PREVALENCE OF ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME AMONG CHILDREN WITH SEVERE RESPIRATORY DISTRESS IN KENYATTA NATIONAL HOSPITAL.

A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT FOR THE AWARD OF MASTERS OF MEDICINE IN PEDIATRICS AND CHILD HEALTH, UNIVERSITY OF NAIROBI.

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MMED PEDIATRICS AND CHILD HEALTH

DECLARATION

This dissertation is my original work and has not been presented for the award of a degree in any other university.

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This dissertation has been presented with our full approval as supervisors

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DEDICATION

This work is dedicated to the children of Africa who deal with difficult clinical conditions amidst poor infrastructure and scarce medical resources and still emerge strong….I pray that one day your story will be different.

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I would like to express my sincere appreciation:

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ABBREVIATIONS

ARDS	Acute respiratory distress syndrome
ALI	Acute lung injury
PaO_2	Partial pressure of oxygen expressed in millimeters of mercury
FiO_2	Fraction of inspired oxygen
SpO_2	Pulse oximetric oxygen saturation
ICU	Intensive care unit
WHO	World Health Organization
ETAT	Emergency triage and treatment
PRISM	Pediatric risk of mortality
PEEP	Positive end expiratory pressure
PIP	Peak inspiratory pressure
ECMO	Extracorporeal membrane oxygenation
PR	Pulse rate
RR	Respiratory rate
AECC	American European Conference Consensus

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ABSTRACT

Background: Acute lung injury (ALI) is defined as a syndrome of acute and persistent lung Inflammation with increased vascular permeability. Acute respiratory distress syndrome (ARDS) refers to a severe spectrum of ALI and shares the same criteria of definition with ALI but with Worse hypoxemia. There are no previous studies on ALI and ARDS carried out locally.

Objectives: To determine the prevalence of ALI and ARDS amongst children hospitalized with respiratory distress at Kenyatta National Hospital (KNH and to describe the spectrum of clinical conditions associated with ALI and ARDS.

Methods: A descriptive cross sectional study was conducted among children aged 2 months to 12 years hospitalized at KNH with respiratory distress (tachypnoea and use of accessory muscles of respiration).

Results: We enrolled a total of 152 children with severe acute respiratory distress. Their median (IQR) age was nine (6 to 14) months. 77(50.7%) were males. Wasting, stunting and being Underweight was reported in 64 (42.1%), 15 (9.9%) and 49 (32.2%) children respectively. Fifty eight children had either ALI or ARDS thus an overall prevalence of 38.2% (95% Confidence Interval (CI) 16.2% - 45.9%). The prevalence of ARDS was 27.0% (95% CI 19.9%-34.0%). Seventeen children (11.2%) met the criteria for ALI. Analysis of the spectrum of clinical conditions associated with ALI/ARDS revealed that almost all the sampled children were suffering from pneumonia (150, 98.7%). Sixteen (10.2%) and three children (2.0%) were diagnosed with bronchiolitis and sepsis respectively. Gender, age, area of residence and having a family member who smokes were not associated with ALI or ARDS. Likewise, none of the anthropometric indices was associated with ALI or ARDS. More children who were reported to have been hospitalized in the past were found to have ALI or ARDS although this association failed to reach statistical significance (p=0.072).

Conclusions and Recommendations: Prevalence of ARDS and ALI among children with severe respiratory distress was found to be 27.0% (95% CI: 19.9%- 34.0%) and 11.2% (95%CI 6.2%-30.4%)respectively.

CHAPTER ONE: BACKGROUND AND LITERATURE REVIEW

INTRODUCTION

Acute lung injury and acute respiratory syndrome are a spectrum of diseases that cause respiratory failure that can be a threat to life. At a cellular point, the diseases are characterized by diffuse damage to the alveolar, pulmonary oedema, and capillary leakage of the alveolar. These pathological aspects eventually lead to decreased lung compliance, decreased oxygenation, and infiltrates on both side of the lungs fields when a chest radiograph is taken.

The two conditions are associated with several causative factors which include severe infection, lower respiratory tract infection, soft tissue injuries after trauma and repeated blood transfusions.

The two conditions, once diagnosed, continue to feature as a burden in the intensive care units and are associated with significant morbidity and mortality. While the world has made significant leaps in diagnosis and management, these two conditions are extensively under diagnosed in our set up and therefore poorly managed.

1.2 Literature Review

1.2.1 Acute Respiratory Distress Syndrome

The first description of acute respiratory distress syndrome (ARDS) appeared in 1967, when Ashbaugh and colleagues (1) described 12 patients with acute respiratory distress, cyanosis refractory to oxygen therapy, decreased lung compliance, and diffuse infiltrates evident on the chest radiograph. Initially it was called the adult respiratory distress syndrome. However, this entity is now termed the acute respiratory distress syndrome, since it does occur in children.

In 1988, Murray et al (2) developed an expanded definition that quantified the physiologic respiratory impairment through the use of a four-point lung injury scoring system that was based on the level of positive end-expiratory pressure, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, the static lung compliance, and the degree of infiltration evident on chest radiographs. Other factors included in the assessment were the inciting clinical disorder and the presence or absence of no pulmonary organ dysfunction.

In 1994, a new definition was recommended by the American–European Consensus Conference Committee (3). The definition was done in a four point criteria (a-d) below. The consensus definition has two advantages. First, it recognizes that the severity of clinical lung injury varies: patients with less severe hypoxemia as defined by a ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FIO_2) of less than 300 and greater than 200 are considered to have acute lung injury, and those with more severe hypoxemia as defined by a ratio of 200 or less are considered to have the acute respiratory distress syndrome. Second, the definition is simple to apply in the clinical setting. The 1994 consensus definition is widely accepted for clinical research and trials. The 1994 American European conference consensus on definition of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) is defined by the presence of the following four:

(NOTE: PaO_2 is expressed in millimetres of mercury (MmHg) and FiO_2 is expressed as a proportion in decimal form between 0.21 and 1.0 and this is determined by what mode of oxygen the patient is on.(The pulse oximetry technique and the blood gas analysis technique are further expounded on under study procedure in appendix 11)

a) Acute onset.

b) Bilateral infiltrates on chest radiograph

c) i) ALI – A ratio of partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) ;

-PaO_2/FiO_2 of 201-300mmHg.

Alternatively it can be expressed as a ratio of pulse oximetric saturation of oxygen (SpO2) to the fraction of inspired oxygen (FIO2) as;

-SpO_2/FiO_2 of 235-315mmHg

ii) ARDS - A ratio of partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) as;

-PaO_2/FiO_2 of less or equal to 200mmHg

Alternatively -SpO_2/FiO_2 of less or equal to 235mmHg

d) Absence of cardiogenic oedema which can be done by;

i) Echocardiography and /or

ii) Measurement of capillary wedge pressures by cardiac catheterization and/or

iii) Clinical assessment using physical examination.

For purposes of this study, the clinical history and clinical examination was used to rule out cardiogenic oedema.

While the above criteria was used, it is important to note that a newer definition of acute respiratory distress syndrome was being discussed in Berlin, Germany and the results were published after the proposal had been passed and collection of data commenced. Researchers had noted that there were some research and clinical gaps that AECC had not addressed. The Berlin definition (4) was designed to close those gaps. The definition also did away with the term acute lung injury and defines acute respiratory distress as mild moderate and severe depending on PEEP values and the partial pressure of oxygen divided by fraction of inspired oxygen. It further defines the term acute and the features to look out for in the chest radiograph. The new Berlin definition is outlined below:

Table 1.The Berlin Definition of Acute Respiratory Distress Syndrome (4)

	Acute Respiratory Distress Syndrome		
Timing	Within one week of a known clinical insult or a new/ worsening respiratory symptoms		
Chest Imaging	Bilateral opacities- not fully explained by effusions, lobar/lung collapse or nodules		
Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload: Need objective assessment (e.g echocardiography) to exclude hydrostatic oedema if no risk factor is present.		
	MILD	MODERATE	SEVERE
Oxygenation	200 <Pa02/FiO2≤300 With PEEP or CPAP≥5cmH2O	100<Pao2/FiO2≤ 200 With PEEP≥5cmH2O	PaO2/FiO2≤100 With PEEP≥5cm H2O

1.2.3 Clinical disorders associated with the development of ALI and ARDS

There are two main categories of disorders that are associated with development of ALI and ARDS (5);

a) Direct Lung Injury.

Direct lung injury is mainly caused by lung infections, chemical lung injury by aspiration of gastric contents or inhalation of hydrocarbons e.g. kerosene. The less common causes include pulmonary contusion (trauma), fat embolism, near drowning and inhalational injury especially with burns patients.

b) Indirect Lung Injury.

Indirect lung injury is mainly caused by sepsis, severe trauma with haemorrhagic shock and multiple blood transfusions. It occurs less commonly in patients who have undergone cardiopulmonary bypass surgery, patients with drug overdose and patients who have had multiple transfusions with blood products e.g. Fresh frozen plasma.

1.2.4 Pathophysiology of ALI and ARDS (6)

In normal physiology, healthy lungs regulate the movement of fluid to maintain a small amount of interstitial fluid and dry alveoli. Following lung injury, there's excessive fluid in both the interstitial space and alveoli resulting in impaired gas exchange, decreased compliance and increased pulmonary arterial pressure. Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are consequences of alveolar injury producing diffuse alveolar damage. This results in release of pro inflammatory cytokines e.g. Tumour necrosis factor, IL-1, IL-6, IL-8.The cytokines recruit neutrophils to the lungs where they become activated and release toxic mediators (e.g. reactive oxygen species and proteases) that damage the capillary endothelium and alveolar epithelium. This allows protein to escape from the vascular space. The oncotic gradient is lost resulting in overwhelmed lymphatic system. Regulation of alveolar fluid clearance is lost and air spaces fill with bloody, protein filled oedema fluid and debris from degenerating cells. Functional surfactant is lost resulting in alveolar collapse. Pathologically there are three distinct stages as defined below:

a) Exudative phase (24-48 hours)

This is characterized by diffuse alveolar damage.

b) Proliferative Stage (7-10 days)

This stage is characterized by resolution of pulmonary oedema, proliferation of type 11 alveolar cells, squamous metaplasia, and interstitial infiltration by myofibroblasts and early deposition of collagen.

c) Fibrotic stage (> 14 days)

In this stage, there's obliteration of normal lung architecture, diffuse fibrosis and cyst formation.

1.2.5 Management

Management of ARDS consists of appropriate treatment of underlying causative illness, excellent supportive care and prevention of complications (7). Supportive measures include infection control, early enteral nutrition, stress ulcer prophylaxis and thrombi prophylaxis. This should be combined with focused ventilator strategies and appropriate treatment of the underlying conditions

Specific management includes;

a) Lung protective ventilation with low tidal volume, moderate positive end expiratory pressure (PEEP), peak inspiratory pressure (PIP) of less than 30cm H2O.

b) Prone positioning.

c) Conservative fluid strategies

d) Low dose early corticosteroids

e) Extra corporeal membrane oxygenation (ECMO) (8)

Many published studies on Acute Lung Injury and Acute Respiratory Distress Syndrome in both the adult, adolescent and paediatric populations estimate a prevalence of 1% to 27%. However there have been very wide variations between different studies from different countries. There are very few researches carried out on children and adult ones have been previously used for comparison purposes.

Goh A et al conducted a research on the prevalence and outcome of ARDS in a paediatric intensive care unit in Malaysia (8). The design was partly retrospective and partly prospective and was carried out over a 2-year period on children aged 12 years and below. The investigators applied both the AECC and the Murray lung scoring criteria. This was partly for comparison of the two diagnostic criteria. Both methods identified the same patients and eventually the same number of patients. A total of 494 patients were recruited for the study, 21 of who fulfilled the diagnostic criteria for ARDS. This gave a prevalence of 4.2% for ARDS. This study however, did not assess for ALI among its recruited patients.

Simon Erickson et al carried out a research that was a prospective multicentre observational study on children aged 16 years and below in intensive care units in Australia and New Zealand over a period of one year (9). All the children admitted in the ICU during the period were screened using the AECC guidelines. The patients were then followed up for 28 days or until discharge or until death. During the period, 5252 children were admitted and mechanically ventilated. Out of this 117 fulfilled the AECC guidelines for both ALI and ARDS which is a prevalence of 2.2%. Acute Lung Injury had 14 out the 117, which gave an overall prevalence of 0.3% while ARDS had 103 of the 117 diagnosed with both conditions and an overall prevalence of 1.9%.

A group led by Dahlem P conducted a cross sectional study on the prevalence and outcome of ALI and ARDS on mechanically ventilated children aged 15 years and below in a paediatric intensive care unit in Netherlands over a period of one year (10). The children were evaluated using the AECC criteria. A total of 443 children were evaluated, 44 of them fulfilled the criteria for both ALI and ARDS giving a prevalence of 9.9%. Patients with ALI were 20 out of 44

giving an overall prevalence of 4.5% while patients with ARDS were 24 out the 44 giving an overall prevalence of 5.4%.

A research by Jerry J Z et al was conducted as a population based prospective cohort study that was designed to determine the population incidence and outcome of paediatric acute lung injury (11). The research was performed at all hospitals admitting critically ill children in King County Washington. It was done on children aged 6 months to 15 years who required invasive (through endotracheal tube or tracheostomy) or non-invasive (through a full face mask) mechanical ventilation. They utilized the AECC criteria. They found a prevalence of 27.6% (39/141) for both ALI and ARDS. Further, ALI accounted for 7 % (10/141) while ARDS accounted for 20.6 %. (29/141).

Andrew A Q et al conducted a prospective cross sectional study on the prevalence of ALI and ARDS outside the intensive care units (12). This group evaluated all the adult patients (above 18 years) who were admitted to respiratory isolation rooms on the general wards of a large tertiary hospital over a period of one year. This group utilized the American-European Conference Consensus (AECC) criteria to diagnose the patients. A total of 715 patients were screened, 62 of which fulfilled the ALI screening criteria with a prevalence of 9%. Further, 15 out of 715 fulfilled the ARDS criteria giving a prevalence of 2%.

In comparison, Hughes M et al conducted a prospective cross sectional study on the prevalence of ARDS in 23 adult intensive care units in Scotland over a period of 8 months(13). A total of 4530 patients aged 15 years and above were recruited into the study. The patients with ARDS were identified using the diagnostic criteria defined by the AECC. About 367 patients were diagnosed with ARDS, giving a prevalence of 8.1%. This study did not assess for patients with ALI.

Research by Gordon D R et al conducted a prospective cohort study in 21 intensive care units in Washington over a period of one year (14). The group applied the AECC criteria to diagnose the patients. They evaluated mechanically ventilated patients aged 15-80 years. A total of 4251 patients were enrolled. The prevalence of ALI was 26.2% (1113 out of 4251) and that of ARDS was 19.5% (828 out of 4251).

1.3 STUDY JUSTIFICATION

Kenyatta National Hospital is the largest public referral center in Kenya (15). In 2011, about 11804 children were seen and admitted. About 1952 were treated for severe pneumonia. 313 (16%) of those who had pneumonia died while on treatment. The trend has been like that in the last few years. According to the 2008/09 Kenya Demographic Health Survey, the under-five mortality is 74/1000 live births while the infant mortality rate is 52/1000 live births (9). As a country, pneumonia and other respiratory infections remain the leading causes of death amongst young children, contributing about 17% of all the under-five mortalities in the country (15).

ALI and its more severe form ARDS are a spectrum of lung diseases characterized by a severe inflammatory process causing diffuse alveolar damage and resulting in a variable degree of ventilation perfusion mismatch, severe hypoxia and poor lung compliance. Various studies carried out among adults, adolescents and children have shown the prevalence of ALI and ARDS to range between 1% to 27% as outlined above. These studies have been carried out in different countries but unfortunately, to the author's best knowledge, none have been carried out within Africa. Evidence also points to high mortality of the two conditions ranging between 26% to 58% with pneumonia and sepsis listed as the main causes of death among patients with ALI and ARDS (5 ,6, 7). There's little or no evidence of what extent ALI and ARDS occur locally among children with severe respiratory distress. There's a high possibility that the two conditions are under recognized with fatal consequences. The understanding of actual prevalence of ALI and ARDS is useful and will guide planning and provision of the requisite intensive care necessary to minimize death in these children as patients with ARDS need to be mechanically ventilated during the course of their illness. Prompt appropriate management with ICU provision is essential to improve outcome.

CHAPTER 2- RESEARCH QUESTIONS AND STUDY OBJECTIVES

2.1 Research Questions

1) What is the prevalence of acute lung injury and acute respiratory distress syndrome amongst children aged two months to twelve years admitted to Kenyatta National Hospital with acute severe respiratory distress.

2) What are the associated clinical conditions in children diagnosed with acute lung injury and acute respiratory distress syndrome in children admitted with acute severe respiratory distress syndrome at Kenyatta National Hospital.

2.2 Study Objectives

2.2.1 Primary Objectives

1. To determine the prevalence of Acute lung injury amongst children aged two months to twelve years hospitalized with acute severe respiratory distress at Kenyatta National Hospital.
2. To determine the prevalence of acute respiratory distress syndrome amongst children aged two months to twelve years hospitalized with acute severe respiratory distress at Kenyatta National Hospital.

2.2.2 Secondary Objectives

1. To describe the spectrum of clinical conditions associated with acute lung injury and acute respiratory distress syndrome in the study population

CHAPTER THREE: METHODOLOGY

3.1 Study Design

The study utilized a descriptive cross sectional design.

3.2 Study Area

The study was carried out in Kenyatta National Hospital; a national tertiary referral centre located about five kilometres from the central business district of Nairobi, the capital city of Kenya. It receives patients from all the forty-seven counties. It serves an inpatient paediatric population of about 11000 per year. The hospital has four major paediatric wards, and an intensive care unit. The paediatric wards have a capacity of 60 beds each. The hospital has an intensive care unit with a capacity of 21 beds. This is where paediatric critical care specialists, anaesthesiologists and paediatricians manage critically ill children. The study was carried out in the acute rooms of paediatric medical wards where most patients with respiratory distress are first admitted.

3.3 Study Population

The study population comprised all children aged 2 months to 12 years admitted to the paediatric wards with acute severe respiratory distress.

3.3.1 Inclusion Criteria

a) Age: 2 months to 12 years.

b) Presence of respiratory distress (tachypnoea and use of accessory muscles of respiration). Presence of respiratory distress is evidenced by having a higher respiratory rate than the recommended for the age bracket. Increased respiratory rate is defined as follows:

i) >5O breaths /minute for a child aged 2-11 months.

ii) ≥40 breaths /minute for a child aged 12-59 months.

Severe respiratory distress is associated with either of the following:

i) Lower chest wall in drawing.

ii) Central cyanosis.

iii) Inability to drink or breastfeed for infants.

iv) Grunting and head nodding for a child less than 12 months.

3.3.2 Exclusion Criteria

a) Known chronic cardiac disease.

b) Chronic lung disease.

c) Renal failure

d) Patients with glomerulonephritis

3.4 Case Definitions

3.4.1 Acute Lung Injury

All children with acute severe respiratory distress who fulfil the inclusion criteria and have;

a) PaO_2/FiO_2 ratio of 201-300mmHg or SpO_2 /FiO_2 of 235-315 mmHg

b) Bilateral infiltrates on CXR –These were bilateral opacities on the chest radiograph that could not fully be explained by effusions, lobar or lung collapse or nodules.

c) Absence of cardiogenic oedema, ruled out clinically.

3.4.2 Acute Respiratory Distress Syndrome

All children with acute severe respiratory distress who fulfil the inclusion criteria and have;

a) PaO_2/FiO_2 ratio of less or equal to 200mmHg or SpO_2/FiO_2 of less or equal to 235mmHg

b) Bilateral infiltrates on chest x-ray

3.5 Sample Size

We used a cross-sectional design to determine the prevalence of ARDS among children. Therefore, Fisher's formula was appropriate since it provides the minimum sample size required to estimate a proportion within a certain degree of confidence (in this case 95% confidence interval). Sample size calculation was done as follows

$$n = \frac{z^2 \times p\,(1-p)}{d^2}$$

Where;

n - Minimum required sample size

z – Standard normal deviate corresponding to 95% confidence interval (1.962)

p - Estimated prevalence of ARDS (10% Dahlem et al)

d - Margin of error/Precision (±5%)

Substituting into the formula; $n = \frac{1.962^2 \times 0.1 (1-0.1)}{0.05^2}$

n=138.

The estimated prevalence was drawn from a research done by Dahlem P et al on the prevalence of acute respiratory distress syndrome at the Emma Children's hospital academic and medical centre in Amsterdam, Netherlands in which the prevalence of ARDS was 10%

3.6 .Sampling Method

Consecutive sampling was done. The principle investigator and the research assistants visited the designated wards on a daily basis and enrolled the children who met the inclusion criteria until the sample size was met.

3.7. Equipment

a) Questionnaire

This data collection tool was structured to collect the social demographic data, general examination findings, respiratory examination findings and the investigations that were relevant to our study which included a blood gas analysis and a chest radiograph. The method of oxygen that the patient was on was recorded as this was later used to determine the partial pressure of oxygen expressed as a proportion (FIO2).

b) Pulse Oximeter

Our study used a portable hand held battery powered pulse oximeter (Nonnin Onyx 9500 manufactured in the UK). This was used to determine the oxygen saturations of each participant.

c) Anthropometric Tools

i) Weighing machine-a calibrated digital salter scale model 9010.

ii) Stadiometer –standard stadiometer was used.

d) Blood Gas Analysis Machine

Blood gas analysis was done using the blood gas analyser machine located in the intensive care unit lab. It is a rapid lab 348 semiautomatic machine manufactured by Bayer UK.

3.8 Study Personnel

Principle investigator, Dr Margaret Wainaina.

Two research assistants - These were qualified clinicians who have completed their diploma course in clinical medicine. They were trained on the standard case definitions as well as all the procedures regarding the study. Further, the principal investigator collected the initial part of the data with the assistants just to make sure they had gotten the case definitions right, the examination required and the procedures done correctly.

3.9 Study Procedures

3.9.1 Patient Enrollment

The principle investigator together with the two research assistants recruited eligible children in the acute rooms of the paediatric wards within 24 hours of admission. Eligible children included patients aged 2 months to 12 years who presented with acute severe respiratory distress and were not known to have chronic respiratory conditions, cardiac failure or renal failure. Recruitment was consecutive. All children who met the inclusion criteria were enrolled into the study. The research assistants were trained on the proper use of the pulse oximeter machine and the blood gas sampling technique. The procedures are further defined in Appendix 11.

3.9.2 Clinical Assessment and Consent

All children with severe respiratory distress were assessed. For any child who met the inclusion criteria, the investigator explained the nature of the study to the parent or guardian and then sought a written consent to allow the child to participate. Demographic data and clinical history were obtained and recorded in a questionnaire. The anthropometric measurements (weight, height, and length) were measured. The weight was taken using a calibrated salter scale model 9010 and recorded to the nearest 0.1 kg. The standing height (for children aged 2 years and above) and the recumbent length (For children aged below 2 years) were measured to the nearest 0.1 cm on a wooden length board with the assistance of the caregiver. Anthropometric z

scores were determined using the 2006 WHO growth standards. (WHO Anthro version 2006 version 3.22 Jan 2011). After this, the investigator did a physical examination on the child and recorded the findings in the questionnaire.

3.9.3 Oxygen Administration and Determination of FiO2

Different methods were used to deliver oxygen to the child with severe respiratory distress. Most devises quoted give a range of the percentage of the oxygen delivered to the patient while given at the standard flow rate. For purposes of this study, the average (mean) of the range will be used as the percentage and will then be used to determine the FiO_2. The calculated mean percentages for different methods (as per World Health Organization guidelines) used will be as follows;

Table 2: Oxygen Administration and Fraction of Inspired Oxygen (FIO2) Determination (16)

Method	**Standard flow rate of oxygen source**	**% Range of inspired oxygen concentration**	**% Mean of inspired oxygen concentration**	**F IO_2**
Nasopharyngeal catheter	1-2 L/min	45-60	52.5	0.525
Nasal prongs	1-2 L/min	30-35	32.5	0.325
Face Mask	5-6 L/ min	40-60	50	0.5
Oxygen face mask with Reservoir bag	10-15L/min	80-90	85	0.85

3.9.4 Drawing of Arterial Blood for Arterial Blood Gas Analysis.

About 3mls of arterial blood was drawn from each study participant and was then taken to the intensive care lab for arterial blood gas analysis (procedure in detail in appendix II). The partial pressure of oxygen from the result would be recorded in the questionnaire. This result was

then used as part of the calculation to determine whether the patient had ALI or ARDS. For any patient who met the criteria for ALI or ARDS, the primary clinician was informed in order to institute the management promptly. The blood gas result would then be handed over to the primary clinician to assist in further management of the patient.

3.9.5 Chest Radiograph

A chest x-ray was needed as part of the diagnostic criteria. For every participating child, the guardian was informed about the need for a chest radiograph. This is often done as part of management of children with severe respiratory distress. For children whose chest radiographs had already been done, the primary clinician was informed and the films forwarded to the radiologist. If none had been done, a requisition form was written and the patient taken for the procedure. The film was then forwarded to the radiologist for reporting. A second radiologist reviewed the films without knowing the diagnosis arrived at by the first radiologist. Bilateral infiltrates were defined as opacities on the left and right side of the chest radiograph that could not be fully explained by effusions, lobar or lung collapse or nodules. Only those with similar reporting were included in the data analysis. The results were recorded in the questionnaire. Bilateral infiltrates were recorded as a positive finding and no bilateral infiltrates recorded as negative. The films and the reports were then handed back to the primary clinician.

3.9.6 Exclusion of Cardiogenic Edema

For purposes of this study exclusion of cardiogenic oedema was done through a clinical evaluation of symptoms and physical examination. Known cardiac patients were excluded from the study. Patients found to have signs and symptoms of congestive cardiac failure were also excluded from the study. The clinical parameters used for this included gallop rhythm or tachycardia, bilateral crackles on the lung bases, sacral or pedal oedema and hepatomegally.

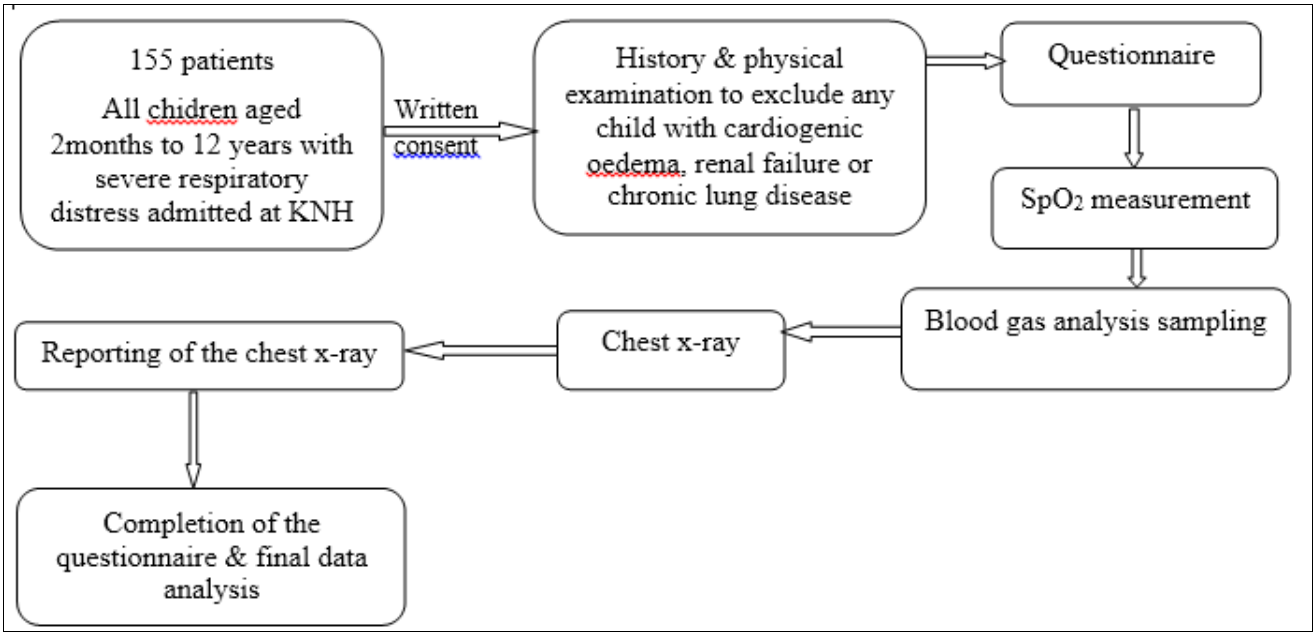


Figure 1- Study Procedures Flow Chart

3.10. Control of Biases and Errors

Data was collected using a standard questionnaire. The principle investigator ensured proper training of the research assistant and also participated in the data collection. During the entire period of data collection, the principal investigator would carry out random spot checks on the research assistant's work against the documents at least 3 times in a week to ensure that quality data was collected. Pre testing of the study tool was done before the full data collection was started and this helped to improve the data collecting tool.

3.11 Ethical Considerations

1) Approval

Ethical approval was sought from Kenyatta National Hospital/University of Nairobi Ethics and Research Committee prior to the commencement of the study.

2) **Risks**

No experimental investigation was employed in this study. All the medical procedures were carried in accordance to the government of Kenya and Kenyatta National Hospitals protocols. The amount of blood drawn from each child was not likely to cause any adverse effects. As much as possible, the procedure was aligned together with the clinical management to avoid any extra discomfort.

3) Benefits

The study participants had an arterial blood gas analysis and a chest radiograph done at no extra cost to the patient and the results were made available to the primary clinical team. Any significant finding was communicated to the paediatric team for appropriate adjustment of the patient's management

4) Confidentiality

Subject confidentiality was strictly adhered to. Study protocol, documentation and all other information were held in strict confidence. No information concerning the study was released to any unauthorised third party.

5) Informed consent

Patient's guardians were given a full explanation of the procedures the patients were to undergo before signing a written consent. The consent described the purpose of the study and the clinical procedures that were carried out. The investigators conducted the consent discussion and ensured that the parents or guardians understood before signing. They also answered any question they had regarding the study. Consent was voluntary and without coercion. Documentation was done in writing before the study procedure commenced.

6) Dissemination of Results

Oral and poster presentations of the findings of the study were presented to the Department of Paediatrics and Child Health, University of Nairobi. An executive summary of the findings and recommendations of the study will be presented to Kenyatta National Hospital within three months of completion of the study

3.12. Data Management and Statistical Analysis

Filled questionnaires were solely utilized for this study and subsequently stored safely at the end of the study after entering the data in Microsoft Excel 2013®. Data was then imported from the spreadsheets to other software for further data management and analyses.

Anthropometric indices including weight-for-age z-scores (WAZ), weight-for-height z-scores (WHZ) and height-for-age z-scores (HAZ) were computed using Epi-Info/ENA® version 3.5.1, 2008 (CDC, Atlanta, Georgia) software, according to WHO reference values [1]. Based on the recommendations of the WHO Global Database on Child Growth and Malnutrition, z-scores < -2

standard deviations (SD) and < -3SD defined moderate and severe under-nutrition, respective1:36 PM16 November 201511/16/2015 1:36:18 PM16 November 2015ly. Statistical analyses were conducted using IBM SPSS Statistics® 21.0 (IBM Corp., Armonk, NY). Analyses involved computation of descriptive statistics such as frequencies, means and standard deviations.

The Wald method of calculating confidence interval (CI) was utilized in calculating 95% CIs for the prevalence. The formula is presented below.

$$p = \hat{p} \pm z_{\alpha/2}\sqrt{p(1-p)/n}$$

Where

n= total no. of children examined (sample size)

$Z_{\alpha/2}$ – Standard normal deviate corresponding to 95% CI (1.962)

p - Proportion of children presenting with the characteristic of interest.

Chi-square (χ^2) test or Fisher's Exact test were used test associations between selected independent variables and the dependent variable (presence of ALI or ARDS).

The threshold for statistical significance was set at $p \leq 0.05$.

3.13 Study Limitations

Evaluation of cardiogenic edema was not done using capillary wedge pressure measurements. This was due to lack of proper equipment to measure the capillary wedge pressure in the facility and the invasive nature of the procedure. Cardiogenic edema was therefore ruled out through clinical evaluation.

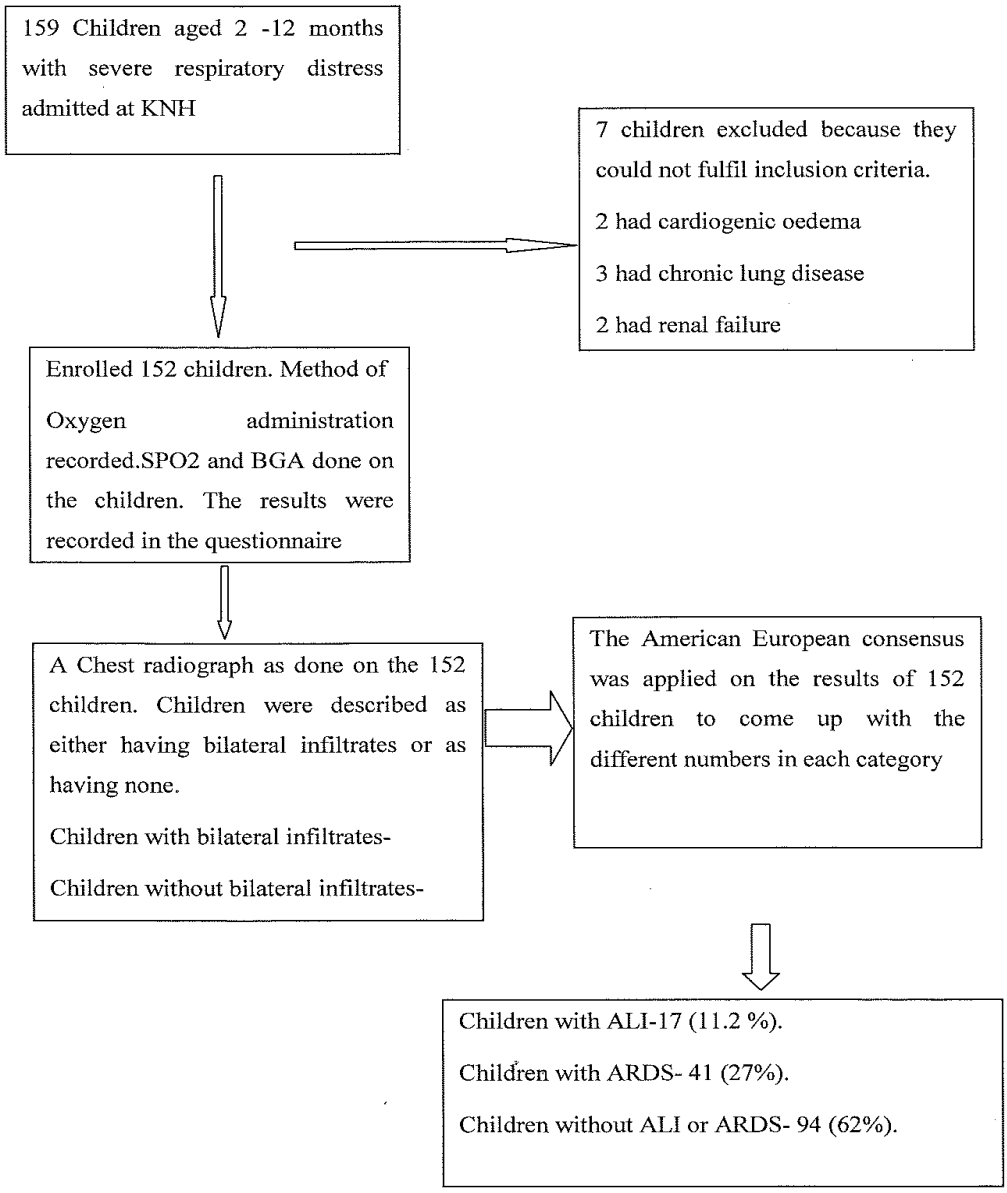
CHAPTER FOUR: RESULTS

A total of 159 children aged 2 months to 12 years, with severe respiratory distress and admitted

At KNH were enrolled in the study. After obtaining a written consent from the caregiver, history and physical examination were conducted to exclude any child with cardiogenic oedema, renal failure or chronic lung disease. An interviewer administered questionnaire was then used to capture data on various aspects concerning the child's social demographic attributes, and nutritional status. Pulse oximeter measurements were taken and blood gas analysis sampling was done. The patients were then taken for a chest radiograph .The films were taken to the study radiologist who reported on them. The results were then recorded in the questionnaire. Data from 152 were included in the analysis (Figure 2) on the following page..

Figure 2- Patient Enrolment and Evaluation Flow Chart

Figure 2- Patient Enrolment and Evaluation Flow Chart



4.1 Characteristics of the Sampled Children

Overall, we enrolled a total of 152 children with severe acute respiratory distress. They were of the median age 9 months (interquartile range (IQR): 6 to 14 months. Seventy seven (50.7%) of the children were males and 75 (49.3%) were females. Forty three (28.3%) of the enrolled children were aged five to eight months. Further, 29 (19.1%) and 16 (10.5%) children were in the age category of thirteen to sixteen months and more than sixteen months of age respectively. Additionally, 13.8% were aged four months or less. Most of the participants were residents of the city of Nairobi (112, 73.7%).

About 55 (36.2%) children had been hospitalized at least once during the period preceding the survey. All the children enrolled in the study had respiratory distress with all these respiratory symptoms reportedly lasting seven days or less. The observed range of symptoms together with the corresponding durations is listed on Table 4.3. An overwhelming majority (151, 99.3%) presented with a cough most of which was reported to have lasted between two and seven days (112, 73.7%). Difficulty in breathing was also reported in most of the children (148, 97.4%). The duration of the breathing difficulties was less than two days, two to seven days and more than 7 days in 36 (23.7%), 104 (68.4%) and 8 (5.3%) children respectively. Inability to breastfeed was reported in 38 children (25.0%) out of whom 16 and 21 had been experiencing this problem for a period lasting less than two days and two to seven days respectively. However, only 24 children had been observed to be abnormally sleepy in the period not exceeding seven days prior to the day that the study took place (Table 3).

Table 3: Sociodemographic and Clinical Characteristics of the Study Population (N=152)

Characteristic	Frequency	%	N
Gender			
Male	77	50.7	152
Female	75	49.3	
Age Category (Months)			
≤ 6	43	28.3	152
7 - 12	64	42.1	
13-18	27	17.8	
>18	18	11.8	
Residence			
Within Nairobi	112	73.7	152
Outside Nairobi	40	26.3	
Wasting			
Wasting (<-2 z-scores)	54	35.5	152
Normal (≥-2 z-scores)	98	64.5	
Underweight			
Underweight (<-2 z-scores)	49	32.2	152
Normal (≥2 z-scores)	103	67.8	
Stunting			
Stunting (<-2 z-scores)	15	9.9	152
Normal (≥-2 z-scores)	137	90.1	
Previous hospitalization			
Yes	55	36.2	152
No	97	63.8	
Respiratory symptoms			
Cough	151	99.3%	152
Difficulty in breathing	148	97.4%	152
Other clinical symptoms			
Inability to breastfeed	38	25.0%	152
Abnormally sleepy	24	15.8%	152

Anthropometric indices for the study children were computed based on WHO standards serving as the reference (WHO standards 2005). Wasting was found in 64 (42.1%) children while 49 (32.2%) children were found to be underweight. Fifteen (9.9%) of the participating children was classified as stunted (figure 3)

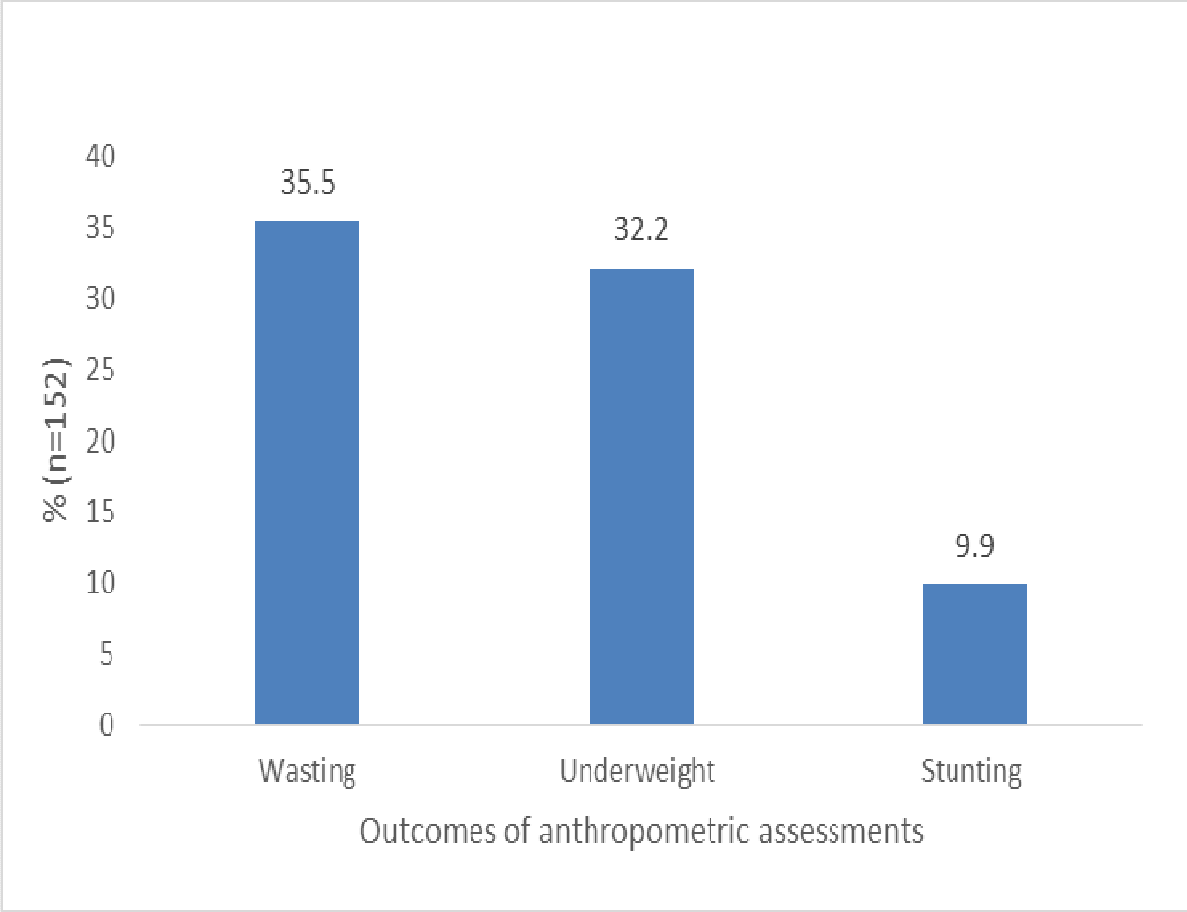


Figure 3. Prevalence of Wasting, Underweight and Stunting in Children Admitted with Severe Respiratory Distress.

4.2: Determination of ALI and ARDS

Table 4. PaO_2, FiO_2, PaO_2/FiO_2 and CXR findings in the study subjects

Characteristic	**Frequency**	**%**
Pao_2 (n=152)		
|<80		
80-100		
>100		
PaO_2/FiO_2 (n=152)		
≤200mmHg	78	51.3
201-300mmHg	54	35.5
>300 mmHg	20	13.2
Bilateral infiltrates in CXR (n=152)		
Present	71	46.7
Absent	81	53.3

The above are determinations according to American European Concensus conference criteria.

4.3: Prevalence of ALI and ARDS

Fifty eight children had either ALI or ARDS thus an overall prevalence of 38.2% (95% Confidence Interval (CI) 16.2% - 45.9%). The prevalence of ARDS was 27.0% (95% CI 19.9%-34.0%). Seventeen children (11.2%) met the criteria for ALI as shown in Table 5.

Table 5. Prevalence of ALI and ARDS

Condition	**Number (n=152)**	**Prevalence (95% CI)**
ALI	17	11.2% (6.2%-30.4%)
ARDS	41	27.0% (19.9%- 34.0%)
ALI/ARDS	58	38.2% (16.2% - 45.9%)

4.4: Spectrum of Clinical Conditions Associated with ALI/ARDS

More children who were reported to have been hospitalized in the past were found to have ALI or ARDS when evaluated against the children who had no history of hospitalization although this was not significant statistically (respectively, 44% versus 35%, p=0.072). Wasting,

stunting, being underweight as well as having a family member who smokes was not associated with having ALI or ARDS (Table 6).

Table 6. Relationship between ALI and ARDS With selected Clinical Characteristics

Characteristic	**ALI/ARDS**		**N**	**OR(95**	**P-value**
	Present(n	**Absent**			
Previous					
Yes	24(44%)	31(56%)	5	1.25(0.8	0.295
No	34(35%)	63(65%)	9	**REF**	
Wasting(<-2 z-					
Yes	18(33%)	36(67%)	5	0.73	0.363
No	40(41%)	58(59%)	9	**REF**	
Underweight(<-2 z-					
Yes	15(31%)	34(69%)	4	0.62(0.3	0.187
No	43(42%)	60(58%)	1	**REF**	
Stunting (<-2 z-					
Yes	4(27%)	11(73%)	1	0.38(0.1	0.101
No	54(39%)	83(61%)	1	**REF**	
Smoking within the					
Yes	7(35%)	13(65%)	2	0.86(0.3	0.755
No	51(39%)	81(61%)	1	**REF**	

Having pneumonia was not associated with the presence of either ALI or ARDS in the sampled children (Table 7). On the other hand, a significantly greater proportion of children with VSP were found to have ALI or ARDS when compared to those with non-severe pneumonia (60% versus 47%, p=0.002). Very severe pneumonia was associated with approximately three-fold increased likelihood of having ALI or ARDS (OR=2.91, 95% CI: 1.49-5.68). A higher percentage of children who were diagnosed with meningitis (52%) were found to have either ALI or ARDS when assessed against those without meningitis (35%). Nonetheless, the association was not significant (p=0.106). The associations between ALI/ARDS with gastroenteritis, rickets, and bronchiolitis were of no significance, statistically, as shown in Table 4.11. Bronchiolitis, sepsis, PEM and being sero-exposed were not associated with the presence of ALI/ARDS in the sampled children (Table 7).

Table 7. Association between the observed spectrum of clinical conditions and ALI/ARDS

Characteristic	ALI/ARDS		N	OR (95%CI)	P-
	Prese	Absen			
Pneumonia					
Yes	57(38	93(62	150	0.62(0.04-	0.925
No	1(50%)	1(50%	2	**REF**	
Severity of					
VSP	38(48	41(52	79	2.54(1.28-	0.007
SP/P	19(27	52(73	71	**REF**	
Meningitis					
Yes	14(52	13(52	27	1.98(0.86-	0.106
No	44(35	81(65	125	**REF**	
Gastroenteritis					
Yes	13(36	23(64	36	0.89(0.41-	0.772
No	45(39	71(61	116	**REF**	
Rickets					
Yes	12(36	21(64	33	0.91(0.41-	0.810
No	46(39	73(61	119	**REF**	
Bronchiolitis					
Yes	6(37%)	10(63	16	0.97(0.33-	0.954
No	52(38	84(62	136	**REF**	
Sepsis					
Yes	2(67%)	1(33%	3	3.32(0.29-	0.558
No	56(38	93(62	149	**REF**	
Sero-exposed					
Yes	3(50%)	3(50%	6	1.66(0.33-	0.675
No	55(38	91(62	146	**REF**	

**P-value based on Fisher's exact test*

4.5 Associations between ALI and ARDS with selected demographic attributes

Table 8 shows the association between ALI and ARDS with selected socio demographic attributes. There were no statistically significant variations in the prevalence of ALI and ARDS between sexes (p=0.456). A slightly higher proportion of children aged six months or less were diagnosed with ALI or ARDS compared to their counterparts aged more than six weeks (41% against 35% respectively). However, the difference failed to reach statistical significance (p=0.183). Place of residence showed no statistically significant associations with having ALI or ARDS (p=0.156).

8: Association between ALI and ARDS with selected Socio demographic attributes

Characteris	**ALI/ARDS**		**N**	**OR**	**P-**
Gender	**Present(n=58)**	**Absent**			
Female	31(41%)	44(59%)	75	1.31(0.68-	0.456
Male	27(35%)	50(65%)	77	**REF**	
Age					
≤6	20(47%)	23(54%)	43	1.33(0.89-	0.183
>6	38(35%)	71(65%)	10	**REF**	
Residence					
Outside	19(48%)	21(53%)	40	1.69(0.81-	0.156
Within	39(35%)	73(65%)	11	**REF**	

CHAPTER FIVE: DISCUSSION

Our study demonstrated a prevalence of about thirty eight percent for both acute lung injury and Acute Respiratory Distress. Acute Lung Injury had a prevalence of eleven percent while Acute Respiratory Distress Syndrome had a prevalence of thirty eight percent in children admitted with severe respiratory distress in Kenyatta National Hospital.

More than a third of the children enrolled into our study were found to have either acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). The prevalence of ARDs was more than two thirds in the subset that had both conditions and that of ALI was slightly less than a third. This is significantly higher than all the other pediatric studies documented in literature. This could partly be due to the fact that no comparison studies are available from a developing African nation and none done purely on black children. None of the studies done previously however showed a higher prevalence among the black race. The researcher found no other comparison studies conducted in the African region to determine the magnitude of the problem. There are several studies conducted on pediatric populations to determine the prevalence of both ALI and ARDS.

All the studies in literature utilized the American European Conference Consensus criteria to identify the patients just as our study did. One study by Simon E. and colleagues, a prevalence of 2.2% was found for both ALI and ARDS in children admitted to intensive care units in both Australia and New Zealand (9). Further, ALI accounted for 0.3% while ARDS accounted for 1.9%. This prevalence is about 19 times less than the prevalence our study got. The study does not characterize the study participants well enough for us to do a comparison between the two populations. Similar to our study, ALI accounted for a smaller percentage as compared to ARDS. In this Australian study, more than half of the patients diagnosed with ALI and ARDS had pneumonia while sepsis accounted for about a fifth of the patients. In our situation, about two thirds of the children who had ARDS had very severe and a third had severe pneumonia. For ALI, four fifths of the patients had either very severe or severe pneumonia. This difference could be explained by the fact that our entry point was acute severe respiratory distress in pediatric medical wards while they assessed all the children admitted from various disciplines in pediatric intensive care units. In another study P Dahlem et al found a prevalence of 9.9% of both ALI and ARDS among ventilated children aged 12 years and below admitted to an intensive care unit at

Emma Children's hospital in Netherlands (10). While the study population was similar to ours in terms of age, no further characterization has been done to allow us to carry out further comparisons between these two groups. The difference in the prevalence could be attributed to the fact that infection and specifically pneumonia has a very high prevalence in our population. Most patients with acute severe respiratory distress are also referred to the hospital after several trials of medications and therefore arrive to the hospital late. Goh A and colleagues found a prevalence of 4.2% of both ALI and ARDS in a study carried out among children aged 15 years and below in a pediatric intensive care unit in Malaysia (8). Their study used the AECC criteria for ARDS.

Having severe or very severe pneumonia was associated with a three-fold risk of developing ALI or ARDS. Although no significant association was found with ALI and ARDS, a child with pneumonia and meningitis had a three and half chance of developing either ALI or ARDS. Interestingly, having rickets, bronchiolitis and malnutrition was not significantly associated with ALI and ARDS. This could be due to the fact that the children with these conditions did not have very severe sepsis as compared to the ones with meningitis or very severe and severe pneumonia. Unfortunately, no documented studies have enrolled children with these unique conditions to the children in our study and we are not able to do a comparison. None of the social demographic factors assessed were found to have any influence on whether the child developed ALI or ARDS. This might be because our sample size lacked the statistical power to achieve this. Previous epidemiological studies on children have focused on mechanically ventilated patients in an intensive care unit (ICU) setting. In 2009, Andrew AQ and colleagues however, conducted a study among an adult population outside the intensive care unit (12). The study was conducted on adult patients aged 15 years and above admitted to respiratory isolation rooms on the general wards of a large tertiary hospital. The study found a prevalence of 9.9% for both ALI and ARDS. In comparison, our study was conducted in the acute rooms of pediatric wards that serve as a high dependency unit and where children with acute severe respiratory distress are first admitted. Although their study was carried out amongst an adult population and the prevalence may not be comparable with our study, it serves to show that it is possible to carry out a prevalence study on patients outside the ICU setting. With regard to this, our study was able to identify a high prevalence of both ALI and ARDS in an area that had not been studied previously by the earlier studies. Jerry J and colleagues found a prevalence of 27.6% for both and ARDS

with ALI accounting for 7% and ARDS accounting for 20.6% (11). The study was conducted among children aged 6 months to 15 years who required both invasive (through endotracheal tube or tracheostomy) and non-invasive (through a full face mask) at King County, Washington. This study in many ways compared to our study. First, their sample size (141) was close to our sample size (152). While they carried out the study on critically ill children, they did not limit their study population to mechanically ventilated children. They however got their children from a slightly older age group (6 months to 15 years) as compared to ours (2months to 12 years). This is the study with the closest prevalence to the prevalence our study found (27.6% as compared to 38.2%) in our study. The study however found a median age of 18 months for patients found to have ALI and ARDS as compared with our study that had a median age of 6 months. Most children in this study had associated sepsis that was found to have a primary focus as pneumonia accounting for two thirds of the children. Pneumonia, sepsis and aspiration were the highest risk factors. Although the demographic set up is very different from our set up, this study compares well with our study in terms of prevalence and associated factors for ALI and ARDS.

Previous published studies have given a prevalence of ALI and ARDS of between 1 - 27.6% with most studies ranging between 1-9.9%. Almost all the studies the investigator came across have been carried on mechanically ventilated children with exception of the study by Jerry J and colleagues that had a few patients on oxygen through a full-face mask. This high prevalence in this study raises a few pertinent issues. While it is it possible that the two conditions are higher in the African populations, it is also possible that our population is more predisposed because of poverty and poor health seeking behavior. It is also possible that the other published studies have been missing out on potential cases of ALI and ARDS by confining their study populations to only mechanically ventilated children.

The boy to girl ratio was 1.4:1 as compared to our study where the boy to girl ratio was 1:1. None of the studies documented have found a significant difference between the two sexes. While our study found that most children with ARDS had a median age of 6 months, their study found the median age of children with ALI/ARDS was 28 months. This could partly be due to the fact that their age cut off was 15 years while ours was 12 years. Slightly less than a half of the children they diagnosed with ALI and ARDS had sepsis and about a third had pneumonia. In our study, all the children with ALI and ARDS had pneumonia but the associated comorbidities

included meningitis, sepsis, HIV exposure, gastroenteritis, rickets, malnutrition and bronchiolitis. This can be explained by the different disease entities between an emerging economic power like Malaysia and a developing country like Kenya.

It would have been nice to do a multi variant association between acute respiratory distress syndrome and Rickets because rickets predisposes children to respiratory infections, this was not possible because the data collected could not support this analysis. This I however is a rich ground for research for future studies.

5.1 Study Strengths

The study utilized an internationally accepted criterion to identify patients with acute lung injury and acute respiratory distress syndrome - The American European conference Consensus criteria. This ensured consistency and allowed us to compare it with other studies that have been done on ALI and ARDS. The study utilized a study population that has not been investigated before in other pediatric studies on ALI and ARDS- patients with severe respiratory distress in the general pediatric wards. The number of children with ALI and ARDS was much larger than in the studies we compared with giving us power and allowing us to make valid conclusions on our findings. The unique patient characteristics in our study population have not been investigated before in the previous studies.

5.2 Study Limitations

Our study was subject to limitations. First, it was not designed to assess the management and even the outcome of the patients we diagnosed with ALI and ARDS. It is therefore difficult to make conclusions on the burden of the two conditions in totality. Further, we cannot comment on whether the management the children got was appropriate or adequate. Our study did not follow the subjects who were diagnosed with ALI and ARDS to find out whether they recovered or progressed to ARDS. Additionally, the study focused on a specific population: that of patients admitted to Kenyatta National Hospital from the city of Nairobi and its environs. This geographical area may differ from other areas in ways that limit generalizability of our findings. The hospital is a busy tertiary hospital and it receives its patients from other hospitals when they are very sick. We may have looked at a very sick cohort of our population that may not necessarily represent the rest of the population.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1Conclusions

1) The prevalence of ALI was 11.2% (95%CI 6.2%-30.4%) in children admitted with acute severe respiratory distress in Kenyatta National Hospital.

2) The prevalence of ARDS was 27.0% (95% CI: 19.9%- 34.0%) in children admitted with acute severe respiratory distress in Kenyatta National Hospital.

3) The clinical conditions described in children with Acute Lung Injury and Acute Respiratory Distress were severe pneumonia, meningitis, rickets and sepsis.

6.2 Recommendations

1) There should be intensive case finding for both ALI and ARDS in children admitted with acute severe respiratory distress. Since both conditions require management in the intensive care unit, early identification is needed in order to appropriately transfer the patients to the intensive care unit.

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Appendix I: Questionnaire

DEMOGRAPHIC DATA

Patient study no…… Initials…… Hospital NO…….

Date of Birth……. Sex…… (1) Male (2) female…..

Residence ……

Tel no of guardian ……. Within Nairobi (1) outside Nairobi (2)

Site of recruitment (tick as appropriate)..Paediatric wards……ICU……. Burns Unit…….. Paediatric surgery…….

Previous hospitalization Yes (1) No (2)……

1) RESPIRATORY SYMPTOMS (1) absent (2) and duration(1) <2 days (2) 2-7 days (3) >7 days

a) Cough……. …… duration…….

b) Difficulty in breathing……duration……

c) Inability to breastfeeding……duration……

d) Abnormally sleepy……duration……

e) Chest pain……duration…….

f) History of trauma……specify……(.RTA, FALL)

g) History of burns……..body %.....

h) History of drowning……

i) Other (specify)……

Physical Examination

a)	Pallor	Y…….N……..
b)	Jaundice	Y…….N……..
c)	Oedema	Y…….N……..
d)	FAN	Y…….N……
e)	Grunting	Y…… N…….
f)	Head nodding	Y…….N……
g)	Cyanosis	Y…….N……
h)	Chest wall in drawing	Y…….N……
i)	Crepitations	Y…… N…….
j)	Ronchi	Y…….N……
k)	R.R	…….
l)	Level of alertness	A……V……P……U……..
m)	Fever	Y……N……...

2) Diagnosis of current illness

a)……

b)……

c)…….

d)……..

3) Oxygen saturation by pulse oximeter (SPO2)

1st reading……

2nd reading……

Average…….

4) Mode of Oxygen

a) Room Air……..FiO_2 - 0.21
b) Mask……FiO_2 - 0.45
c) Nasal prongs……FiO_2 - 0.325
d) Nasal catheter……FiO_2 - .375
e) Nasopharyngeal catheter……..FiO_2 - 0.525
f) Ventilated…….Monitor FiO_2 reading.

FiO_2……..

SPO_2/ $Fi0_2$ Ratio……

5) BGA report;

PaO_2……..

$Pa0_2/FiO_2$ ratio……..

6) CXR Report……..

Presence of bilateral infiltrates (1)

Absence of bilateral infiltrates (2)

7) Echocardiography Report

(Whereavailable)……
……
……
8) Conclusion……

Appendix II a: Patient information (English)

INVESTIGATORS STATEMENT

Dear Patient/ Parent/ Guardian,

My name is Dr. M Wainaina. I am a postgraduate student in the school of medicine (Paediatrics). One of the short term complications of severe respiratory distress is a disease called Acute respiratory distress syndrome. The disease, if detected early and managed well resolves and does not cause long term complications. A blood test and a chest X ray are necessary for the early detection of this condition. I am conducting a research study to find out what proportion of children with severe respiratory distress at the Kenyatta National Hospital have this early condition . I would like to include you/ your child as a participant.

This will require that I administer to you a questionnaire, examine and take a blood sample and order for a Chest X ray from you/ your child. The blood sample will be about 3mls and is a fairly safe procedure that will not cause further harm to you/your child. The chest X ray is also a safe procedure and will be coordinated with routine hospital care such that you/your child will not have to go for an extra CXR during management .The investigations done will be at no added cost to you as a participant.

Participation in this study is voluntary and your decision on whether to participate or not will not prejudice your/ your child's care in any way. Strict confidentiality will be observed at all times. In all instances, your primary caregiver will be informed of all the results in view of more stringent follow up and added therapy.

I hope that you accept for yourself/ your child to participate in this study, as its outcome will impact on the future management of children with severe respiratory distress.

APPENDIX II b: Patient information (Swahili)

MAELEZO YA MPELELEZI

Kwa mshiriki;

Jina langu ni Dk. Margaret Wainaina, mwanafunzi katika Chuo Kikuu cha Nairobi, shule ya dawa. Mimi nafanya utafiti kuhusu ugonjwa wa Acute respiratory distress syndrome,ugonjwa ambao waweza kufuatia kupumua kwa haraka kwa mgonjwa, katika Hospitali ya Taifa ya Kenyatta. Matokeo ya utafiti huu yatatumiwa kusaidia kuutafuta ugonjwa huu kwa kina na kuutibu mapema na hivyo kuzuia adhari hatari za kudumu. Habari kutoka hapa itabaki siri na kutumika tu kwa madhumuni ya utafiti. Hakuna faida ya moja kwa moja kwa wewe mshiriki binafsi. Ningependa kushirikisha wewe, mtoto wako katika utafiti huu. Uuamuzi wa kushiriki ni kwa hiari yako na kama hautashiriki, haitazuiya huduma kwa wewe/ mtoto wako kwa njia yoyote. Hakuna hatari ya kushiriki ila wakati wewe utachukua katika kujibu maswali na kufanya uchunguzi ya X-Ray ya kifua na kutolwa damu kiasi cha 3ml. Uchunguzi itakayofanyika itakuwa bila gharama yoyote kwako kama mshiriki.

Kwa maswali yoyote/ ufafanuzi zaidi, wasiliana na mpelezi kwa anwani ifatayo:

P.O BOX 20734-00202, Nairobi , Kenya.

Nambari ya simu: 0722691418

Anwani ya barua pepe:njokimv@gmail.com

Unaweza pia kuwasiliana na KNH/ UON-ERC kwa:

P.O BOX 19676, Nairobi, Kenya.

Anwani ya barua pepe: uonknh_erc@uonbi.ac.ke

Appendix III a: Informed consent form (English)

PARTICIPANTS STATEMENT

I Mr/Mrs/Miss..... being a person aged 18 years and over, having read/ been explained to the above and in the knowledge that it is voluntary, do hereby give consent for myself/ my child to participate in this study.

I understand that I/ my child have the right to withdraw from the research at any time, for any reason, without penalty or harm.

.....

Patient/ Parent/ Guardian's signature

Date:.....

.....

Child's signature if above 7 years (Assent)

Date:.....

.....

Investigator's signature

Date:.....

For any questions/ clarification, contact the principle investigator on:

Telephone number: 0722691418

E mail address: njokimv@gmail.com.

You can also contact KNH/UON-ERC on:

P.O BOX 19676, Nairobi, Kenya.Email address**: uonknh_erc@uonbi.ac.ke**

Appendix III b: Informed consent form (Swahili)

Taarifa ya mshiriki

Mimi Bwana/ Bi.....mwenye umri wa miaka 18 na zaidi, baada ya kusoma/ kuelezwa hapo juu na kufahamu, kwahiari yangu, natoa idhini kwa mwenyewe/ mtoto wangu kushiriki katika utafiti huu.

Ninaelewa kwamba mimi/ mtoto wangu nina haki ya kujiondoa katika utafiti wakati wowote, kwa sababu yoyote bila ya adhabu au madhara.

Sahihi ya mzazi au mlinzi wa mtoto... ... ... Tarehe ... ...

Sahihi ya mtoto zaidi ya miaka 7.....Tarehe.....

Shahidi: Jina ... ... sahihi... ... ...Tarehe.....

Appendix IV: Determination of Oxygen Saturation

The principle of pulse oximetry is based on the red and infra-red light absorption of oxygenated and deoxygenated haemoglobin. A transcutaneous sensor is used to measure the percentage of haemoglobin that is fully saturated with oxygen (Spo2). Pulse oximetry uses spectrophotometry and plethysmography. It consists of a computerized unit and a sensor probe that is attached to the patient's finger, toe, or ear lobe. The sensor emits two different wavelengths of light (red -600-750nm wavelength light band and infrared 850-1000 nanometre wavelength band. These lights are absorbed by haemoglobin and transmitted through tissues to a photo detector. Oxygenated haemoglobin absorbs more infrared light and allows more red light to pass through the photo detector. Deoxygenated haemoglobin absorbs more red light and allows more infrared light to pass through to the photo detector. The amount of light transmitted is converted to a digital value. The ratio of absorbed red to infrared light indicated the degree of oxygenation. The height of the plethysmography wave (pulse) indicates the arterial pulsation. The signal between the pulse waves (baseline) is subtracted from the signal at the peak of the plethysmography wave, the difference being due to inflowing arterial blood so reflecting the saturation of arterial blood. A microprocessor compares the absorption of light at the peak (arterial pulse) and trough (baseline) at both red and infrared waveforms of light (18).

For purposes of our study, we will use a portable hand held battery powered pulse oximeter (Nonin Onyx 9500 manufactured in the United Kingdom). The examiner will explain to the parent or guardian briefly on the pulse oximeter and its value. Ensuring that the child is comfortably positioned and calm, the examiner will select the site and place the pulse oximeter on the selected site (toe or finger). The finger or toe selected should have a good capillary refill at a point closest to the selected site. The probe will be held into position until a steady reading is obtained. Two such values will be taken and the average of the two recorded in the questionnaire.

Appendix V: Arterial Blood Draw Procedure

Arterial blood sampling by direct vascular access is a procedure that has a relatively low incidence of major complications. It can either be performed at the radial, brachial of femoral artery. The examiner will be required to demonstrate adequate collateral blood flow of either the lower or the upper limb before staring the procedure. Appropriate positioning of the patient and knowledge of the vascular anatomy increases the chance of a successful arterial vascular sampling and diminish the risk of complications. For radial artery sampling, the patient should lie supine with the arm lying at his/her hard surface. The forearm should be supinated and the wrist dorsi flexed at 40 degrees. One should palpate the patient's radial pulse with the index and middle finger of the non dominant hand. The desired puncture site should be cleaned in a circular motion with an antiseptic. A pre heparinised syringe should be held with the two fingers of the dominant hand and introduced at a 45 degrees angle aiming at the direction of the artery. The needle is then advanced slowly and once it enters the lumen of the artery, the arterial blood starts to fill the syringe. After 2-3mls of arterial blood, remove the needle and apply a firm occlusive local pressure at the puncture site for 5 minutes. After 5 minutes check for haemostasis and apply an adhesive bandage over the puncture site. One should ensure there are no gas bubbles before uncapping the syringe and taking it for analysis. The same principle is applied to the other sites with consideration to the anatomy. (19)

Blood taking for the purpose of this study will be coordinated with that required for routine hospital care to avoid additional discomfort attributable to the study. The investigator will explain the procedure to the guardian and its importance and will then proceed to carry out the sampling at the most appropriate site as explained above.

Appendix VI: Determination of the Blood Gas Analysis

Determination of blood gases will be done using a rapid lab 348 semiautomatic machine manufactured by Bayer UK. This machine is located in the intensive care unit and the lab deals primarily with blood gas analysis. Quality control is done every morning using the recommended quality control materials which include Rapid QC plus, rapid QC complete and haematocrit A and B. The machine determines different arterial gas parameters and this includes Ph, i.e. the concentration of hydrogen ions, partial pressure of carbon dioxide (pCO_2) and partial pressure of oxygen (Po_2) in whole blood. It may also measure electrolytes and metabolites and this includes potassium(K^+), sodium (Na^+) ,bicarbonate (HCO_3) and base excess (BE).The Ph value of blood, serum or plasma is an indicator of the balance between blood, renal (kidney) and the respiratory (lung) systems and is a tightly controlled parameter in the body. The $PaCO_2$ of arterial blood is used to access how well the body eliminates carbon dioxide, a by-product of metabolism. The PaO_2 value is a measure of how well the body is able to absorb oxygen from the lungs. The machine determines the parameters in the following way; blood is collected from the patient and introduced to the analyser. The analyser aspirates the blood into a measurement chamber which has ion selective electrodes i.e. the electrodes that are sensitive only to the measurements of interest. The P^h electrode compares a potential developed at the electrode tip with a reference potential, the resulting voltage is proportional to the concentration of hydrogen ions (H+).The $PaCO_2$ electrode is a Ph E electrode with a Teflon or silicone rubber CO_2 semi permeable membrane covering the tip. Carbon dioxide (CO_2) combines with water in the space between the membrane and the electrode to produce free hydrogen ions in proportion to the partial pressure of CO_2. The voltmeter, although actually measuring hydrogen ions is calibrated in $PaCO_2$. For PaO_2, oxygen permeates a poly propylene membrane and reacts chemically with a phosphate buffer, producing current that is in proportion to the number of oxygen molecules. The current is measured and expressed as partial pressure of oxygen. After measurement, the blood is automatically expelled into a waste container and the sample path cleaned ready for the next sample. Results are then printed out. Units of measurements are in millimetres of mercury (mmHg) or in kilopascals (kpa) (20).

Appendix VII: KNH/UON-ERC Letter of Approval

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
(254-020) 2726300 Ext 44355

KNH/UON-ERC
Email: uonknh_erc@uonbi.ac.ke
Website: www.uonbi.ac.ke

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/370 **Link:www.uonbi.ac.ke/activities/KNHUoN** 14th November 2013

Dr. Margaret Njoki Wainaina
Dept.of Paediatrics & Child Health
School of Medicine
University of Nairobi

Dear Dr. Wainaina

RESEARCH PROPOSAL: PREVALENCE OF ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME (P269/5/2013)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 14th November 2013 to 13th November 2014.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website **www.uonbi.ac.ke/activities/KNHUoN.**

"Protect to Discover"

Yours sincerely

PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. Prof. A.N.Guantai, Chairperson, KNH/UoN-ERC
The Deputy Director CS, KNH
The Principal, College of Health Sciences, UoN
The Dean,School of Medicine, UoN
The Chairman, Dept.of Paediatrics & Child Health, UoN
AD/Health Information, KNH
Supervisors: Prof. A.O.Wasunna, Prof.Elizabeth Obimbo, Dr.R. Kumar, Dr. Mulama