary). However, neonates are referred to the Red Cross War Memorial Children's Hospital (RCWMCH), for specialised surgical (abdominal, cardiac, neurosurgical, ophthalmological) services. Neonates who become sick after discharge home from the neonatal services are referred to the hospital via the paediatric services. Located in Cape Town, South Africa, the RCWMCH is a 300-bed paediatric centre with a 22-bed PICU providing medical and surgical care. There is limited access to VA ECMO. The hospital does not have a dedicated NICU, and any critically unwell neonates are therefore admitted to the PICU. Any pre- and post-operative cardiac patients are admitted to PICU and not a specialised cardiac ICU.

The aim of the study was to describe the profile of neonates admitted into the PICU at RCWMCH and to identify risk factors for mortality of these babies.

METHODS

Data were collected prospectively between 1 November 2018 – 31 October 2019. Patients were included if they had a post-menstrual age (PMA) of <44 weeks and were admitted to the PICU at RCWMCH. There were no exclusion criteria. A list of variables collected is provided in Appendix B. Deidentified data were recorded in a password protected Microsoft Excel spreadsheet and exported to IBM SPSS Statistics for Windows, version 27(IBM Corp., Armonk, N.Y., USA) for statistical analysis.

Continuous variables are reported as means (standard deviation, SD) or medians (interquartile range, IQR) depending on the normality of distribution, tested using the Shapiro Wilks W test.

Categorical variables are reported as absolute numbers and percentages. Univariate comparisons were done using chi-square, independent t-tests, or Mann-Whitney U tests appropriate to the variable and distribution. Data found to be significantly associated with mortality on univariate analysis were entered into a stepwise binary logistic regression model to determine independent risk factors. Two tailed p-values and an alpha value of 0.05 were used. Ethical approval for this study was obtained from the UCT Faculty of Health Sciences Research Ethics committee.

RESULTS

Between November 2018 and December 2019, a total of 1444 patients were admitted to the PICU. Of these 266 (18.4%) met the neonatal case definition.

Cohort demographics are presented in the first column of **Table 1**.

Median birth weight was 2210g with n=113 (42%) being ≥ 2500g (**Figure 1)**. Median chronological age on admission was 11 days with 70 (26%) admissions occurring in the first 72 hours of life (**Figure 2)**. Median PMA was 38 weeks.

Seventy-five percent (195/266) of neonatal admissions were referred from outside RCWMCH. Tertiary hospitals referred the highest proportion of patients (n=100, 37.6%).

Eighty-six (32%) of all admissions were preterm (< 37 weeks PMA). Most of these preterm babies needed surgical services (82/86). Among these surgical preterm admissions 29 (35%) had a congenital abnormality and 52 (63%) had an acquired surgical condition of which 29/52 (55.7%) had NEC.

Among the 180 term patients (≥ 37 weeks PMA) the distribution of surgical and medical patients was 95/180 (52.8%) and 85/180 (47.2%) respectively).

Sixty-two (23%) of all the admissions were ex-premature neonates (born with a gestational age of <37 weeks but admitted with a PMA of ≥ 37 weeks).

Of the 27 patients referred from emergency units 17 (63%) were term babies in the third and fourth week of life. The remaining 10 (37%) were ex-premature infants with pneumonia or other infections. Four of 27 (14,8%) had congenital cardiac lesions.

Sixty-eight (14.3%) babies were exposed to maternal Human Immunodeficiency Virus (HIV). Half of these mothers had a suppressed viral load within 3 months of delivery (n = 38, 55.9%). Three (4.4%) neonates tested HIV positive.

Congenital abnormalities were present in 135 (50.4%) neonates. Of these 130 were considered major abnormalities (requiring ICU support or surgical intervention in the neonatal period). The majority involved the cardiovascular system (n = 53 of 135, 39.2%)**(Figure 6)**. If a baby required surgical interventions for a cardiac abnormality, they were admitted as a cardiothoracic patient.

Chromosomal screening was done in 34 (12.8% of all 266 patients) with 12/34 (35,3%) positive for abnormalities, most commonly Trisomy 21 (6/12).

During the study period the overall unit mortality was 5.12%. Non-neonatal mortality was 45/1178 (3.8%), significantly lower than neonatal mortality of 29/266 (10.9%) (OR 3.08; CI 1.89 – 5.02; p = <0.001). The risk adjusted PICU mortality (actual/mean predicted) based on PIM3 was 1.12. An additional 15 neonates were transferred out with a life-limiting condition for palliation. All these babies died before hospital discharge. These patients were incorporated in a non-survivor's group of 44 (**Table 1),** resulting in a neonatal mortality rate at hospital discharge of 16.5% (44 of 266).

The most common underlying cause of death or palliation (as defined by the World Health Organisation (4), was congenital abnormalities (n = 22, 50%), followed by necrotising enterocolitis (NEC) (n = 9, 20.5%) and sepsis (n = 8, 18.2%) (**Figure 4**). Congenital abnormalities were prevalent in all age groups with respect to the underlying cause of death, while NEC and sepsis were more prevalent in the preterm groups. Deaths following cardiac surgery were only in the older ages of 40 – 43 weeks **(Figure 5).** All but one of the babies who were palliated had life-limiting congenital abnormalities. The one baby that did not had NEC.

The PICU course, therapies and outcomes are presented in **Table 2**.

SURVIVORS VS. NON-SURVIVOR'S

On univariate analysis, non-survivors were younger than survivors (p = 0.022; **Table 1**), however there was no difference in survival across different birth weight categories (**Figure 1**, p = 0.437). Comparing chronological ages on admission there were fewer survivors in babies admitted on day 4 – 7 (**Figure 2**, p <0.05). Similarly, there were fewer survivors amongst neonates who had a PMA of 28 – 32 weeks' gestation (**Figure 3**, p <0.05).

There were more confirmed sepsis episodes among non-survivors (p = 0.025), however there were fewer viral infections (p = 0.039) and fewer cases of suspected sepsis in non-survivors (p = 0.013).

Non-survivors had a higher risk of mortality for both PIM3 and SNAPPE-II (p < 0.001 for both; **Table 1**).

Non-survivors received more high frequency oscillatory ventilation (HFOV) (p = 0.0004) and fewer non-survivors received continuous positive airway pressure (CPAP) (p = 0.026) **(Table 2).** Of the survivors n = 25 (11%) got surfactant and 76% of those were preterm, compared to non-survivors of whom n = 8 (18%) got surfactant and all were preterm **(Table 1).**

Newborns with haemodynamic instability requiring inotropes were associated with non-survival (p<0.001). Additionally, these newborns had higher inotrope requirements than survivors (p = 0.003). Total Parenteral Nutrition (TPN) was used more in survivors (p = 0.009). Non-survivors were more likely to receive no feeds (p <0.0001). There was a higher proportion of AKI in non-survivors (p<0.0001). Only two neonates received Renal Replacement Therapy (RRT) and both died (p = 0.026).

Non-survivors presented more often with signs of coagulopathy and required Fresh Frozen Plasma (FFP) (p < 0.001), platelets (p = 0.003) and cryoprecipitate (p <0.001).

Binary logistic regression analysis was carried out building a model with variables that had a p-value on univariate analysis of < 0.05 (**Table 3**). The only variable independently associated with the outcome of death/palliation was HFOV. TPN and any feed received were associated with survivors.

DISCUSSION

We describe a population with a higher mortality rate compared to older PICU admissions, is more likely to be term and normal birth weight, with a high burden of disease due to congenital abnormalities, NEC, and sepsis. The demand for neonatal care in our PICU was mostly driven by support for centralised surgical services.

Our study contributes to a small body of literature that profiles neonates admitted in a PICU. Vasudevan et al have profiled such a cohort in Northern India (5). Theirs was a smaller unit and there is no evidence in the paper that their unit offered specialist cardiac and surgical services. Half of their admissions were diagnosed with sepsis. Our cohort had a small for gestational age (SGA) prevalence of 7.6%, which was lower than the 12,7% reported by the associated tertiary neonatal unit (6).

The percentage of HIV exposure in our study was lower than the 2019 local prevalence of 17% (7) but the HIV transmission rate was higher than reported 3.5% for South Africa (8).

Congenital abnormalities are increasingly being identified as contributing to under-5 mortality(9). In South Africa policies that sought to deal with their care and prevention have been overshadowed by a worsening HIV and TB epidemic(10). While congenital abnormalities were not associated with mortality in our study, they did contribute a significant burden of disease. Genetic screening is not routinely done in our centre due to resource limitations but there is increasing evidence that critically ill neonates may have genetic abnormalities (11, 12).In future studies it would be useful to consider further genetic studies including whole genome sequencing in this group of patients.

The proportion of neonates admitted in our study was 18.4%, which corresponds with a range previously reported of between 12 – 22% (5, 13-17). Although not specifically measured in our study this likely reflects a substantial percentage of bed days in our PICU. Many of these are surgical admissions because of centralised paediatric surgical services. Most of the patients with a cardiac abnormality were admitted with a confirmed diagnosis suggesting that the current screening programme is working well.

Ex-premature infants are a high-risk group. The ex-premature surgical patients were mostly admitted from lower acuity wards at RCWMCH with post-operative complications while medical patients were admitted from emergency and outpatient units with infections. This phenomenon highlights the need for development of neonatal services within the RCWMCH, and it is encouraging that a neonatal high care area has recently been opened in the institution.

Neonatal mortality for babies admitted to PICU varies widely amongst reports, likely reflecting different resource environments as well as contexts (5, 13, 14, 16-19). Our neonatal mortality is lower than rates published by other PICU's from upper middle income countries, including Paraguay with 24%(18) and Johannesburg, South Africa with 32.4%(19). Direct comparison is difficult as the latter is primarily a neonatal unit that additionally offers ventilation to older children, whilst the RCWMCH is primarily a PICU providing some neonatal services. Our study showed a higher neonatal mortality at PICU discharge compared to older children. The high mortality in the 28 – 32 weeks PMA group probably represents a select group of immature babies with an added high-risk condition. The high mortality for babies admitted on day 4 – 7 of life likely reflects organ pathology associated with major congenital abnormalities.

As mortality predictors PIM3 and SNAPPE-II scores underestimated the actual mortality. Although PIM3 has been validated in South Africa, this was in a population that excluded neonates (20). Similarly, SNAPPE-II has not been validated in the PICU context. This highlights the need to develop prediction scores for this population for us to evaluate our quality of care and compare with other units.

It is difficult to associate therapeutic interventions with outcome as decisions around management are complex, taking into account many clinical, situational and resource availability factors that are not captured in our data. We have noted the outcomes that differ between survivors and non-survivors but have chosen not to analyse them extensively. It is likely there are multiple confounders. We have some thoughts around why these differences occur.

Survivors primarily got non-invasive, and some conventional ventilation compared to non-survivors, who received mostly conventional and HFOV. Looking closer, more non-survivors received surfactant (although this was not statistically significant) and all of those who received surfactant were premature. Non-survivors were possibly more likely to have under-developed lungs and an element of bronchopulmonary dysplasia.

A large proportion of non-survivors received no feeds most likely because they were too unstable to receive enteral nutrition. The shorter length of stay for these babies probably also explains why they received less TPN, as they were early deaths before TPN was considered in their management.

We anticipated that infection would play a significant role in this cohort as neonates are vulnerable to pathogens(21). Not surprisingly there was more proven sepsis (where a bacterial or fungal pathogen was identified) among non-survivors. Viral infections were more common in survivors and can probably be explained by the higher number of survivors being admitted from home. It also validates the reluctance of neonatal units to admit outpatients if isolation beds are not available. There may be less severe organ dysfunction with viral organisms but survival may also just reflect older neonates with more physiological reserve.

Acute kidney injury in the neonatal period may be challenging to diagnose(22, 23). It is likely that the severity of renal injury was under-represented in our study as a creatinine peak was probably not reached before some babies died and significant oliguria is often an absent feature of neonatal AKI (24). Nearly half of the survivors had some measure of AKI and almost 20% had grade 3 AKI, yet no survivors received RRT. Neonates tend to continue to produce urine even when their creatinine triples so fluid overload is less of a concern. A large proportion of abdominal pathology in the cohort would have excluded the use of peritoneal dialysis. Lastly, providing haemodialysis in such small patients is limited by the availability of adequately sized dialysis catheters.

Overall, it appears that non-survivors use a considerable amount of resource (inotropes, blood products, HFOV, bed days) with disappointing results. Palliative care support is an important component of care for children with life-limiting congenital abnormalities and their families.

Our study is strengthened by its prospective design as well as its focus on a unique cohort not well described in the literature. The single-centre observational study design does limit external validity and generalisability and the results cannot be extrapolated to other neonatal PICU populations. Lack of information on mode of death i.e., haemodynamic, respiratory, neurological, or multi-organ failure, limits our ability to interpret mortality data.

CONCLUSION

Sometimes neonatal care takes place in critical care spaces outside of the neonatal services. This population differs from neonates that are typically seen in a NICU. Congenital abnormalities as well as infection and NEC featured strongly. Our study provides insight into risk factors and resources used in caring for this sub-group of the paediatric population. More research is needed to build on this data including auditing of referral pathways and time sensitive interventions as well as developing a severity of illness score specifically for neonates and ex-premature babies. This will inform policy makers and hospital managers how to improve care and invest in available resources for neonates.

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TABLES AND FIGURES

Table 1: Cohort Demographics

		Cohort N = 266	Survivors N = 222	Non-Survivors N = 44	p-value
Chronological Age (days)		11 (3 – 28)	12 (3.3 – 32)	5 (2.8 – 16)	0.022
PMA (weeks)		38 (35 – 40)	38.3 (35.3 – 40.9)	37.6 (33.3 – 40.3)	0.193
Birth weight (grams)		2210 (1397–2995)	2245 (1410–2980)	2140 (1396 – 3000)	0.718
Admission weight (grams)		2400 (1766–3124)	2400 (1785–3150)	2205 (1600–2933)	0.270
Referred from (%)	**Inpatient***	71 (26.7)	63 (28.4)	8 (18.1)	0.365
	Emergency Unit	27 (10.2)	25 (11.2)	2 (4.5)	
	Tertiary	100 (37.6)	80 (36.0)	20 (45.5)	
	Regional	43 (16.2)	35 (15.8)	8 (18.1)	
	District	10 (3.8)	8 (3.6)	2 (2.3)	
	Clinic	10 (3.8)	7 (3.2)	3 (6.8)	
	Private	5 (1.9)	4 (1.8)	1 (2.3)	
Primary Discipline (%)	**Ophthalmology**	2 (0.8)	2 (0.9)	0	0.629
	Surgical	125 (47.0)	105 (47.3)	20 (45.5)	
	Cardiology	34 (12.8)	25 (11.3)	9 (20.5)	
	Cardiothoracic	22 (8.2%)	18 (8.1)	4 (9.1)	
	Medical	55 (20.7)	48 (21.6)	7 (15.9)	
	ENT	14 (5.3)	13 (5.9)	1 (2.3)	
	Neurosurgical	14 (5.3)	11 (5.0)	3 (6.8)	
HIV exposed		68 (14.3)	52 (23.4)	16 (36.4)	0.088
Male		150 (56.4)	123 (55.4)	27 (61.4)	0.509
Congenital Abnormality		135 (50.4)	107 (48.2)	27 (61.4)	0.137
Chromosomal Abnormality (34/266 tested)		12 (4.5)	9/25 (4.1)	3/9 (6.8)	1.000
SGA		20 (7.6)	17 (7.7)	3 (6.8)	1.00
Post-operative		44 (17.1)	38 (13)	6 (14)	0.378
Steroid mature (93 eligible/266)		30 (32.3)	21/78 (26.9)	7/15 (46.7)	0.13
Surfactant		33 (12.4)	25 (11,2)	8 (18.6)	0.255
PIM 3 % (SD)		**9.7 (13.5)**	**7.4 (9.7)**	**21.0 (21.9)**	**<0.001**
SNAPPE-II % (SD)		**3.5 (6.7)**	**2.7 (5.4)**	**7.6 (10.6)**	**<0.001**

PMA = Postmenstrual age, HIV = Human Immunodeficiency virus, SGA = small for gestational age, PIM = paediatric index of mortality, SNAPPE = Score of Neonatal Physiology Perinatal Extension)

***Patients initially admitted to a lower acuity ward at Red Cross War Memorial Children's Hospital**

Table 2: PICU interventions, complications, investigations and outcomes

	Cohort	Survivors	Non-Survivors	p-value
Maximum Ventilation Support		N = 222	N = 44	0.001
HFOV	27 (10.2)	16 (7.2)	11 (25%)	0.0004
IPPV	162 (60.9)	134 (59.9)	28 (65.9)	0.46
CPAP	33 (12.4)	31 (14.4)	2 (2.3)	0.026
High Flow	27 (2.6)	7 (3.2)	0	0.2
Inotropes	83 (32.3)	58 (26.5)	25 (58.1)	<0.001
Median max Vasoactive infusion Score.	10 (6 – 17.5))	8.5 (5.25-12.3)	17.3 (8 – 27.5)	0.003
Nitric Oxide	5 (1.9)	3 (1.4)	2 (4.8)	0.184
Prostaglandin	25 (9.6)	18 (8.2)	7 (16.7)	0.146
TPN	75 (28.7)	70 (32.0)	5 (11.9)	0.009
Feeds Received				<0.001
EBM	113 (44.5)	**105 (49.5)**	8 (19.0)	0.0002
Formula	60 (23.6)	**55 (25.9)**	5 (11.9)	0.046
Mixed	31 (12.2)	31 (14.6)	4 (9.5)	0.37
None	46 (18.1)	21 (9.9)	**25 (59.5)**	0.0001
AKI Grade				<0.001
0	116 (45.3)	**109 (50.7)**	7 (17.1)	0.0001
1	49 (19.1)	31 (14.4)	**18 (43.9)**	0.0001
2	45 (17.6)	37 (17.2)	8 (19.5)	0.71
3	46 (18.0)	38 (17.7)	8 (19.5)	0.78
RRT	2 (0.8)	0	2 (4.8)	0.026
Sepsis episodes confirmed	71 (26.7)	53 (23.9)	18 (40.9)	0.025
Sepsis episodes suspected	144 (54,1)	128 (57,7)	16 (36,4)	0.013
Antibiotics received	189 (73.8)	159 (71,6)	30 (68,2)	0.716
Viral infection (143/266 tested)	42 (29.3)	40 (33.1)	2 (9.1)	0.039
Blood Products received				
PRBC	78 (30.6)	60 (28.0)	18 (44.0)	0.063
FFP	35 (13.7)	19 (8.9)	16 (39.0)	<0.001
Platelets	48 (18.0	33 (14.9)	15 (34.1)	0.003
Cryoprecipitate	37 (13.9)	23 (10.4)	14 (31.8)	<0.001
Surgical Procedures	167 (62.8)	145 (64.9)	22 (50)	0.403
1	138	119	19	
2	21	19	2	
3	4	4	0	
4	3	2	1	
6	1	1	0	
Radiology Procedures				
CT scans	38 (14.7)	30 (13.8)	8 (19)	0.474
Ultrasound	38 (14.6)	27 (14.6)	11 ((26.2)	0.03
Echocardiography	73 (28.1)	56 (25.7)	17 (40.5)	0.061
MRI	2 (0.8)	2 (0.92)	0	1.00
Contrast Study	15 (5.8)	14	1	0.103
Length of Stay (days)	4 (2 – 8)	5 (2 – 8)	3 (1 – 7)	0.015

HFOV = High Frequency Oscillatory Ventilation. IPPV = Intermittent Positive Pressure Ventilation. CPAP = continuous positive airway pressure. TPN = total parenteral nutrition. EBM = expressed breast milk. AKI = acute kidney injury. RRT = renal replacement therapy. PRBC = packed red blood cells. FFP = fresh frozen plasma. MRI= magnetic resonance imaging.

Table 3: Variables associated with death/palliation after logistic regression analysis

Variable	B	S.E	WALD	Df	Sig.	Exp(B)	95% CI for Exp(B)
HFOV	7.413	2.505	8.760	1	0.003	1657.407	12.232 – 224581.436
TPN	-4.233	1.602	8,760	1	0.008	0.15	0.001 – 0.338
NO FEEDS (REFERENCE)			15.681	4	0.003		
EBM	-8.083	2.079	15.121	1	<0.001	0.000	0.000 – 0.018
FORMULA	-4.387	1.464	8.987	1	0.003	0.012	0.001 – 0.219
MIXED	-4.439	1.484	8.947	1	0.003	0.012	0.001 – 0.216

HFOV = High Frequency Oscillatory ventilation, TPN = Total Parenteral Nutrition, EBM = expressed breast milk.

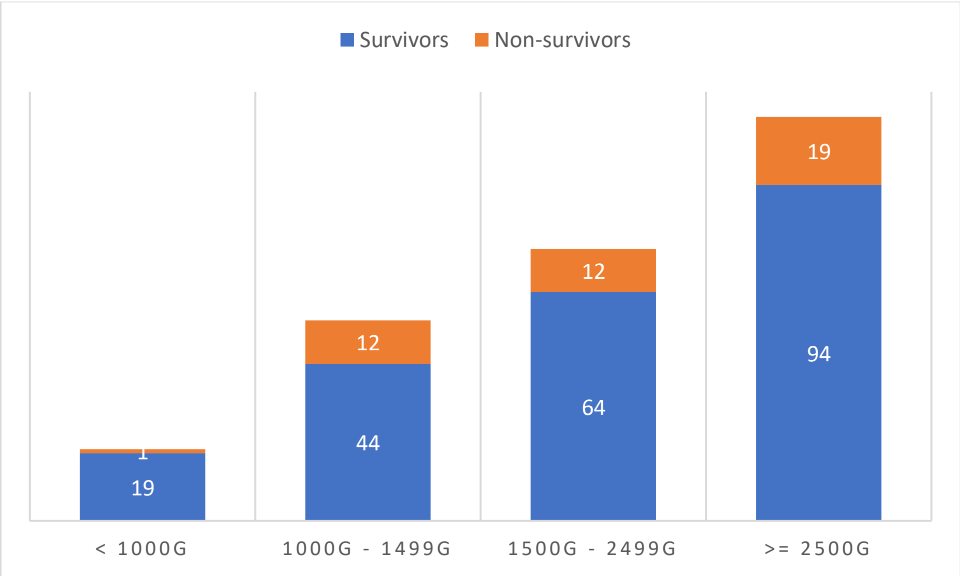

Figure 1: Comparison of total admissions and survival across birth weight categories.

(Fisher exact test p = 0.437)

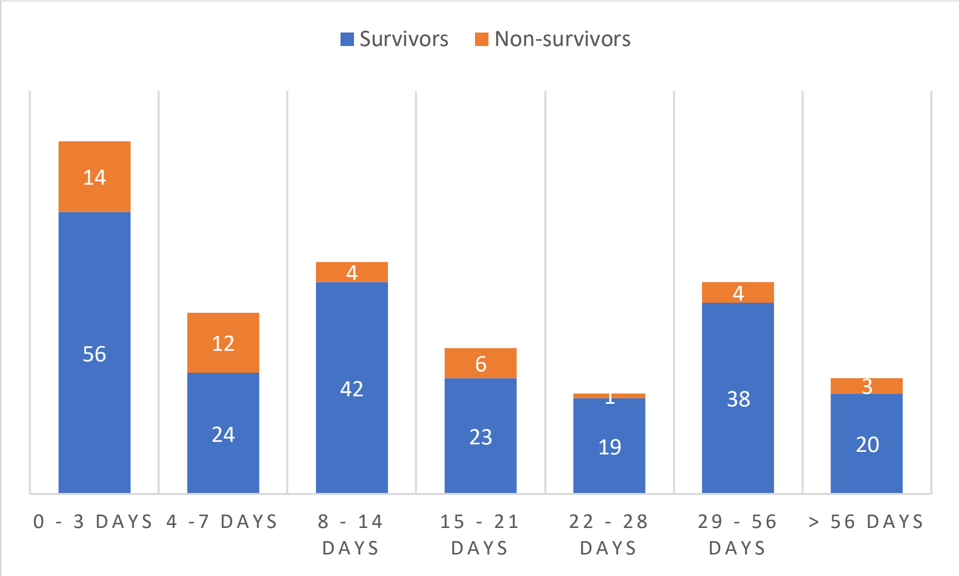

Figure 2: Comparison of total admissions and survival across categories of 'age on admission'.

(Fisher exact test p =0.041. Bonferroni post-hoc analysis p < 0.05 for day 4 – 7)

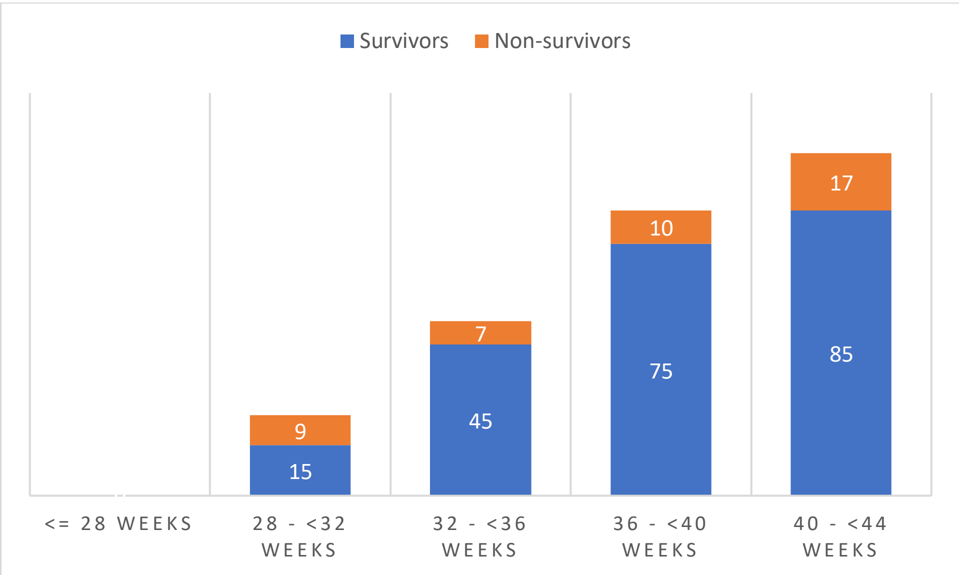

Figure 3: Comparison of total admissions and survival across PMA on admission categories.

(Fisher-exact test p = 0.044. Bonferroni post-hoc analysis p <0.05 for 28 - 32 weeks.)

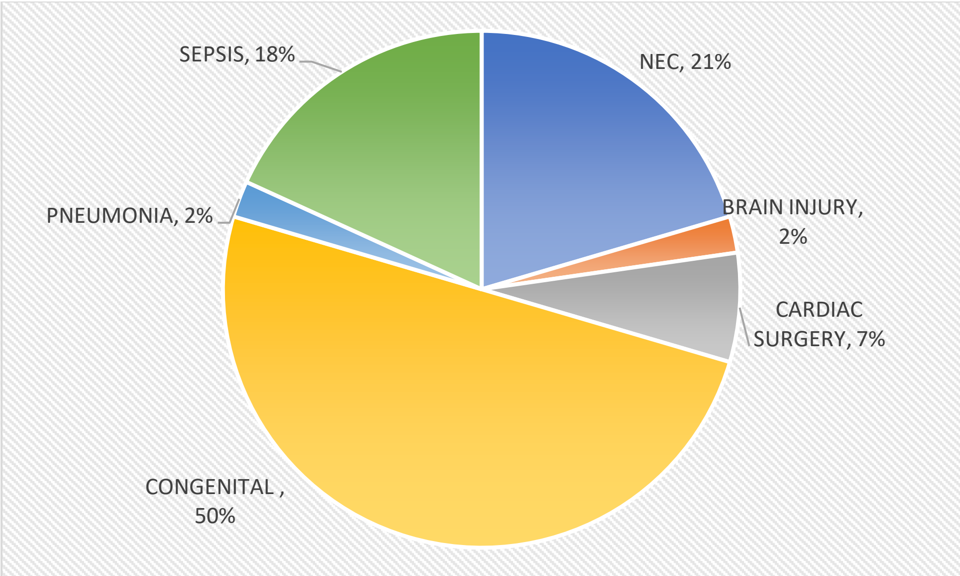

Figure 4: Underlying causes of death

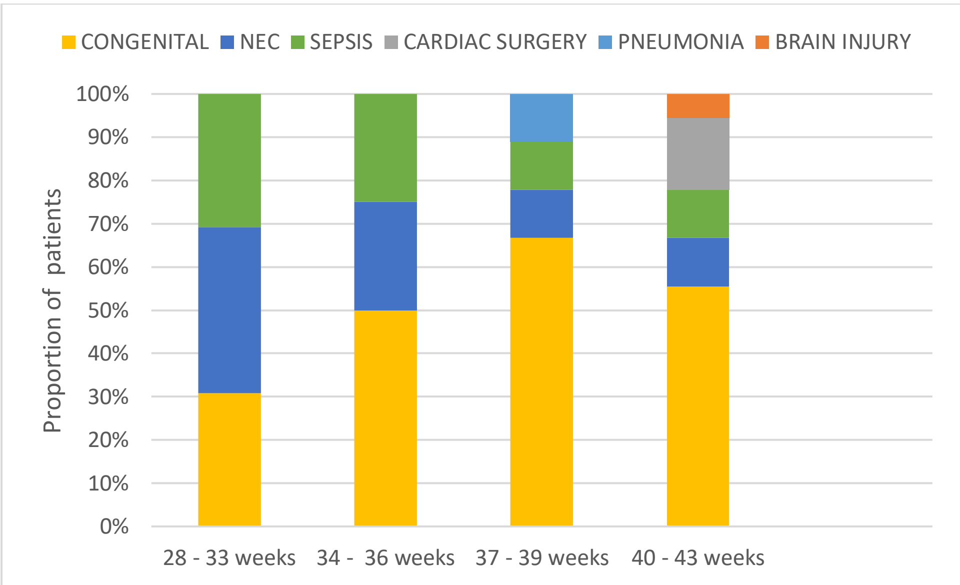

Figure 5: Proportion of underlying causes of death by Post-menstrual age group

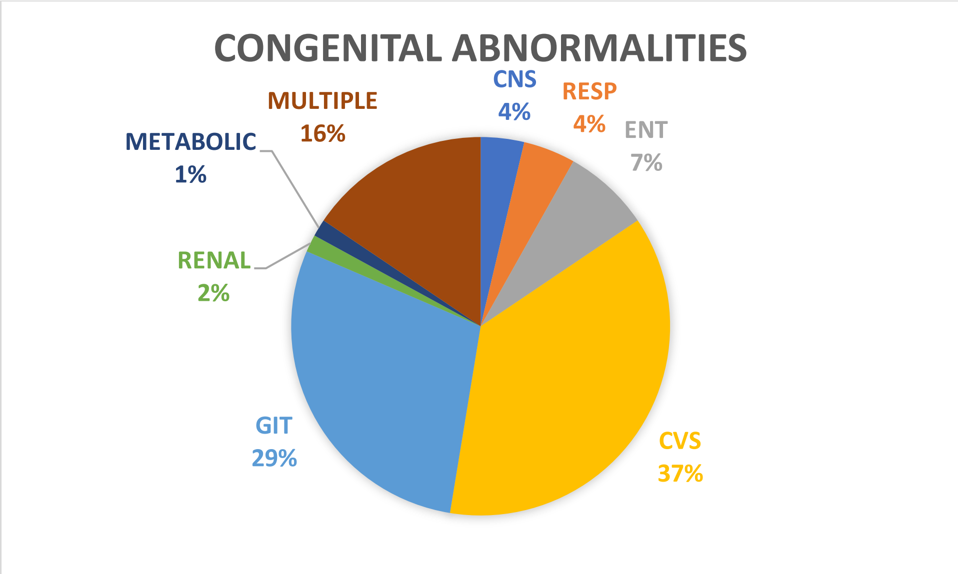

Figure 6: Proportion of congenital abnormalities per system

CNS = central nervous system, RESP =respiratory system(includes congenital diaphragmatic hernia), ENT = ear nose and throat, CVS = cardiovascular system; GIT = gastrointestinal system

APPENDIX A: AUTHOR GUIDELINES FOR THE JOURNAL OF PAEDIATRICS AND CHILD HEALTH

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The journal supports the **Resource Identification Initiative**, which aims to promote research resource identification, discovery, and reuse. This initiative, led by the **Neuroscience Information Framework**and the **Oregon Health and Science University Library**, provides unique identifiers for antibodies, model organisms, cell lines, and tools including software and databases. These IDs, called Research Resource Identifiers (RRIDs), are machine-readable and can be used to search for all papers where a particular resource was used and to increase access to critical data to help researchers identify suitable reagents and tools.

Authors are asked to use RRIDs to cite the resources used in their research where applicable in the text, similar to a regular citation or Genbank Accession number. For antibodies, authors should include in the citation the vendor, catalogue number, and RRID both in the text upon first mention in the Methods section. For software tools and databases, please provide the name of the resource followed by the resource website, if available, and the RRID. For model organisms, the RRID alone is sufficient.

Additionally, authors must include the RIIDs in the list of key words associated with the manuscript.

To Obtain Research Resource Identifiers

1. Use the Resource Identification Portal, created by the Resource Identification Initiative Working Group.
2. Search for the research resource (please see the section titled ‘Search Features and Tips’ for more information).
3. Click on the ‘Cite This’ button to obtain the citation and insert the citation into the manuscript text.

If there is a resource that is not found within the Portal, authors are asked to register the resource with the appropriate resource authority. Information on how to do this is provided in the ‘Resource Citation Guidelines’ section of the Portal.

If any difficulties in obtaining identifiers arise, please contact **rii-help@scicrunch.org** for assistance.

Example Citations:

Antibodies: Wnt3 was localized using a rabbit polyclonal antibody C64F2 against Wnt3 (Cell Signaling Technology, Cat# 2721S, RRID: AB_2215411).
Model Organisms: Experiments were conducted in c. elegans strain SP304 (RRID:CGC_SP304).
Cell lines: Experiments were conducted in PC12 CLS cells (CLS Cat# 500311/p701_PC-12, RRID:CVCL_0481).
Tools, Software and Databases: Image analysis was conducted with CellProfiler Image Analysis Software, V2.0 (http://www.cellprofiler.org, RRID:nif-0000-00280).

Guidelines updated 29 January 2021

APPENDIX B: VARIABLES COLLECTED

ANTENATAL, BIRTH AND PRE-ADMISSION HISTORY

Date of birth

Gender

Place of Birth

Birth weight

Gestational Age

Small for Gestational age

Mode of delivery

Antenatal steroids

- Steroid doses
- Steroid mature?

Surfactant

Apgar

HIV-exposed

- Maternal viral load
- PMTCT received
- Birth PCR

Feeding choice

Preadmission antibiotics (defined as >72 hours of antibiotic exposure)

Cranial ultrasound done and IVH present.

Referral source

Inside or outside drainage area

ADMISSION DATA

Date of admission

Chronological age on admission

Post-menstrual age on admission

Admission weight

Diagnosis

Admitting speciality

Post-operative admission?

PIM 3 score and risk of mortality

SNAPPE II score and risk of mortality

Physiological variables

- Worst mean BP in first 12 hours
- Worst Temperature in first 12 hours
- FiO2 on admission
- PaO2 on admission
- PaCO2 on admission
- pH on admission
- Base Deficit on admission
- Lactate on admission
- Sodium, Creatinine, Haemoglobin and Platelet levels on admission
- Urine output in the first 12 hours

Date of discharge

Disposition

Cause of death

RESOURCES USED AND DIAGNOSIS DURING PICU STAY

Bedside EEG monitoring and presence of seizures

Maximum ventilation support

- High Frequency Oscillation
- Intermittent positive pressure ventilation
- Continuous Positive Airway Pressure
- High Flow

Inotropes received

- Maximum Vasoactive infusion score

Nitric Oxide

Prostaglandin

TPN

Feeds received

- Expressed Breast Milk
- Formula
- Mixed
- None

Acute Kidney injury Grade based on KDIGO definitions

Renal Replacement Therapy

Sepsis episodes confirmed (Positive culture from blood, tracheal aspirate, urine, cerebrospinal fluid, peritoneal fluid)

- Organism cultured and site

Sepsis episode suspected (Clinical suspicion with or without increased inflammatory markers – WCC, PCT, CRP

Antibiotics received – Completed a full course of antibiotics

Virus identified

- Virus and site

Blood products received

- Packed red blood cells
- Platelets
- Fresh Frozen Plasma
- Cryoprecipitate

Surgical procedure performed

Radiology procedure

- CT scan
- Ultrasound
- Echo
- MRI
- Fluoroscopy

Congenital abnormality

Chromosomal abnormality

APPENDIX C: ETHICS APPROVAL

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

29 November 2018

HREC REF: 695/2018

Prof A Argent
Medical Director
Paediatric ICU
School of Child & Adolescent Health
Red Cross War Memorial Children's Hospital

Dear Prof Argent

PROJECT TITLE: DISEASE PROFILE AND OUTCOMES OF NEONATES ADMITTED TO THE PAEDIATRIC INTENSIVE CARE UNIT AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL IN CAPE TOWN, SOUTH AFRICA (MPhil Candidate - Dr L Riemer)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 November 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Linda Riemer will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

pp
PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

APPENDIX D: RCWMCH PERMISSION LETTER

Western Cape Government
Health

DR AN PARBHOO
Manager: Medical Services
Red Cross War Memorial Children's Hospital
Email: Anita.Parbhoo@westerncape.gov.za
Tel: +27 21 658 5430 Fax: +27 21 658 5006/5166

21 December 2018

Dr L Riemer
Paediatric Critical Care

Dear Dr Riemer,

RESEARCH: RXH: RCC 167

PROJECT TITLE: Disease Profile and outcomes of neonates admitted to the Paediatric Intensive Care Unit at Red Cross War Memorial Children's Hospital in Cape Town, South Africa

It is a pleasure to inform you that the hospital Research Review Committee has approved your application to conduct above-mentioned study at Red Cross War Memorial Children's Hospital.

Yours sincerely,

DR AN PARBHOO
MANAGER: MEDICAL SERVICES

APPENDIX E: Distribution of admissions by month and season

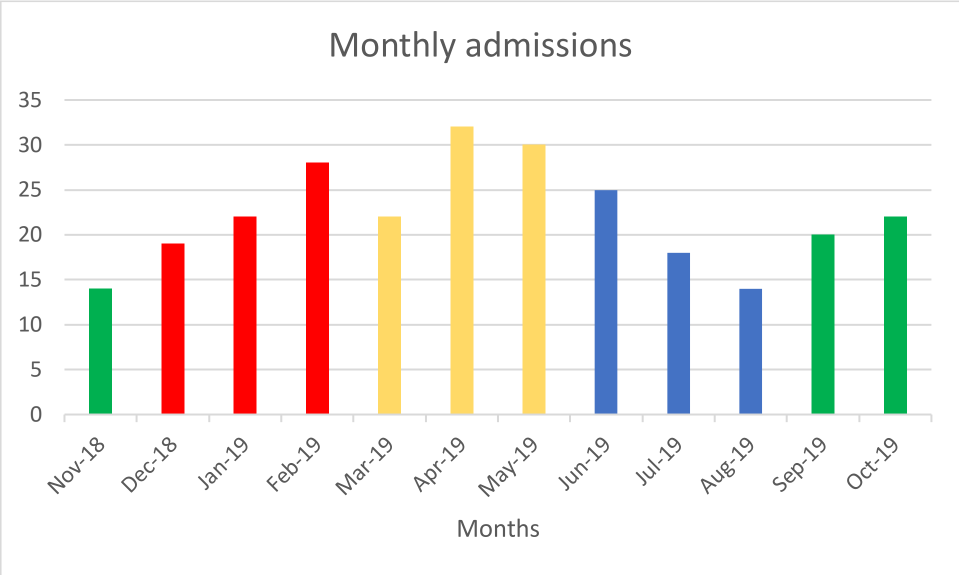

Figure 7: Admission numbers by month

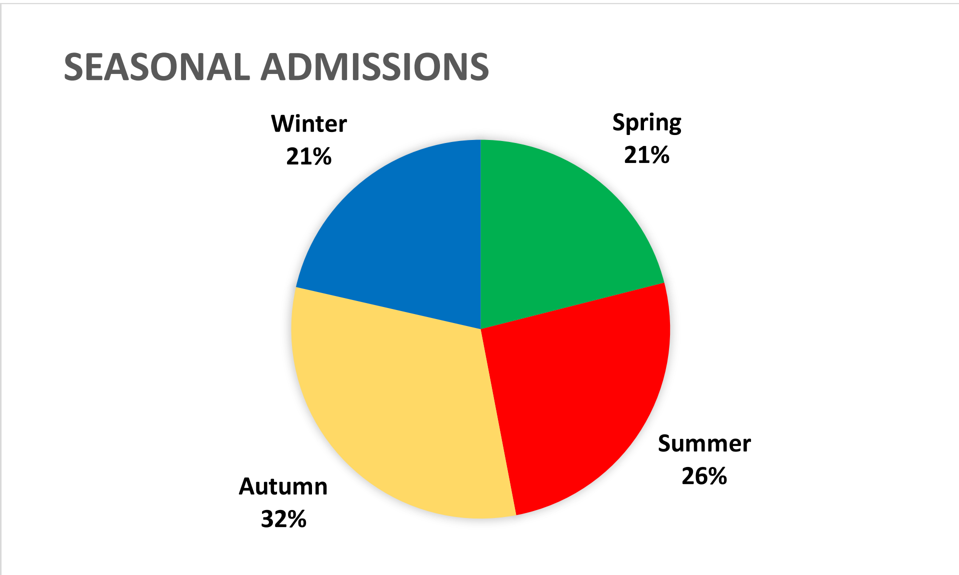

Figure 8: Admission proportions by season