Comparison of outcomes between children ventilated in a non-paediatric intensive care and a paediatric intensive care unit: A retrospective analysis

X L Jingxi,[1] MB ChB; **P Tinarwo,**[2] PhD; **R Masekela,**[1,3] MB BCh, MMed (Paeds), PhD; **M Archary,**[1,4] MB ChB, FCPaeds (SA), PhD

[1] *Department of Paediatrics and Child Health, School of Clinical Medicine, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa*
[2] *Department of Paediatrics, King Edward VIII Hospital, Durban, South Africa*
[3] *Department of Dietetics, King Edward VIII Hospital, Durban, South Africa*
[4] *Department of Biostatistics, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa*

Corresponding author*: X Jingxi (xolisiwejingxi@gmail.com)*

Background. Lack of paediatric intensive care infrastructure, human resources and expertise in low- and middle-income countries (LMICs) often results in critically ill children being managed in non-intensive-care unit (ICU) settings.
Objectives. To compare the mortality between critically ill patients who required ventilation for more than 24 hours in a non-paediatric ICU (PICU) setting v. those admitted directly to a PICU.
Methods. Participants were enrolled if they were between one month and 13 years of age and were ventilated in a non-PICU ward in a regional hospital and a PICU ward in a tertiary/quaternary hospital during the study period of January 2015 - December 2017 in KwaZulu-Natal, South Africa. Descriptive statistics, chi-square test, Wilcoxon test and binary logistic regression were used for data analysis. Ethics approval was obtained (approval number BE568/18 BREC) from the Biostatistics Research Council of the University of KwaZulu-Natal.
Results. Of the 904 admissions, 25.1% (n=227) were admitted to non-PICU and 74.9% (n=677) to a PICU. A significantly higher proportion of non-PICU patients were malnourished than PICU patients (26.4% v. 13.3%, $p<0.001$). Patients ventilated in a PICU were 76% less likely to die ($p<0.001$), while patients who required inotropes were 15.08 (9.68 - 24.34) times more likely to die ($p<0.001$). There was a statistically significant association between admission setting and survival outcome, with higher mortality in the non-PICU setting than in the PICU setting (46.3% v. 19.5%, $p<0.001$).
Conclusion. Critically ill children ventilated in a non-PICU setting in KwaZulu-Natal are more likely to be malnourished, require inotropes and have higher mortality. Although increasing access to PICU bed availability is a long-term goal, the high mortality in the non-PICU setting highlights the need to optimise the availability of resources in these non-PICU wards, optimise and train the staff, and improve primary healthcare services.
Keywords. PICU, non-PICU setting, interim ventilation, outcomes, mortality.

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The World Health Organization (WHO) estimated in 2019 that 5.2 million children under the age of five years died from preventable and treatable causes. Children aged 1 - 11 months accounted for 1.5 million deaths, while children of 1 - 4 years accounted for 1.3 million.[1]

Leading causes of death in children under five include preterm birth complications, birth asphyxia, pneumonia, diarrhoea and congenital anomalies.[2] The majority of deaths in 2003 occurred in sub-Saharan Africa (41%) and southern Asia (34%). While improvements in water and sanitation infrastructure, immunisation and nutrition can prevent many deaths, there is a need to provide for children requiring care in an intensive-care unit (ICU) in low- and middle-income countries (LMICs) to further decrease paediatric mortality and morbidity.[3]

Most hospitals in LMICs lack designated paediatric ICUs (PICUs) with paediatric-trained nursing staff, adequate nurse-to-patient ratio to care for critical patients, and appropriate equipment and monitoring capacity.[3,4] A significant number of deaths in LMICs (40 - 60%) occur within the first 24 hours of admission in paediatric general wards caring for acute and critically ill children.[5,6] In paediatric general wards, patients should be assessed to evaluate the severity of the illness, stabilised and safely transferred to a specialised PICU. However, owing to lack of space in ICUs, interim ventilation in general wards has been one of the short-term alternatives.

While many studies have looked at outcomes of critically ill patients admitted to a PICU, limited data exist that examine outcomes of critically ill patients ventilated in a non-PICU setting. Two recent studies in Western Cape and Gauteng provinces also showed a significant increase in mortality in those ventilated in a non-ICU setting.[2] There are no available data looking at the outcomes of patients managed in non-PICU wards in KwaZulu-Natal.

The present study aimed to describe and compare the outcomes of critically ill paediatric patients admitted and ventilated in a non-PICU ward in a regional hospital and an ICU ward in a tertiary hospital in the eThekwini district, KwaZulu-Natal, South Africa.

Methods

Study design

A retrospective descriptive chart review of clinical characteristics, demographics and outcomes of all children (1 month - 13 years) admitted and requiring ventilation at King Edward VIII Hospital (KEH) and Inkosi Albert Luthuli Central Hospital (IALCH) from January 2015 to December 2017 was conducted.

Patients admitted to the 14-bed paediatric admission ward at KEH, a regional hospital in eThekwini district, comprised the non-PICU cohort. Two paediatric high-care beds dedicated to interim ventilation (for at least 24 - 72 hours) of critically ill patients were available at KEH while awaiting transfer to the PICU. Care of patients in the non-PICU ward was provided by a team that included two paediatricians, a paediatric registrar, medical officers and interns, and non-ICU-trained nursing staff consisting of professional and staff nurses. The nurse:patient ratio in the admission ward at KEH ranged between 1:2 and 1:4.

The comparator PICU cohort included all patients admitted directly to the PICU at IALCH during the study period. The unit is a 14-bed ICU at a quaternary institution run by four pulmonologists, critical care specialists, paediatric registrars, experienced medical officers, and nursing personnel consisting mainly of ICU-trained professional nurses. The patient-to-nurse ratio in this unit is 1:1. The PICU cohort started with 1 402 patients admitted during the study period; 725 surgical patients were excluded from the study to allow for direct comparison with medical patients in the non-PICU cohort. Eligible participants included all admissions to the respective units requiring ventilation for non-surgical conditions between 1 January 2015 and 31 December 2017.

The primary objective of the present study was to compare mortality between critically ill patients who required ventilation for more than 24 hours in a non-PICU setting v. those admitted directly to a PICU. The secondary objective was to describe patients' clinical characteristics and demographics and to correlate clinical features with outcomes, i.e. mortality or survival to discharge.

Data collection

The investigator reviewed charts of all eligible participants and entered them on an Excel (Microsoft Corp., USA) spreadsheet. All patient identifiers were removed, and the database was password protected.

Statistical analysis

The statistical data analysis was conducted in R Statistical computing software of the R Core Team, 2020, version 3.6.3. The results are presented in the form of descriptive and inferential statistics. The descriptive statistics of numerical measurements are summarised as the minimum, maximum, quartiles and interquartile range. The categorical variables are described as counts and percentage frequencies. The inferential statistics for the categorical included the chi-square test or Fisher's exact test, while the difference in medians was based on the Wilcoxon test. Binary logistic regression was used to determine the factors associated with the outcomes. All inferential statistical analysis tests were conducted at 5% significance levels.

Ethical consideration

Ethical approval was obtained from the Biostatistics Research Council (BREC) of the University of KwaZulu-Natal (KZN) (ref. no. BE568/18 BREC), and gatekeeper approval was obtained from KEH, IALCH and the KZN Department of Health.

Results

A total of 904 charts were reviewed, with 25.1% (n=227) of participants ventilated in the non-PICU setting, while 74.9% (n=677) of patients were admitted directly to PICU during the study period, with 56.0% (n=506) males (Table 1) with a similar proportion of males and females in the non-PICU and PICU (p=0.284). The age distribution of the cohort was 55.4% (n=501) between the age of 1 - <6 months, 15.0% (n=136) were 6 - <12 months, and 29.4% (n=266) were >12 months. The majority were HIV negative and well-nourished (83.5% and 83.4%), respectively. The proportions of HIV-positive to -negative patients were similar in both settings (p=0.593). There was a statistically significant difference in age by admission setting, with a higher proportion of patients under 12 months admitted in non-PICU than PICU (78% v. 67%, p=0.005). A significantly higher proportion of patients >12 months old were admitted to the PICU than the non-PICU (32.1% v. 21.6%, p=0.005). There was a statistically significant difference in nutritional status by admission setting, with a higher proportion of non-PICU patients classified as severe acute malnutrition (SAM) than PICU patients (26.4% v. 13.3%, p<0.001).

Overall, the most common admission diagnosis was pneumonia 59.0% (n=538), followed by septicaemia with septic shock 18.3% (n=165) and central nervous system (CNS) disorders 8.1% (n=73) (Table 2). Other diagnoses, including anaemia, renal disorders, malignancies, poisoning, and upper airway obstruction, contributed to a significant proportion of admission diagnoses (37.1% (n=335)). Admission diagnoses were similar in both the non-PICU and the PICU (p=0.683).

The results showed a significant correlation between admission setting and final diagnosis (p<0.001), where severe pneumonia, sepsis, septic shock, and acute gastroenteritis with hypovolaemic shock are the leading causes of admission and are confirmed as the most common final diagnosis in both the non-PICU and PICU. Patients admitted to non-PICU with septicaemia and septic shock were found to comprise 22.5% (n=51/227), while for the PICU were 14.9% (n=101/677), resulting in a significantly higher proportion of patients (51% (n=116/227)) on inotropic support in the non-PICU, than 39.6% (n=268/677) in the PICU setting (p=0.002).

Patients admitted to the non-PICU with septicaemia and septic shock comprised 22.5% compared with 14.9% (n=101/677) admitted to the PICU.

The overall median (IQR) length of hospital stay was 10.0 (5.0 - 17.0) days, with 25% of patients staying for a maximum of 5 days. Patients in the non-PICU setting had a significantly shorter hospital stay, with a median duration of 7.0 (IQR 3.0 - 14.0) days v. 11.0 (IQR 7.0 - 18.0) days in PICU (p<0.001).

Of the 904 patients included in the study, 26.5% (n=240) died. There was a statistically significant difference in mortality rates between the non-PICU setting and the PICU setting (46.3% v. 19.5%, p<0.001).

An adjusted multiple regression analysis of clinical characteristics (Table 3) shows that patients admitted to a non-PICU requiring

Table 1. Basic characteristics of paediatric patients requiring ventilation

Setting	Non-PICU (*n*=227)	PICU (*n*=677)	**p*-value	Overall (*N*=904)
Gender			chi-square, *p*=0.284	
Male	372 (54.9%)	134 (59.0%)		506 (56.0%)
Female	305 (45.1%)	93 (41.0%)		398 (44.0%)
HIV status			chi-square, *p*=0.593	
Negative	568 (83.9%)	187 (82.4%)		755 (83.5%)
Positive	109 (16.1%)	40 (17.6%)		149 (16.5%)
Nutritional status			chi-square, *p*<0.001	
NAM	587 (86.7%)	167 (73.6%)	<0.001[†]	754 (83.4%)
SAM	90 (13.3%)	60 (26.4%)	<0.001	150 (16.6%)
Age group			chi-square, *p*=0.005	
1 - <6 months	368 (54.4%)	133 (58.8%)	0.741	501 (55.5%)
6 - <12 months	92 (13.6%)	44 (19.5%)	0.122	136 (15.1%)
>12 months	217 (32.1%)	49 (21.7%)	0.009	266 (29.5%)

PICU = paediatric intensive care unit; HIV = human immunodeficiency virus; NAM = not acutely malnourished; SAM = severe acute malnutrition.
% and *p*-values based on non-missing cases.
*Parametric *p*-value.
[†]Row-wise proportional test.

Table 2. Analysis comparing non-PICU and PICU settings

Setting	Non-PICU (*n*=227)	PICU (*n*=677)	**p*-value	Overall (*N*=904)
Admission diagnosis			0.683	
Severe pneumonia	131 (57.7%)	407 (60.1%)		538 (59.5%)
Septicaemia, septic shock	40 (17.6%)	125 (18.5%)		165 (18.3%)
CNS disorders	22 (9.7%)	51 (7.5%)		73 (8.1%)
AGE, hypovolaemic shock	17 (7.5%)	35 (5.2%)		52 (5.8%)
Other	10 (4.4%)	35 (5.2%)		45 (5.0%)
CVS disorders	7 (3.1%)	24 (3.5%)		31 (3.4%)
Final diagnosis			chi-square, *p*<0.001	
Severe pneumonia	315 (46.5%)	112 (49.3%)	1.000	427 (47.2%)
Septicaemia, septic shock	101 (14.9%)	51 (22.5%)	0.062	152 (16.8%)
Other	148 (21.9%)	18 (7.9%)	<0.001	166 (18.4%)
CNS disorders	60 (8.9%)	22 (9.7%)	1.000	82 (9.1%)
CVS disorders	23 (3.4%)	6 (2.6%)	1.000	29 (3.2%)
AGE, hypovolaemic shock	30 (4.4%)	18 (7.9%)	0.349	48 (5.3%)
Total hospital stay			Rank sum	
Mean ±SD(CV%)				
Median(Q1 - Q3)	11.0 (7.00 - 18.0)	7.00 (3.00 - 14.0)	<0.001	10.0 (5.00 - 17.0)
n (min - max)	669 (1.00 - 130)	227 (0 - 136)		896 (0 - 136)
Inotropes			chi-square, *p*=0.002	
No	409 (60.4%)	111 (48.9%)	0.006	520 (57.5%)
Yes	268 (39.6%)	116 (51.1%)	0.006	384 (42.5%)
Outcome			chi-square, *p*<0.001	
Discharged	542 (80.1%)	122 (53.7%)	<0.001	664 (73.5%)
Died	135 (19.9%)	105 (46.3%)	<0.001	240 (26.5%)

PICU = paediatric intensive care unit; CNS = central nervous system; CVS = cardiovascular system; AGE = acute gastroenteritis.
% and *p*-values based on non-missing cases.
*Parametric *p*-value.

inotropes were 15 times more likely to die, with an odds ratio (OR) of 15.08 (95%CI, 9.68 - 24.34, *p*<0.001), while patients who were admitted to a PICU were 76% less likely to die (OR 0.24, 95%CI, 0.16 - 0.37, *p*<0.001).

Discussion

When comparing the characteristics and the outcomes of critically ill paediatric patients on mechanical ventilation in a non-PICU setting against those admitted to a PICU, we found higher mortality in the

Table 3. Univariate and multiple logistic regression to identify factors associated with mortality risk

Setting	PICU (*n*=677)	Non-PICU (*n*=227)	**p*-value	Overall (*N*=904)
Gender			chi-square, *p*=0.284	
Male	372 (54.9%)	134 (59.0%)		506 (56.0%)
Female	305 (45.1%)	93 (41.0%)		398 (44.0%)
HIV status			chi-square, *p*=0.593	
Negative	568 (83.9%)	187 (82.4%)		755 (83.5%)
Positive	109 (16.1%)	40 (17.6%)		149 (16.5%)
Nutritional status			chi-square, *p*<0.001	
NAM	587 (86.7%)	167 (73.6%)	<0.001†	754 (83.4%)
SAM	90 (13.3%)	60 (26.4%)	<0.001	150 (16.6%)
Inotropes			chi-square, *p*=0.002	
No	409 (60.4%)	111 (48.9%)	0.006	520 (57.5%)
Yes	268 (39.6%)	116 (51.1%)	0.006	384 (42.5%)
Age group			chi-square, *p*=0.005	
1-<6 months	368 (54.4%)	133 (58.8%)	0.741	501 (55.5%)
6-<12 months	92 (13.6%)	44 (19.5%)	0.122	136 (15.1%)
12+ months	217 (32.1%)	49 (21.7%)	0.009	266 (29.5%)

PICU = paediatric intensive care unit; HIV = human immunodeficiency virus; NAM = not acutely malnourished; SAM = severe acute malnutrition.
% and *p*-values based on non-missing cases.
*Parametric *p*-value.
†Row wise proportional test.

non-PICU than the PICU setting (46.3% v. 19.5%, *p*<0.001). This finding was similar to that in a study conducted in South Africa which showed higher mortality in the non-PICU than the PICU wards (46.2% v. 24.2%).[7] Patients >12 months old were 77% more likely to die (OR 1.77 (1.13 - 2.75), *p*=0.012)). These findings correlate with a study by Cawood *et al.*[7] which found higher mortality (48%) in the age group 1 - 5 years. However, in contrast, a study by Kruger *et al.*[2] in the Western Cape found higher mortality (75%) in children less than one year, and a study by Hendricks *et al.*[9] in KZN found 22.2% in the <1-year age group. The factors contributing to the higher mortality in the non-PICU were attributed to PICU admission criteria, with some patients (*i)* being too critically ill to be transferred to PICU, (*ii*) patients with an underlying lethal condition, (*iii*) patients with severe acute malnutrition, and (*iv*) patients assessed with poor prognosis. Therefore, those patients who did not meet the PICU admission criteria were admitted and managed in a non-PICU ward.[10,11] Admission to PICU follows the international guidelines for PICU admission. The policies include acting in the best interest of the child, assessing the severity of illness, and the presence of comorbidities to determine the benefit of PICU admission and the likelihood of a successful outcome.

We also found a significantly shorter duration of stay in the non-PICU than in the PICU setting (7 v. 11 days). This finding may be due to a referral bias, with only children surviving acute resuscitation and requiring longer ventilation being transferred to the PICU. Some children admitted for ventilation in the non-PICU setting may not require referral to the PICU as they improve from the acute condition, or the admission of critically ill patients who were ventilated and died during resuscitation and stabilisation in the non-PICU. The potential factors that resulted in patients presenting with critical conditions included delay in seeking healthcare services, consulting traditional healers, and using herbal medicine and home remedies.[12]

In our study, there was higher mortality among patients who required inotropes, with these patients being 15 times more likely to die (OR 15.08 (9.68 - 24.34), *p*<0.001). In addition, the use of inotropes, which may be used as a proxy for disease severity, was significantly more frequent in the non-PICU setting. The patients who required vasoactive agents had a higher mortality risk than those patients who did not require inotropic support.[13] These factors suggest that the cohort of patients admitted to the non-PICU were critically ill patients, and this can be attributed to delay in seeking medical care and delayed intervention.

There was a statistically significant association between admission setting and malnutrition, with 26.4% of patients in the non-PICU with severe acute malnutrition (SAM) which is often associated with major complications and high mortality (10 - 40%),[14] and it is still a serious public health concern in LMICs. In sub-Saharan Africa, 80% of deaths occur in children under five, with half of those deaths occurring among children with malnutrition.[15] Patients with SAM are deemed not suitable PICU candidates. Studies in the two rural hospitals in South Africa show higher mortality (25.9% and 24.4%) of patients admitted to PICU with SAM.[16] Various studies have reported adverse effects of SAM on respiratory function, affecting the ventilation drive and pulmonary defence mechanism and depleting energy reserves, causing loss of muscle mass and various electrolyte abnormalities. This may prolong respiratory failure, delay weaning from mechanical ventilation and prolong the PICU stay.[17]

Lack of resources and an insufficient number of ICU-trained nursing staff influence the suitability of the non-PICU setting to function as a PICU and may also contribute to the higher mortality in non-PICU settings.[18] For example, in regional hospitals, less than 25% of nursing staff are ICU trained, far below the international guidelines that recommend that a minimum of 50% of nursing staff be ICU trained in settings providing critical care.[19] Another contributory factor to patients being admitted and ventilated in the non-PICU is the lack of PICU beds nationwide.[19]

Severe pneumonia, sepsis, septic shock and acute gastroenteritis (AGE) with hypovolaemic shock are reported in the literature to be the leading causes of admission and death in children under five,[3] and it was confirmed in our study, as these were the most common final diagnoses in both the non-PICU and PICU. Severe pneumonia is also the leading indication for ventilation, followed by septicaemia and septic shock, CNS disorders, and AGE with hypovolaemic shock. These are all treatable conditions and have good outcomes with early recognition and early presentation. However, the high mortality from these causes suggests that these patients present in critically ill conditions with multiple organ dysfunction requiring extensive resuscitation and critical care. Most of the patients admitted to the non-PICU with sepsis and septic shock have a community-acquired infection, and present critically ill with multiple organ dysfunction, requiring inotropic support. Evidence suggests that these patients admitted to non-ICU wards decompensate rapidly and have higher adjusted mortality than patients admitted directly to PICU.[20] A study conducted by Lundberg *et al.*[21] showed that adult patients admitted with sepsis and septic shock in non-ICU wards had higher mortality than patients admitted directly to ICU (70% v. 39%). Contributing factors to this high mortality include delay in transferring to ICU and receiving intensive care.[21] While global mortality from septic shock may be reduced by encouraging critical care interventions which are feasible outside the formal PICU, including rapid recognition through screening all acutely ill patients for sepsis, checking blood lactate levels, antimicrobial therapy to treat sepsis and optimal fluid resuscitation using crystalloids for intravascular volume replacement, there is a long-term need to increase access to PICU for patients who require intensive care.[8]

We found a higher proportion (78%) of patients <12 months of age admitted and ventilated in the non-PICU ward. These findings were similar to studies in Western Cape and Gauteng, respectively, which found that most non-PICU admissions were patients <12 months.[2,7] The most frequent reason these patients were admitted and ventilated in a non-PICU was limited bed availability in the PICU,[10] which was described as a nationwide crisis in the national audit.[18] This correlates with the study findings conducted in KwaZulu-Natal in 2008/9, which showed that only 23% of public sector hospitals have ICUs compared with 84% in the private sector.[22] This means that there is high demand for PICU beds and effective triaging and prioritising patients for PICU admissions in the public sector throughout the country.[23] This results in critically ill children being managed in non-PICU wards with limited resources, and most of the nursing staff are not ICU trained, with a low nurse-to-patient ratio. Other potentially contributing factors include delayed presentation, which can be attributed to social factors such as income and poverty, location and availability of transport, leading to more advanced disease at presentation and poorer outcomes,[10] potential delays in the transfer of patients to the regional hospital from district/local clinics, and delays in transfer to ICU owing to lack of advanced life support services, longer waiting hours for ambulance services and emergency transport not being adequately equipped to transport critically ill children.

A major limitation of the present study was that we could not report on the severity of illness scores as this was a retrospective chart review, and some parameters were not consistently recorded in the clinical notes. However, the researchers feel that the study reflects the real-life differences between admissions to non-PICU and PICU wards. The finding may be generalisable to other settings in South Africa. Differences in the available resources and access to paediatric specialists in the non-PICU ward may make the findings difficult to extrapolate to less-resourced settings.

Conclusion

Critically ill children ventilated in a non-PICU setting at a regional hospital in KZN are more likely to be malnourished, require inotropes and have higher mortality. Although increasing access to PICU bed availability is a long-term goal, the high mortality in the non-PICU setting highlights the need to optimise the availability of resources in these non-PICU wards, optimise the effectiveness of transport to regional hospitals and ICU, intensive care training of the staff, and improve primary healthcare services.

Recommendations

Our recommendation is for a collaborative study involving several hospitals across South Africa to look at the outcomes of critically ill children receiving life-support therapies such as mechanical ventilation in non-PICU wards and also look at the factors that contribute to high mortality in these non-PICUs such as availability of resources to provide ICU care in these non-PICU wards, challenges with transfer to ICUs and availability of PICU beds.

Declaration. The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors. RM is a member of the AJTCCM editorial board. This manuscript was not given any priority over other manuscripts and was subject to the same review process as any other. Another editor assumed responsibility for overseeing the peer review of this submission, and the author's editorial board member status had no bearing on editorial consideration and a final decision.

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